Brief Reports

Intestinal Parasites in Malaysian Children with Cancer

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Summary

In this prospective study, we examined stool specimens from children with cancer receiving chemotherapy who were admitted for fever to the Universiti Sains Malaysia Hospital in Kota Baru, Kelantan. Stool specimens were examined for ova and cysts of parasites. Over a period of 15 months, there were 129 febrile episodes in 50 children with cancer and, in all, 237 stool specimens were examined. Sixty-six per cent of febrile episodes were associated with neutropenia and 9 per cent were associated with diarrhoea. Stool parasites were found in 42 per cent of children. The most common were helminths, followed by protozoa. *Trichuris trichiura* was the most common parasite (24 per cent), followed by *Ascaris lumbricoides* (22 per cent). Hookworm was found in 2 per cent. *Giardia lamblia* was found in 6 per cent of children, *Blastocystis hominis* in 4 per cent, and *Cryptosporidium parvum* in 2 per cent.

Introduction

Enteric parasitic diseases are prevalent in Malaysia, particularly in disadvantaged communities.[1] Kelantan is a state in the north-east of peninsular Malaysia, with a largely rural population. A study in 1992 showed a high prevalence of *Cryptosporidium parvum* (11.4 per cent) in children with diarrhoea from this state.[2] This organism has been reported as a cause of life-threatening diarrhoea in children with cancer.[3] The aim of this study was to determine the prevalence of *Cryptosporidium parvum* as well as other stool parasites in children with cancer.

Patients and Methods

This was a prospective study over 15 months from August 1996 to October 1997. Three stool specimens were collected on consecutive days from children with cancer receiving chemotherapy who were admitted for fever to the Hospital Universiti Sains Malaysia in Kota Baru. Fever was defined as a temperature of 38°C on two occasions 4 h apart or > 38°C on one occasion. A questionnaire was completed for each patient documenting clinical information such as diarrhoea, animal contact, and neutropenia. Diarrhoea was defined as an alteration in bowel habit and the passage of loose or watery stools. Neutropenia was defined as a granulocyte count of less than or equal to 1.0×19^9/l.

Stool samples were examined for ova and cysts of parasites by direct microscopy. The modified Ziehl–Neelsen stain was used to examine for *Cryptosporidium* oocysts.

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Results

During the study period, there were 129 episodes of fever in 50 children with cancer. Two hundred and thirty-seven stool samples were collected. The age range of patients was from 9 months to 11 years, with an average of 5 years. There were 31 males and 19 females. Thirty-two children had leukaemia and 18 had solid tumours.

Each child had an average of 2.5 episodes of fever. Eighty-four episodes were associated with neutropenia (66 per cent). Twenty-five children (50 per cent) had a history of exposure to animals, either livestock or domestic pets.

Twenty-one children had positive stool parasites (42 per cent) (Table 1). Diarrhoea occurred in 12 children (9 per cent of febrile episodes). In all cases the duration was less than 1 week. Four of the 12 had positive stool parasites. The organisms were *Giardia lamblia* in two cases, *Blastocystis hominis*, and *Ascaris lumbricoides*.

Cryptosporidium parvum

One child had a positive stool specimen for *C. parvum*. This was a 2-year-old girl with Down syndrome and bilateral retinoblastoma. She was not neutropenic at the time and did not have loose stools. However, she did have bronchopneumonia. Three months earlier she had

TABLE 1
Prevalence of stool parasites in children with cancer

Parasite	Prevalence (%)
Trichuris trichiura	24
Ascaris lumbricoides	22
Giardia lamblia	6
Blastocystis hominis	4
Hookworm	2
Cryptosporidium parvum	2

diarrhoea lasting 1 week but stool samples were negative for *C. parvum*. Four further stool samples 1 and 3 months following the positive sample were also negative. There was no history of animal contact.

Giardia lamblia
Three children had positive stool samples for *Giardia lamblia*—two had symptoms of diarrhoea. One child had profuse diarrhoea (20 times/day) and abdominal pain. She was neutropenic at the time and had numerous trophozoites and cysts in her stool. She was treated with metronidazole as well as broad-spectrum antibiotics. Despite this, she died, most probably due to a multi-resistant bacterial septicaemia.

Blastocystis hominis
Two children were positive for *Blastocystis hominis*, one of whom had diarrhoea. This child also had *B. hominis* in his stool 2 weeks prior to the diarrhoea when he was febrile but had no loose stools.

Helminthiasis
Sixteen children (32 per cent) had helminthiasis and seven children (14 per cent) had more than one helminth. Twelve children were positive for *Trichuris trichiura* and 11 for *Ascaris lumbricoides*. Only one child had hookworm ova—this child had a mixed infection with *Giardia lamblia* as well as *Ascaris lumbricoides*.

Discussion

Parasites are reported to be rare pathogens (1 per cent of infectious episodes) in neutropenic patients in developed countries.[4] The prevalence in developing countries is not known. Our study showed that 42 per cent of children with cancer were positive for stool parasites. Our numbers, however, were too small to show any significant association with neutropenia. The majority of children infected with helminths were asymptomatic; only one child had hookworm infection which might have exacerbated the anaemia.

C. parvum was found in only 2 per cent of children with cancer despite a history of animal exposure in 50 per cent. *C. parvum* has been transmitted from infected domestic pets[5] as well as cattle.[6] The index case had bronchopneumonia but no diarrhoea. *C. parvum* is known to cause respiratory disease.[7] However, in this case, we cannot be certain that the protozoan was the cause as bronchial washings were not done. Only one of the 10 stool samples from this patient was positive for *C. parvum*. Multiple stool samples are necessary due to intermittent oocyst excretion.

In Mexico, *C. parvum* was found only in the diarrhoeal stools of adult cancer patients.[8] There were few diarrhoeal episodes in our study, which may explain the low prevalence of the organism. However, a large study in India in 560 cancer patients with diarrhoea showed a similar prevalence to ours of 1.3 per cent.[9]

Two children had significant symptoms due to giardiasis. Severe giardiasis has been reported previously in a child on chemotherapy.[10] The death in our case was attributed to bacterial infection rather than giardiasis. There is controversy as to whether *Blastocystis hominis* is a pathogen in humans.[11] Both children with this organism had negative stool samples subsequently without any specific treatment.

In conclusion, we found a high prevalence of enteric parasites in children with cancer in Kelantan, Malaysia. However, this was mainly due to helminthiases rather than protozoal infections and the majority of patients were asymptomatic.

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Cure of β-Thalassaemia Major by Umbilical Cord Blood Transplantation – A Case Report of Malaysia's First Cord Blood Transplantation

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Summary

A 25-month-old boy with β-thalassaemia major was presented with an opportunity for umbilical cord blood transplantation when his unborn sibling was diagnosed *in utero* to be a β-thalassaemia carrier and also human leucocyte antigen compatible. A barely adequate amount of cord blood was collected at the birth of his sibling and infused into the patient after appropriate chemo-conditioning. Engraftment occurred without major complications. The subject is now alive and well 9 months post-transplant, thus marking our first success in umbilical cord blood transplantation.

Introduction

β-Thalassaemia major is one of the commonest inherited haematological disorders in the Malaysian population.[1] Current optimal treatment requires regular transfusion with leucofiltered blood and adequate iron chelation. There is ample evidence that this disease can be cured by human leucocyte antigen (HLA) matched sibling bone marrow transplantation (BMT) both from experience overseas[2,3] and locally.[4] Indeed, in a country where blood transfusion services or iron chelation therapy are not optimal, bone marrow transplantation should become the treatment of choice. The patient's genetically abnormal marrow is destroyed by chemo-conditioning and replaced by healthy haematopoietic stem cells from an appropriate donor who is almost always an HLA-matched sibling. The use of mismatched sibling or matched unrelated donors is not generally recommended[5] as such transplants have been beset by graft rejections and early deaths.[6]

Another source of haematopoietic stem cells is umbilical cord blood (UCB). This usually discarded material has been shown to contain the requisite stem cells for engraftment in patients with malignant and non-malignant diseases.[7,8] The greater proliferative potential of UCB cells[9] and their relative immunological naivety[10,11] have resulted in their increased application in the fields of stem cell transplantation. The first matched sibling umbilical cord blood transplantation (UCBT) occurred in 1988 for a patient with Fanconi's anaemia.[12] The first UCBT for β-thalassaemia major was performed in Thailand in June 1993.[13] Thus far only 10 patients with this disease have received transplanted UCB.[8,14–16] Eight out of 10 were completely successful. Success with matched sibling UCBT for β-thalassaemia major is dependent on several factors. One of these is the ability to diagnose the fetus *in utero* as being free of the disease. Normal or thalassaemia trait donors are acceptable. Another requirement would be HLA compatibility between the fetus and the recipient. The expertise to collect UCB and the technology to cryopreserve stem cells play an important role. Last but not least the adequacy and suitability of the collected UCB can determine the success of UCBT. We report our first experience in the emerging field of UCBT in a patient with β-thalassaemia major.

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Case History

TEH presented at the age of 3 months with pallor and was diagnosed as having β-thalassaemia major. As his only sibling, an elder sister, was found to be HLA incompatible, the patient could only be treated conservatively with regular blood transfusions.

A new sibling was conceived when the patient was 7 months old. *In utero* examination of a sample of chorionic villous biopsy by molecular techniques for the β gene mutation identified the fetus to be a carrier. In October 1996 a live female baby was born by normal vaginal delivery and 60 ml of UCB were collected. A small portion of the UCB was sent for HLA typing while the remainder was cryopreserved in 10 per cent dimethylsulfoxide (DMSO) and kept frozen in a liquid nitrogen storage tank. The total numbers of nucleated cells and CD34+ cells in the collected cord blood were 65×10^7 and 0.54×10^6 respectively. Infection screen

on the UCB and newborn sibling confirmed the absence of hepatitis B, hepatitis C, and human immunodeficiency viruses. Results of HLA typing showed the UCB to be compatible with the patient at six out of six HLA loci.

The recipient was prepared for cord blood transplantation by a combination of busulphan at 22 mg/kg and cyclophosphamide at 200 mg/kg recipient body weight. On 31 July 1997, the cryopreserved cord blood was rapidly thawed in a water bath at 37°C and infused into the recipient. Apart from some patient discomfort manifested by crying and mild restlessness, there were no untoward side-effects.

The post-transplant recovery was complicated by mild veno-occlussive disease of the liver, which responded to conservative management, and methicillin-resistant *Staphyloccoccus epidermidis* septicaemia, necessitating a change of his central venous catheter. Haematopoiesis was slow and the patient's total white blood cell count exceeded 1000/μl on day 59 with platelets exceeding 50 000/μl on day 74. Bone marrow examination on day 88 confirmed trilineage engraftment while chromosomal analysis demonstrated full chimerism with a karyotype of 46XX. When reviewed in April 1998 the patient remained well and free of blood transfusions.

Discussion

Patients with β-thalassaemia major who are treated conservatively with optimal blood transfusions and iron chelation are now living up to their late 30s.[17–19] The introduction of iron chelation with desferrioxamine has contributed to this improved survival,[20,21] albeit accompanied by restrictions in lifestyle related to daily subcutaneous infusions, drug toxicities, and late endocrine abnormalities. The possibility of cure from this autosomal recessive disorder by stem cell transplantation brings hope and cheer to patients, families, and physicians alike. Unfortunately not many patients with thalassaemia major will meet the criteria for successful transplantation. These include availability of a matched sibling donor, low number of blood transfusions received (related to alloimmunization and graft rejection), and absence of significant liver damage from hepatitis or haemosiderosis.

On average only 30 per cent of patients would be able to find a matched sibling donor for transplantation.[22] The elder sister of our patient was HLA incompatible and he was lucky when the newborn sibling was found to be HLA compatible with him.

Couples who already have a child with thalassaemia major are faced with at least two immediate dilemmas. One involves the question of having more children. This case demonstrates the utility of DNA technology in their decision making. *In utero* diagnosis by chorionic villous sampling using molecular studies on β gene mutations are informative for 90 per cent of couples.[23] Having made the decision to have another child and being able to exclude the diagnosis of β-thalassaemia major *in utero*, couples are then confronted with the anxiety of whether the fetus would be a suitable donor for their affected child. In fact some couples try for another child on the 25 per cent chance of conceiving an HLA-matched sibling. A second dilemma involves the decision to transplant or not. Indeed, some couples agonize over the decision to proceed with transplantation even when a suitable donor has been identified because of the current transplant-related mortality of approximately 5–10 per cent for the recipient. Determination of compatibility by HLA testing can be performed on chorionic villous samples but this is not often done and hence expertise and accuracy are limited. *In utero* determination of HLA compatibility has not been performed in Malaysia. More often, as with our patient, a small sample of the cord blood collected at delivery is sent for HLA typing.

UCBT is undoubtedly gaining momentum. The relative ease of UCB collection, lack of risks to the donor, and immediate availability make it an attractive option compared with bone marrow or peripheral blood stem cell transplantation. Although all but one of the 10 cases of thalassaemia treated by UCBT used matched sibling donors,[8,14–16] it is expected that more mismatched UCBT will be performed in future. Early results from mismatched UCBT are encouraging with low levels of graft rejection and lower than expected rates of graft-versus-host disease.[24] This may be due to the lower T-cell reactivity in UCB, hence the term 'immunologically naive'.[11] This is one of the major advantages of UCB over bone marrow or peripheral blood stem cells and whether the lower incidence of graft-versus-host disease will stand the test of time remains to be seen.

The availability of expertise and facilities for *in utero* diagnosis of β haemoglobinopathy and stem cell collection and cryopreservation in the University Hospital, Kuala Lumpur is the culmination of years of work in the field of stem cell transplantation. Traditionally, HLA-matched bone marrow stem cells have been used for thalassaemia transplantation with reasonable success. Our experience using matched sibling UCBT in this patient is encouraging but insufficient for any definite conclusions to be drawn. Even as issues relating to incidence of acute and chronic graft-versus-host disease, UCB banking,[25–27] and inadvertent transmission of genetic disease are being addressed, the application of UCBT, especially in the unrelated donor setting, is bound to widen.

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Adenosine Deaminase in Childhood Pulmonary Tuberculosis: Diagnostic Value in Serum

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Summary

The diagnostic value of serum adenosine deaminase (ADA) activity was evaluated in childhood pulmonary tuberculosis. Serum ADA levels were measured in 20 children diagnosed with pulmonary tuberculosis (group 1) and 150 children (group 2) including 128 with tuberculosis infection (Mantoux test positive) and 22 healthy children. In group 1, the mean serum ADA activity was 74.06 ± 18.5 U/l, which was significantly ($p < 0.001$) higher than that of group 2 (40.36 ± 12.0 U/l). A serum ADA level of ≥53.76 U/l had a sensitivity of 100 per cent, specificity of 90.7 per cent, positive predictive value of

58.8 per cent, and a negative predictive value of 100 per cent in children with tuberculosis disease. To conclude, measurement of serum ADA activity was a useful diagnostic tool in childhood pulmonary tuberculosis.

Introduction

Tuberculosis is still one of the leading causes of morbidity and mortality in the world despite continued multinational efforts to control the disease. Unfortunately, diagnosis of tuberculosis infection and disease is somewhat difficult in children.[1] In recent years there has been a desire for the development of new microbiologic, genetic, immunologic, and biochemical methods for the rapid and accurate diagnosis of tuberculosis. One such biochemical method is measurement of the adenosine deaminase (ADA) activity, which has been proposed to be a useful marker for tuberculosis disease in the pleura, pericardium, peritoneum, and central nervous system.[2–4]

The aim of this study was to evaluate the diagnostic value of serum ADA activity measurement in pulmonary tuberculosis.

Materials and Methods

The study group comprised 170 2–14-year-old children who had undergone tuberculosis disease and infection screening at the outpatient clinics. In all children, a detailed history about symptoms suggestive of tuberculosis and a past history of tuberculosis were obtained. Physical examinations and chest X-rays were performed and BCG scar numbers were determined in all participants. Tuberculin skin testing with 5 U of purified protein derivative (PPD) was administered by the standard technique. Acid-fast bacilli examination in early morning gastric aspirates or sputum by Ziehl–Neelsen staining was done on three consecutive days if there was a clinical suspicion of pulmonary tuberculosis. If necessary, specimens were examined by radiometric culture (BACTEC) and polymerase chain reaction (PCR) for *M. tuberculosis*. In all children, a detailed family history of tuberculosis was obtained and family screening by tuberculin testing, chest X-ray, and, when needed, smear examination of acid-fast bacilli in sputum was conducted.

According to the final diagnosis, cases were subdivided into two groups. Group 1 included 20 children diagnosed as having pulmonary tuberculosis by physical, radiological, and microbiological findings compatible with the disease. Group 2 consisted of 150 children who did not have tuberculosis disease. Of these children, 128 had a PPD induration >15 min and positive family history, but were lacking physical and laboratory findings of tuberculosis. The remaining 22 were healthy children having a PPD $\leq$15 mm.

The adenosine deaminase activity was determined in the serum of all 170 children by the calorimetric method of Giusti,[5] which is based on the measurement of ammonia produced when adenosine deaminase acts on an excess of adenosine.

The Mann–Whitney U test was used in statistical evaluation of the data. The diagnostic value of the ADA was assessed in terms of sensitivity, specificity, and positive and negative predictive values.

Results

The age, tuberculin reaction size, and serum ADA enzyme activity values of the subjects are presented in Table 1. Mean induration size of group 1 and group 2 were similar ($p < 0.05$). Serum ADA activity was significantly ($p < 0.001$) higher in group 1 than in group 2.

Taking the 80th percentile value (53.76 U/l) serum level of ADA as a cut-off point, there was a specificity of 90.7 per cent and sensitivity of 100 per cent (Table 2). However, with higher values of ADA activity (85th, 90th, and 95th percentiles) the specificity increased but the sensitivity decreased. In contrast, with lower values of the activity (70th and 75th) the sensitivity didn't change but the specificity decreased. A cut-off value of $\geq$53.76 U/l for serum ADA therefore seems to suggest a diagnosis of pulmonary tuberculosis with a positive predictive value of 58.8 per cent and negative predictive value of 100 per cent.

Discussion

Adenosine deaminase is essential for the differentiation of lymphoid cells, particularly T cells, and plays a role in the maturation of monocytes to macrophages.[6] ADA is considered to be an indicator of cell-mediated immunity.[7] In recent years, measurement of ADA in pleural, pericardial, meningeal, and peritoneal effusions has gained importance in the diagnosis of tuberculosis.[2–4] The diagnostic value of serum ADA is pulmonary tuberculosis has been investigated in only a few studies[4,8–10] which revealed its usefulness as a supportive finding.

The immunologic reactions taking place during the course of tuberculosis infection and disease are complex. Especially, the factors responsible for the elevation of serum ADA activity during tuberculosis disease are not yet clear. CD4 and CD8 $\alpha\,\beta$ T cells play a pivotal role in the development of delayed type hypersensitivity and in the control of both tuberculosis infection and

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TABLE 1
Demographic data and serum ADA values in each group

	No. of patients	Age (years)	Tuberculin reaction size (mm)	Serum ADA (U/l)
Group 1	20	9.55 ± 3.3	15.25 ± 6.8	74.06 ± 18.5
Group 2	150	9.64 ± 2.3	17.58 ± 3.6	40.36 ± 12.0

All values mean ± SD.

TABLE 2
Sensitivity and specificity of serum ADA values in pulmonary tuberculosis

Percentile	70th	75th	80th	85th	90th	95th
Serum ADA (U/l)	48.60	51.85	53.76	57.17	64.85	80.99
Sensitivity (%)	100	100	100	70	65	30
Specificity (%)	80	85.3	90.7	92.7	97.3	98.7

disease.[8] Elevation of ADA activity, especially in pleural effusions, has been proposed to result from an increase in the T-cell population, notably the immature and reactive cells.[9,10] However, in other studies no correlation has been found between ADA activity and T-cell CD4 and CD8 numbers or the CD4/CD8 ratio.[11,12]

Our results suggest that the determination of serum ADA activity has a high sensitivity and specificity for the diagnosis of tuberculosis disease. A serum value of ≥53.76 U/l has been found to be optimal in differentiating tuberculosis disease from the infection and healthy controls. On the other hand, the present study could not reveal any diagnostic value of the measurement of serum ADA activity in tuberculosis infection.

Bhargava *et al.*[4] found a mean serum ADA activity of 78.12 ± 17 U/l in adult patients with pulmonary tuberculosis and they concluded that values above 54 U/l had a specificity of 97.6 per cent and sensitivity of 81.5 per cent in the diagnosis of pulmonary tuberculosis. Our results are in agreement.

In conclusion, we would like to point out that the measurement of ADA activity in the serum as well as peritoneal or pleural fluids may be a beneficial diagnostic tool in childhood tuberculosis disease.

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Classification Trees and Logistic Regression Applied to Prognostic Studies: A Comparison using Meningococcal Disease as an Example

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Summary

The authors used logistic regression and classification trees to develop prediction models for fatal outcomes in meningococcal disease in a cohort of 829 children hospitalized for meningococcal disease during 1989–1990 in Rio de Janeiro. The area under the receiver operator characteristic (ROC) curve was 92 per cent for logistic regression and 88 per cent for classification trees. Logistic regression may be preferred when the main objective is to obtain explicit measures for statistical inference and measures of the force of the association between each variable and the outcome. However, estimation of the probability of dying for each patient involves manipulation of the logistic regression formula, which would not easily be done in an emergency room. Classification trees provided comparable discrimination between fatal and non-fatal outcomes, and yielded a graphical display of the results that is easier to understand and is straightforward to apply in clinical settings.

Introduction

Meningococcal disease (MD) is hyperendemic in the city of Rio de Janeiro, Brazil, with incidence rates of around 5 per 100 000 for the past decade.[1,2] During these years the case-fatality rates have remained between 15 and 20 per cent.[2]

One possible way to deal with the problem of high fatality rates is to identify prognostic factors that can easily be assessed and used to aid clinical decision making. Much effort has been invested in the development of prognostic scores to predict mortality from MD.[3–11] However, much of this work has been done in developed countries and the results may not be directly applicable in other settings. As a preliminary effort to build a predictive model for MD in a developing country, this study compares the ability of logistic regression and classification trees to discriminate between fatal and non-fatal cases in a cohort of children from Rio de Janeiro, Brazil.

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Subjects and Methods

During 1989–1990 a total of 829 MD cases (< 16 years) were admitted to the Instituto Estadual de Infectologia São Sebastião in the city of Rio de Janeiro, Brazil. Cases of MD were defined by the presence of one of the following criteria:

(1) isolation of *N. meningitidis* from blood or cerebrospinal fluid (CSF);
(2) identification of Gram-negative diplococci or meningococcal antigens in CSF; or
(3) typical clinical picture with fever and haemorrhagic skin lesions.

Outcome status and putative prognostic factors were obtained from medical and epidemiological surveillance records.

We undertook the analysis in two stages. First, we used multiple logistic regression and classification trees to identify the most important independent prognostic factors for death in MD. Second, the predicted probability of death for each individual in the cohort was estimated from each model, and then compared to the actual

outcomes. We used the area under the receiver operator characteristic (ROC) curve, sensitivity, specificity, and positive and negative predictive values as the criteria to assess the performance of these models. Multiple logistic regression was carried out in STATA.[12] Classification trees were performed using S-Plus.[13]

In logistic regression, backward elimination was used to select the significant prognostic factors to be in the final model. A 10 per cent significant level was chosen. We tested for two-way interactions, but none were significant.

Classification trees (or CART, for classification and regression trees) provide an alternative to logistic models for classification problems.[13,14] CART builds a binary classification system (tree) through recursive partitioning, so a data set is successfully split into increasingly homogeneous subgroups.[13] At each stage (node) the CART algorithm selects the explanatory variable and splitting value that gives the best discrimination between two outcome classes.

A full CART algorithm adds nodes until they are homogeneous or contain few observations ($\leq$5 is the standard cut-off in S-plus).[14] CART creates a full tree that has a minimal misclassification rate, but may have a poor predictive power for a new sample, since it may be too closely tied to the original data (the 'learning sample').[15] The problem of creating a useful tree is to find a suitable guideline to cut back (to 'prune') the tree.

The general principle of pruning is that the tree of best size would have the lowest misclassification rate for individuals not included in the learning sample.[15] If a second data set is available (the 'validation sample'), one could apply trees of various sizes to it and then choose the one with the lowest misclassification rate. If no validation sample is available it is possible to make one by dividing the learning sample. CART performs this approach using the method of cross-validation.[14] Cross-validation works by dividing the learning sample into groups of equal size, building the tree on part of the data, and then assessing the tree misclassification rate on the remaining part of the data. We used cross-validation, splitting the data into four groups.

Results

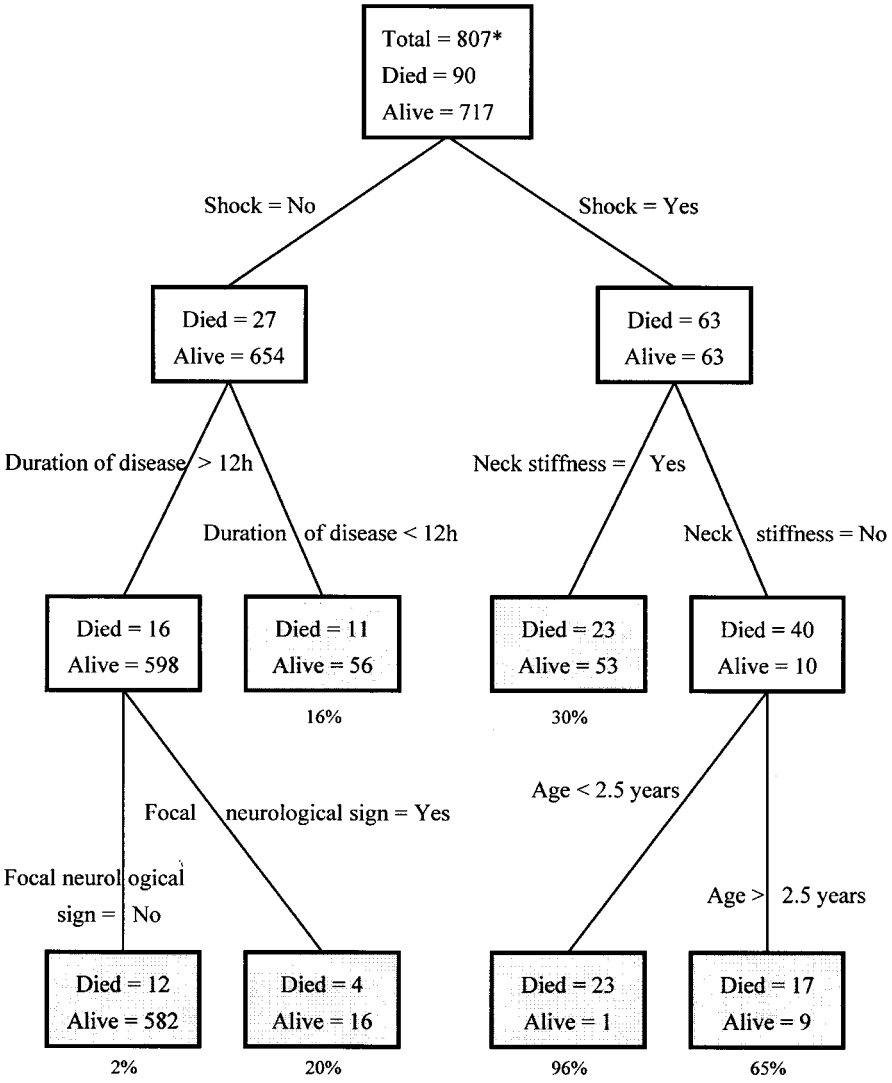
Table 1 presents the variables significantly associated with death in the logistic regression model. Age above 1 year, neck stiffness, and a longer duration of disease were associated with a lower risk of death. Seizures, diarrhoea, a clinical diagnosis of shock, focal neurological sign, and residence outside Rio de Janeiro city were positively associated with death.

Figure 1 presents the best classification tree obtained by the cross-validation procedure. There are six terminal nodes (shaded boxes), to be compared with a total of 53 in the complete generated tree. For each node in the tree, the numbers of fatal and non-fatal cases and the variable used to split the parent node are displayed. The percentages displayed under each terminal node represent the risk of death among those who eventually reached this node.

Table 2 compares the predictive power of the two

TABLE 1
Variables significantly associated with death in meningococcal disease (multiple logistic regression)

Prognostic factor	Category	Relative risk	95% CI	*p* value
Age	< 1	1.00		
	1–4	0.45	0.19–1.07	0.07
	5–9	0.41	0.17–1.01	0.05
	10–15	0.18	0.06–0.60	0.005
Shock	No	1.00		
	Yes	21.2	11.3–39.8	< 0.001
Neck stiffness	No	1.00		
	Yes	0.17	0.09–0.32	< 0.001
Seizures	No	1.00		
	Yes	3.03	1.19–7.71	0.02
Focal neurological sign	No	1.00		
	Yes	3.37	0.95–12.0	0.06
Diarrhoea	No	1.00		
	Yes	3.87	1.35–11.1	0.01
Geographical residence	Rio de Janeiro	1.00		
	Other counties	1.65	0.91–3.01	0.10
Duration of disease	< 12 h	1.00		
	12 h–24 h	0.27	0.12–0.58	0.001
	24 h–48 h	0.19	0.06–0.59	0.004
	48 h–76 h	0.16	0.04–0.61	0.004
	> 76 h	0.26	0.08–0.81	0.02



* Some observations not included due to missing values

FIG. 1. Classification tree selected by the cross-classification procedure. Terminal nodes are shaded.

TABLE 2
Performance of the two multivariate techniques

Technique	Area under ROC curve[a] (%)	Sensitivity[b] (%)	Specificity[b] (%)	Positive predictive value[b] (%)	Negative predictive value[b] (%)
Logistic regression	92	86	84	40	98
Classification tree	88	86	82	37	98

[a]The ROC curve provides a summary of the discriminant ability of the model over all possible predicted values associated with variations in the cut-off point in the estimated probability of dying.

[b]Sensitivity, specificity, positive and negative predictive values are calculated on the basis of a 'prediction' of death for any individual for whom the estimated probability of dying is greater than 10 per cent.

techniques in terms of the area under the ROC curve, specificity, sensitivity, and positive and negative predictive values. Logistic regression has a marginally better overall performance than the classification tree.

Discussion

The main objective of this study was to compare the performance of logistic regression and classification trees in identifying the best prognostic system for death in MD. The prognostic models generated by the two techniques are statistically equivalent. The two methods seem to complement each other. Logistic regression provides explicit measures for statistical inference and measures of the force of the association between each variable and the outcome. However, estimating of the probability of dying for each patient involves manipulation of the logistic regression formula, which would not easily be done in an emergency room. The tree model provided comparable discrimination between fatal and non-fatal cases using only five variables (logistic regression used eight). The graphical display of the results from a tree is easier to understand and is straightforward to apply in clinical settings.

Prognostic systems based only on clinical data are thought to be not as powerful as those based on laboratory findings. Nevertheless, they are simple and inexpensive, and they may be more useful in developing countries. The prognostic models developed in this study are still preliminary and need to be improved and validated using more recent samples. In order to take advantage of the complementary information provided by the two techniques we suggest considering both approaches when developing prognostic systems.

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