PROBLEMS IN THE OPTIMAL MANAGEMENT OF MYASTHENIA GRAVIS PATIENTS - A PROSPECTIVE CLINICAL SURVEY AT KALAFONG HOSPITAL

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Objectives. This study forms part of a clinical survey of problems in the optimal management of patients with inherited neuromuscular diseases seen at Kalafong Hospital in Pretoria. Our objectives were to determine the problems associated with providing patients with optimal management until true remission (cure), and to apply the findings to ongoing improvement of optimal management. This is the first report of the series.

Methods. Twenty-six patients were studied prospectively from 1986 to 1998. Early sternal-splitting thymectomy on class II-V patients as well as anticholinesterases, corticosteroids, azathioprine, plasma exchange, intensive care and various combinations of these constituted part of the optimal management. An assessment of the total monthly income and distance from hospital was done for each patient.

Results. Five of the 15 thymectomised patients (33.3%) were lost to follow-up after reaching remission. Of the remaining 10 patients, 6 (60%) are in true remission and the remaining 4 (26.7%) are in pharmacological remission. Four of the 11 patients (36%) treated non-surgically were lost to follow-up. Of the remaining patients, 1 (9.1%) is in true remission and the remaining 6 (54.5%) are in pharmacological remission.

The average monthly income of patients lost to follow-up in the thymectomised group was lower than that of patients who continued follow-up, and their homes were further away from hospital. In the non-surgical group the average monthly income of patients lost to follow-up was higher than that of patients who continued follow-up and their homes were nearer to the hospital.

Conclusion. Early thymectomy (the aggressive approach) resulted in 40% cures, 26.7% pharmacological remissions, no mortality, minimal morbidity, and early discharge. Loss to follow-up was one of the biggest problems in providing optimal management for these patients. We modified optimal management in response to our patients’ concerns without sacrificing excellence, and found that poverty and poor access to tertiary hospitals were possible contributory factors to loss to follow-up. Suggestions are made with regard to tackling the problems.

Myasthenia gravis (MG) is a disorder of neuromuscular function resulting from an immunologically based premature destruction of acetylcholine receptors.

Although Mendelian genetics does not seem important in the aetiology of MG, there is increasing evidence that susceptibility genes do play a role and that what is inherited is a genetic predisposition. In addition, the genetic contribution to MG susceptibility is significant, with a 36% concordance in monozygotic twins and a family history of the disease in 2-3% of all patients. There are hereditary forms of MG as well. For the abovementioned reasons as well as for the sake of continuity in covering disorders from the anterior horn cells to skeletal muscles, MG patients were included in the survey. Treatment of the MG patient is generally lifelong, extending into all areas of his or her activity.

The goal of MG therapy is to produce normal function, with rapid onset of the effect. Although the number of therapeutic options available has increased greatly over the past three decades, experts in the field continue to debate over the most successful therapeutic approach. It has been stated that the art of providing safe care for patients with myasthenia gravis lies in deciding when to treat and when not to treat aggressively.

A number of factors influence the decision on the mode of therapy to use, namely:

1. The rate of progression, which along with the severity and distribution of the weakness, is the most important consideration for immediate therapeutic decisions.

2. Clinical considerations, including resources available or ability to comply with a therapeutic strategy. At Kalafong Hospital we were faced with a unique set of circumstances that influenced our choice of management; i.e.: (i) limited resources from the national health services; (ii) 14 (93.3%) of the 15 patients who underwent thymectomy were either employed and contributing to the family income or were in the age group in which they should have been doing so - they were all unwilling to spend many months in hospital and we anticipated that follow-up would be unreliable in some of...
them; (iii) all our patients were from the poorest section of the South African population; and (iv) a significant correlation had been found between the brevity of the interval between the onset of MG and thymectomy, and the likelihood of a good response to the operation.7

Because of the abovementioned factors our management protocol had to aim for the shortest possible stay in hospital. This dictated that we adopt an aggressive approach to management of generalised MG in an attempt to meet our patients' expectations, with the resources at our disposal. These circumstances led us to embark on the present study.

**Objectives**

The objectives of the present study form part of a prospective clinical survey of problems in the optimal management of patients with inherited neuromuscular disorders seen at Kalafong Hospital.

Our objectives were: (i) to determine, prospectively, the problems associated with providing optimal management to these patients; (ii) to assess the effectiveness of optimal management, in other words to attempt to answer the question 'Are we providing effective care to MG patients in our region, and are they appearing to benefit from it?' - this was especially with regard to the favourable outcome of early thymectomy in generalised MG reflected in the literature; (iii) to apply the experience obtained to ongoing improvement of optimal management; and (iv) ultimately to devise appropriate, cost-effective, evidence-based guidelines to manage these patients.

**Materials and Methods**

Twenty-six consecutive MG patients were studied prospectively from 1986 to 1998. Patients were admitted to the study if they satisfied the following two minimum inclusion criteria: (i) if they showed typical clinical features of MG; and (ii) if one of the following supportive tests was positive: (a) the intravenous (IV) edrophonium test or intramuscular (IM) atropine/neostigmine test, (b) the decremental response to repetitive nerve stimulation test, (c) the response to anticholinesterase medication, and (d) the serum acetylcholine receptor antibody test.

The following were recorded for each patient: (i) total monthly income, and the total number of people per household that the income had to support; and (ii) the distance between each patient's home and the hospital (justification for including these two parameters will be given in the discussion section).

In addition to the above tests, the following laboratory tests were done on each patient: antinuclear factor, thyroid function tests, auto-antibodies to the thyroid gland, rheumatoid factor, full blood count with differential count and erythrocyte sedimentation rate, antistriated muscle antibodies, creatine phosphokinase, and chest radiographs. Serum anti-acetylcholine receptor antibodies were measured in some of the patients. A computed tomography (CT) scan of the superior mediastinum was also done on all patients to assess thymus size.

The aggressive management of generalised MG (classes II-V) consisted of restoration of normal strength using high-dose daily or alternate-day corticosteroids orally or parenterally, equivalent to 50 - 100 mg prednisone, and early thymectomy (within a year of diagnosis).

Long-term follow-up until true remission (cure) was carried out on all the patients.

**Classification**

The patients were then classified according to the Modified Osserman Classification as used at the University of Virginia (Table I).

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Mild to moderate</td>
<td>Ocular</td>
</tr>
<tr>
<td>II</td>
<td>Disease</td>
<td>Mild generalised weakness, usually with ocular muscle weakness</td>
</tr>
<tr>
<td>III</td>
<td>Severe disease</td>
<td>Predominantly opharyngeal involvement, usually with mild generalised weakness</td>
</tr>
<tr>
<td>IV</td>
<td>Moderate generalised weakness</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>Severe generalised weakness (crisis)</td>
<td></td>
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</tbody>
</table>

**Management**

The aggressive management of generalised MG consisted of:

1. Restoration of normal strength using high-dose daily (50 - 100 mg) or alternate-day corticosteroids orally or parenterally (Table II). For various reasons restoration of normal strength using high-dose corticosteroids was achieved in only 7 patients who underwent thymectomy. In the remaining 8 patients who underwent thymectomy restoration of strength was initiated using lower doses of corticosteroids, or pyridostigmine bromide.

2. Following thymectomy the patients were kept on doses of corticosteroids and/or azathioprine sufficient to maintain normal strength. Small reductions in dose of corticosteroids, namely 5 - 10 mg, were effected at the end of every month until true remission, that is normal strength while off all medications for a period of at least 2 years, was reached. The minimum maintenance dose varied and was established by trial and error for each patient who deteriorated on lower doses.

3. Anticholinesterase medication was used as supplementary
The time interval between admission and thymectomy ranged
3.05
from 2 weeks to 1 year and 3 months, with an average of
THYMECTOMY
2 mg/kg of body weight to replace or reduce corticosteroids in
those patients requiring high doses of corticosteroids to
period. The dose of corticosteroids was then slowly reduced,
and if at all possible, stopped.

complications from high-dose corticosteroids over a prolonged
and calcium supplements.

pyridostigmine used ranged from 60 mg three times a day to
60 mg five times a day orally.

4. Patients were also treated with isoniazid (INH) as
prophylaxis against tuberculosis, as well as with potassium
and calcium supplements. Oral cinetidine was used as
prophylaxis against peptic ulceration.

5. Azathioprine (Imuran) was given orally at a dose of
2 mg/kg of body weight to replace or reduce corticosteroids in
those patients requiring high doses of corticosteroids to
maintain normal strength. This was to reduce the likelihood of
complications from high-dose corticosteroids over a prolonged
period. The dose of corticosteroids was then slowly reduced,
and if at all possible, stopped.

Table II. Treatment with corticosteroids and anticholinesterase
drugs

<table>
<thead>
<tr>
<th>Patient</th>
<th>Class</th>
<th>Initial doses of corticosteroids daily or on alternate days (A/D)</th>
<th>Route of administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I</td>
<td>Prednisone 60 mg/day</td>
<td>Oral</td>
</tr>
<tr>
<td>2</td>
<td>I</td>
<td>Pyridostigmine</td>
<td>Oral</td>
</tr>
<tr>
<td>3</td>
<td>I</td>
<td>Pyridostigmine</td>
<td>Oral</td>
</tr>
<tr>
<td>4</td>
<td>I</td>
<td>Pyridostigmine</td>
<td>Oral</td>
</tr>
<tr>
<td>5</td>
<td>I</td>
<td>10 mg A/D and pyridostigmine</td>
<td>Oral</td>
</tr>
<tr>
<td>6</td>
<td>I</td>
<td>Pyridostigmine</td>
<td>Oral</td>
</tr>
<tr>
<td>7</td>
<td>II</td>
<td>Prednisone 20 mg/day</td>
<td>Oral</td>
</tr>
<tr>
<td>8</td>
<td>II</td>
<td>Pyridostigmine</td>
<td>Oral</td>
</tr>
<tr>
<td>9</td>
<td>II</td>
<td>No treatment given</td>
<td>Oral</td>
</tr>
<tr>
<td>10</td>
<td>II</td>
<td>Pyridostigmine</td>
<td>Oral</td>
</tr>
<tr>
<td>11</td>
<td>II</td>
<td>Pyridostigmine</td>
<td>Oral</td>
</tr>
<tr>
<td>12</td>
<td>II</td>
<td>Prednisone</td>
<td>Oral</td>
</tr>
<tr>
<td>13</td>
<td>II</td>
<td>Prednisone</td>
<td>Oral</td>
</tr>
<tr>
<td>14</td>
<td>III</td>
<td>Prednisone 100 mg A/D</td>
<td>Oral</td>
</tr>
<tr>
<td>15</td>
<td>III</td>
<td>Prednisone</td>
<td>Oral</td>
</tr>
<tr>
<td>16</td>
<td>IV</td>
<td>Prednisone 55 mg/day</td>
<td>Oral</td>
</tr>
<tr>
<td>17</td>
<td>IV</td>
<td>Prednisone 60 mg/day</td>
<td>Oral</td>
</tr>
<tr>
<td>18</td>
<td>IV</td>
<td>Prednisone 35 mg A/D</td>
<td>Oral</td>
</tr>
<tr>
<td>19</td>
<td>IV</td>
<td>Prednisone 10 mg/day</td>
<td>Oral</td>
</tr>
<tr>
<td>20</td>
<td>IV</td>
<td>Prednisone 60 mg/day</td>
<td>Oral</td>
</tr>
<tr>
<td>21</td>
<td>IV</td>
<td>Prednisone 30 mg A/D</td>
<td>Oral</td>
</tr>
<tr>
<td>22</td>
<td>V</td>
<td>Prednisone 60 mg/day</td>
<td>Oral</td>
</tr>
<tr>
<td>23</td>
<td>V</td>
<td>Prednisone 60 mg/day</td>
<td>Oral</td>
</tr>
<tr>
<td>24</td>
<td>V</td>
<td>Prednisone 60 mg/day</td>
<td>Oral</td>
</tr>
<tr>
<td>25</td>
<td>V</td>
<td>Decadron 10 mg IV 4 times a day Intavenous</td>
<td>Intravenous</td>
</tr>
<tr>
<td>26</td>
<td>V</td>
<td>Prednisone 40 mg/day</td>
<td>Oral</td>
</tr>
</tbody>
</table>

time interval as required by the patient. The doses of
pyridostigmine used ranged from 60 mg three times a day to
60 mg five times a day orally.

4. Patients were also treated with isoniazid (INH) as
prophylaxis against tuberculosis, as well as with potassium
and calcium supplements. Oral cinetidine was used as
prophylaxis against peptic ulceration.

5. Azathioprine (Imuran) was given orally at a dose of
2 mg/kg of body weight to replace or reduce corticosteroids in
those patients requiring high doses of corticosteroids to
maintain normal strength. This was to reduce the likelihood of
complications from high-dose corticosteroids over a prolonged
period. The dose of corticosteroids was then slowly reduced,
and if at all possible, stopped.

TIME INTERVAL BETWEEN ADMISSION AND THYMECTOMY
The time interval between admission and thymectomy ranged
from 2 weeks to 1 year and 3 months, with an average of
3.05 months. The only exception was patient number 20 in
class IV, a member of our hospital staff, who eventually
underwent thymectomy 2.5 years after diagnosis when she
started becoming hypertensive as a result of the corticosteroid
treatment. The average of 3.05 months was well within our
guideline of 1 year.

RESULTS
Confirmatory tests — edrophonium chloride tests
The edrophonium chloride test (also known as the Tensilon
test) or the atropine-neostigmine tests were positive in all
patients. The repetitive nerve stimulation at 2 Hz test was
positive in all the patients in whom it was done (except for one
(class 1) patient, in whom it was negative. Single-fibre
electromyography was positive in 1 of 2 patients in class I.

Thymic histology
Histological examination of the thymus gland showed thymitis
in 10 patients, thymoma in 2 patients and was normal in the
remaining 3 patients.

Serum anti-acetylcholine receptor antibodies
Serum anti-acetylcholine receptor antibodies, done in 9
patients, were positive in 5 patients (38.5%) and negative in 4
(44.4%).

Additional tests
Two patients had primary thyrotoxicosis on thyroid function
testing. The remaining tests were normal.

Results of treatment
Classification of treatment results
We modified Pascuzzi and Johns's
classification of treatment
results as follows: (i) unimproved: absence of objective
improvement; (ii) moderate improvement: objective
improvement but functionally limited by weakness;
(iii) marked improvement: without significant symptoms and
return to ordinary activities of daily living, but with slight
weakness on examination; (iv) pharmacological remission:
asymptomatic on treatment with no weakness on examination,
but weakness of eye-closure allowed; (v) remission:
asymptomatic off all treatment with no weakness on
examination, for a period of less than 2 years; and (vi) true
remission (cured): asymptomatic off all treatment with no
weakness on examination, for a period of at least 2 years.

Results of classes I and II patients treated without
thymectomy
Four of the 11 patients (36%) were lost to follow-up. Of the
remaining 7 patients who continued follow-up, 1 (9.1%) reached true remission (cured) and the rest are in
pharmacological remission.
The average monthly income, per person, of patients lost to follow-up was R29.40, and their average distance from hospital was 72 km. On the other hand, the average monthly income of patients still on follow-up was R18.50, and their average distance from hospital was 157 km.

**Results of classes II - V patients who underwent thymectomy**

Of the 15 patients who underwent sternal-splitting thymectomy, 5 (33.3%) were lost to follow-up. Six of the post-thymectomy patients (40%) still on follow-up are in true remission (cured) and the rest are in pharmacological remission. The 40% true remissions (cures) and the 26.7% remissions means that 66.7% of the patients went back to their normal lives. All the patients in true remission were female and aged 35 years and younger.

Histological examination of the thymus gland showed thymitis in 4 patients and was normal in the other 2 patients. The duration of disease before treatment ranged from 3 months to 7 years, with an average of 2 years and 4 months. The period from thymectomy to remission in this group ranged from 5 months to 9 years, with an average of 2 years and 2 months.

The time interval between admission and thymectomy (classes II - V patients) in the 7 patients who achieved restoration to normal strength with high-dose corticosteroids averaged 4.5 months and ranged from 0.75 months to 1 year and 3 months. In the other 5 patients who received lower doses of corticosteroids for induction the time interval averaged 1.32 months and ranged from 0.5 months to 2.32 months.

**DISCUSSION**

The 100% positivity of edrophonium chloride (Tensilon test) or the atropine-neostigmine tests is in agreement with reports in the literature of high (88%) yield for the test. The test was done in only 2 of the patients who were 'cured' following thymectomy, with 1 positive and 1 negative. These tests, even with the availability in recent years of the acetylcholine receptor antibody titre and single-fibre electromyography, have remained the gold standard for the diagnosis of MG.

The serum anti-acetylcholine receptor antibodies done in 9 patients were positive in 5 patients (55.6%) and negative in 4 patients (44.4%).

The distribution of positives according to class was 2 patients out of 4 (50%) in class II, 1 out of 3 (33.33%) in class IV, and 1 each (100%) in classes III and V.

The test was done in only 2 of the patients who were 'cured' following thymectomy, with 1 positive and 1 negative. The numbers are too small to address the question, raised by Mossmann et al., namely whether thymectomy constitutes appropriate management for the group of anti-acetylcholine-negative patients.

Untreated, there is a 40% mortality rate over 10 years for MG. The immediate and short-term goal of therapy is to produce normal function of weak muscles rapidly. As the disorder of neuromuscular function results from premature destruction of acetylcholine receptors by antibodies, therapy aims at preventing or slowing down synthesis of these acetylcholine receptor antibodies. The ultimate goal of therapy in MG is a cure.

There is general agreement on four principles of therapy, namely: (i) anticholinesterase drugs are useful in all clinical forms of MG; (ii) they are the mainstay of treatment in ocular MG; (iii) plasmapheresis confers only transient improvement; and (iv) the presence of thymoma is an absolute indication for thymectomy.

Six of our post-thymectomy patients (40%) still on follow-up are in true remission (cured) and the rest are in pharmacological remission. This means that 100% of the post-thymectomy patients who continued follow-up returned to normal life. The results of the aggressive approach to management of generalised MG show that our optimum management is effective and beneficial to our patients.

The 40% true remission (cures) and 26.7% remission means that 66.7% of the patients went back to their normal lives. This, together with the zero mortality and minimal morbidity, compares with the best results in the world literature. Thymectomy is generally accepted as being effective in 66-86% of patients in whom there is no thymoma and Lindberg et al. have also stated that the probability of long-term spontaneous remission after thymectomy is about 50%.

One aspect of our aggressive approach, namely restoration of normal strength using high-dose corticosteroids, was achieved in only 7 of the 15 patients who underwent thymectomy. The main reason is that some of the patients had already been started on treatment before referral. The 4.5-month time interval between admission and thymectomy in this group is longer than the 1.32-month average time interval for the group that received lower doses of corticosteroids. Unfortunately the time interval is not an accurate reflection of the speed of achieving normal strength as for personal reasons there were delays to thymectomy in some of the patients when the patient was in a state of marked improvement or normal strength. However, in almost the whole group thymectomy was performed within a year of diagnosis.

The advantages of our aggressive approach include: (i) rapid induction of marked improvement or remission in a high percentage of MG patients within a predictable time period; (ii) markedly reduced morbidity at thymectomy, usually performed approximately 3 months after commencement of prednisone treatment, and when the patient was in a state of marked improvement or remission; and (iii) early return to
normal activities of daily living, with outpatient management.\textsuperscript{22} The one potentially dangerous disadvantage of the aggressive approach is the occurrence of exacerbations early in therapy. This occurred in 1 (6.7\%) of our 15 patients. Our policy is that all patients have to be in hospital during this period in order to monitor and treat this complication.

Some researchers have suggested that beginning therapy with low-dose alternate-day steroid treatment with gradual increase in dosage may reduce the frequency of early exacerbations.\textsuperscript{23} However, according to other authors\textsuperscript{7} that regimen does not eliminate the risk of exacerbation, and had the potential disadvantages of prolonged time in achieving improvement and fluctuating strength on an alternate-day basis.\textsuperscript{24}

All our patients in true remission were females 35 years old and younger. Histological examination of their thymus glands showed hyperplasia in 4 and normal thymus in 2. Thymectomy was performed early in 5 and late in 1 patient. Several recent studies concur that thymectomy in generalised MG patients hastens the onset and increases the frequency of remission and that most remissions occur in young women with hyperplastic glands and high antibody titres.\textsuperscript{25,26}

Other researchers further state that thymectomy done early, i.e. during the first year of disease, seems to improve outcome significantly.\textsuperscript{27} In contrast, Grob and colleagues\textsuperscript{28} believe that thymectomy should be limited to more seriously ill patients.

The rationale behind thymectomy remains unknown. Thymic lymphocytes from over 70\% of patients with MG and thymitis spontaneously synthesise antibodies against the acetylcholine receptors in vitro, suggesting that they are already primed and that in vivo antibody production takes place in the thymus.\textsuperscript{29}

Plasmapheresis leads to transient reduction of serum anti-acetylcholine receptor antibody levels, while thymectomy and corticosteroids lead to longer-lasting reduction.

The 9.1\% true remission (cure) rate in the class I and II patients treated without thymectomy compares well with the spontaneous cure rate of 10\% reported in the literature.\textsuperscript{30} Results for this group of patients cannot be compared with those of the thymectomised patients as they are not strictly comparable in terms of disease severity (class).

The total monthly income per household of thymectomised patients ranged from R40 to R1 200. According to the Department of SOCIAL WELFARE’S MEANS TEST (M Steenkamp — unpublished data, 1998), if the household income is below R800 per month, then the child qualifies for a child support grant. Eleven of the 15 patients in this group (73\%) had household incomes below R800. Our project therefore turned out to be one of finding out whether loss to follow-up would be higher among the poorers of the poor living furthest from tertiary hospitals. This fact was confirmed by our results in the surgical (thymectomy) group where the average distance from hospital of patients lost to follow-up was greater and their average monthly income per household lower than those of patients who continued follow-up.

The total monthly income per household of patients treated without thymectomy ranged from R50 to R1 200. Nine of the 11 patients (82\%) had monthly incomes below R800 per month. The finding in the surgical (thymectomy) group with regard to loss to follow-up being related to the lowest income and furthest distance from hospital was not confirmed. Some of the patients had higher incomes and lived nearer hospital than those who continued follow-up. This suggests that there are reasons for loss to follow-up other than poverty and long distances from hospital. However, what was confirmed in this group was that the majority of patients fell into the poor group according to the Department of SOCIAL WELFARE’S MEANS TEST. In addition, it was also found that most of the patients lived long distances from tertiary hospitals.

in choosing household income and distance from hospital we were using common sense to assess the means of our patients with the resources available to us. How valid are these two parameters as a means test? It is reassuring and gratifying to see that the Gauteng Provincial Government, Department of Social Welfare and Population Development: Social Security uses the same two parameters plus the type of dwelling as a simple test for a child-support grant. Furthermore, according to their calculations this simple means test was so accurate that it enabled them to identify 99\% of children from the poorest households in South Africa (M Steenkamp — unpublished data, 1998).

The results of the patients who continued follow-up are promising with regard to the outcome of our aggressive approach, but they are hampered by the percentage of patients lost to follow-up (up to 36\% of our patients).

It is government policy to improve the social circumstances of all South African citizens, especially the circumstances of the poor. It is also government policy to bring health services to within reasonable reach of all citizens, in particular those living in rural areas. These are medium- to long-term measures. Until this ideal situation is reached our efforts to provide optimal management are likely to be frustrated in up to 36\% of patients, as shown in our results.

It is incumbent upon all doctors with the welfare of their patients at heart to devise simple, cost-effective, imaginative ways to try to overcome these problems. However, problem finding is the necessary precursor of problem solving.

CONCLUSION

We took disease severity, the patients’ social circumstances and available therapeutic resources into consideration in our choice of management approach for MG patients. In other words, we
structured our therapeutic resources to try to lessen the disadvantages of poverty.

The optimal management was effective and beneficial to our patients. The main constraints on optimal management were socio-economic, with the result that tertiary centres were not fully accessible to the poorest sections of our population. Since socio-economic upliftment is a long-term process we will have to continue to find creative ways of modifying our management procedures to overcome this constraint. Failure to achieve this will perpetuate suboptimal management of patients. Our research project has also illustrated how clinical research can identify those aspects of poverty of special importance to the health of the population.

We agree with Cook when he states: In developing countries defining what constitutes appropriate services and working to achieve this will perpetuate suboptimal management of patients.

We are grateful to the Medical Research Council of South Africa for supporting this project financially. We would like to thank the Immunology Department, Professor L Dreyer of the Pathology Department, Dr H Dafel, Chief Superintendent of Kalafong Hospital, for advice; and Ms K Bosch for secretarial work.

References