PRACTICE REVIEW

Childhood pneumonia – progress and challenges

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Remarkable progress has been made in the development of antimicrobial therapy, effective vaccines and pneumonia management guidelines in the past 50 years. However, pneumonia is currently the leading cause of death in children younger than 5 years in developing countries, accounting for approximately 20% of childhood deaths. This article reviews changes in the epidemiology, management and prevention of childhood pneumonia in developing countries, specifically in Africa and South Africa, and addresses future challenges.

Main findings. The HIV epidemic has sharply increased the incidence, severity of, and mortality due to, childhood pneumonia. Bacterial infection remains a major cause of pneumonia mortality. Additional pathogens such as *Pneumocystis jirovecii* and Gram-negative bacteria are found in HIV-infected children, associated with a high mortality. *Mycobacterium tuberculosis* is an important cause of acute pneumonia in both HIV-infected and uninfected children. Use of case management guidelines can substantially reduce neonatal, infant and under-5 mortality and pneumonia-specific mortality. General preventive interventions including micronutrient supplementation with zinc and vitamin A, and immunisations can substantially reduce the burden of childhood pneumonia. Despite a lower efficacy in HIV-infected children, vaccination protects against disease in a significant proportion of children.

In South Africa, new advances over the past 50 years have included greater access to primary health care for children, the use of Integrated Management of Childhood Illness guidelines in primary care, development of guidelines for diagnosis and management of childhood pneumonia and adoption of an expanded immunisation programme that includes coverage for *Haemophilus influenza*e type b. The pneumococcal conjugate vaccine recently licensed in South Africa also has the potential to significantly reduce the burden of childhood pneumonia. Recent rollout of the national antiretroviral programme can reduce the incidence and severity of HIV-associated pneumonia through the prevention of HIV infection, use of co-trimoxazole prophylaxis and treatment with antiretrovirals.

Conclusion. Available, effective interventions for prevention and treatment of childhood pneumonia exist; the challenge is to achieve widespread implementation and high coverage rates in developing countries. Greater access to newer vaccines and to antiretroviral therapy and co-trimoxazole prophylaxis in HIV-infected children is necessary to further reduce the burden of childhood pneumonia and the discrepancies in global child lung health.

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In the past 50 years, major progress has occurred in the fields of molecular biology and vaccinology and in the development and use of antimicrobials. These have contributed to greater understanding of childhood pneumonia and resulted in improved management and intervention strategies. Pneumonia nevertheless remains a major cause of childhood morbidity and mortality in developing countries.[1-4] Acute respiratory infections (ARIs), principally pneumonia, account for approximately 1.9 million (95% confidence interval (CI) 1.6 - 2.2 million) deaths globally in children under 5 years of age each year,[4] 90% of which occur in the developing world.[1,4] This has been exacerbated by the human immunodeficiency virus (HIV) epidemic, especially in sub-Saharan Africa, as pneumonia is the commonest cause of illness, hospitalisation and mortality in HIV-infected children.[5] This article reviews changes in the epidemiology, management and prevention of childhood pneumonia in developing countries with emphasis on Africa and South Africa.

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Epidemiology of childhood pneumonia

Pneumonia constitutes a major proportion of the global burden of childhood disease, being responsible for around 20% of childhood deaths, the majority of which occur in developing countries.[1-4] Annually, almost half of the 1.9 million deaths due to acute respiratory tract infections in children under 5 years of age occur in Africa.[6] Childhood community-acquired pneumonia accounts for between 30% and 40% of hospital admissions with associated case fatality rates of between 15% and 28%.[7,8] Studies from South Africa have estimated the proportion of under-5 deaths due to pneumonia to range from

8% to 22%.[9,10] These studies, done during the apartheid era, found marked differences in pneumonia-specific mortality between ethnic groups with the highest rates for black African children and the lowest rates for Caucasians. A study investigating childhood pneumonia deaths from 1968 to 1985 reported high rates in all population groups, ranging from 7 to 270 times those in developed countries, and highlighted the large differences in rates by ethnic group.[9] This is consistent with the observation that the proportion of children dying from pneumonia is related to the general under-5 mortality rate, declining as the under-5 mortality rate diminishes.[4] In South Africa, under-5 mortality for 2003 was reported as 66 per 1 000, representing a 1.3% increase from 1995 to 1999 and a 1.6% increase from 2000 to 2003.[6] Moreover, in South Africa there is wide variation in under-5 mortality rates accord-ing to geographical and socio-economic factors.[9-11] Besides directly causing childhood deaths, pneumonia is frequently an associated cause of mortality in children with other underlying conditions. Thus for every death directly attributable to pneumonia, 2 or 3 additional deaths associated with pneumonia may occur.[4] Co-morbid conditions, especially malnutrition, measles or immunosuppression, increase the risk of mortality from pneumonia.[1,5,12]

The HIV pandemic has resulted in a large increase in the incidence, severity and outcome of childhood pneumonia in developing countries. Globally, there are approximately 2.3 million HIV-infected children, living predominantly in sub-Saharan Africa.[13] Approximately 540 000 children are infected with HIV annually, the majority in developing countries where few interventions to prevent perinatal HIV acquisition are available and where access to antiretroviral agents is extremely limited.[13] Thus infant, under-5 and pneumonia-specific mortality rates have increased in sub-Saharan Africa. Studies have reported that 26 - 59% of HIV-infected African children die within the first years of life while under-5 mortality rates exceed 60% in some countries.[8] Moreover, respiratory disease has been reported to be the dominant cause of hospitalisation and death in HIV-infected African children.[7,14-16]

The impact of the HIV epidemic on childhood pneumonia has been compounded by poor access and unavailability of preventive strategies and limited availability of highly active antiretroviral therapy (HAART) for African HIV-infected children. As a result, HIV-associated lung disease is a major cause of childhood morbidity, hospitalisation and mortality in sub-Saharan Africa with 90% of HIV-infected children developing a respiratory illness during the course of their HIV disease.[5,8]

The impact of HIV on childhood pneumonia in Africa

The HIV epidemic poses a threat to many of the gains made in child health over the last few decades in sub-Saharan Africa. Besides the impact on the epidemiology and outcome from childhood pneumonia, HIV has changed the spectrum of pathogens responsible for childhood pneumonia and their antimicrobial susceptibility. Opportunistic infections, especially *Pneumocystis jirovecii* pneumonia (PCP), have become an important cause of mortality among HIV-infected infants.[5,17-20] In sub-Saharan Africa, a dual HIV and tuberculosis (TB) epidemic has resulted in a large increase in TB incidence, with impact on the epidemiology and severity of childhood TB. HIV infection has also been associated with an increase in the antimicrobial resistance patterns of common bacterial pathogens.[21] Changes in the microbial pathogens and susceptibility patterns have implications for the choice of empirical antibiotic therapy for childhood pneumonia. Furthermore, although respiratory viruses are identified less frequently in HIV-infected children hospitalised for pneumonia (15%) compared with HIV-negative children (45%), the absolute burden of hospitalisation for viral associated pneumonia is 2 - 8-fold greater in HIV-infected children. HIV-infected children in whom respiratory viruses are identified have a more prolonged hospital stay and a higher case fatality rate than HIV-uninfected children.[22]

The reliability of diagnostic methods for childhood pneumonia including clinical assessment differ in HIV-infected and uninfected children. Diagnosis of specific infections such as pulmonary TB is more difficult in HIV-infected children because of nonspecific clinical signs, other HIV-associated illnesses and the development of anergy. The efficacy of usual management strategies such as choice of empirical antibiotic therapy or duration of therapy differs for HIV-infected children. The efficacy of preventive measures such as immunisation is reduced in HIV-infected children particularly if they are not receiving antiretroviral therapy.[23]

Pneumonia is the commonest reason for hospitalisation among African HIV-infected children.[7,14-16] Pneumonia-specific mortality rates are higher in HIV-infected children with case fatality rates consistently reported as 3 - 6 times those of HIV-negative patients.[21,22,24] Therefore, the HIV-epidemic has increased the demand for health care resources with more children requiring ambulatory treatment, hospital admission and intensive care for pneumonia. This also raises important ethical considerations for allocation of resources.

Aetiology of childhood pneumonia

Bacterial infections, particularly *Streptoccocus pneumoniae*, *H. influenzae* type b and *Staphyloccocus aureus*, have remained the major reasons for hospitalisation and causes of death from pneumonia in children in developing countries. *S. pneumoniae* is the most important bacterial pathogen in HIV-infected and uninfected children.[21,24] HIV-infected children are at increased risk for severe pneumonia, bacteraemia and recurrent infections. A Zambian study of children dying of respiratory

disease reported that pyogenic pneumonia, occurring in 41% and 50% of HIV-infected and uninfected children respectively, was most common and frequently occurred with other non-bacterial respiratory pathogens.[20] *M. tuberculosis* is also an important cause of acute pneumonia in children living in high TB and high HIV prevalence areas, accounting for approximately 8% of pneumonia cases.[21,24,25] In a Zambian postmortem study, TB occurred in 18% of HIV-infected and 26% of HIV-uninfected children and was the second most commonly identified cause of death in children older than 1 year.[20]

Viruses occur in 30 - 40% of acute respiratory infections in hospitalised children; among viral pathogens, respiratory syncytial virus (RSV) predominates, accounting for 20 - 25% of such infections.[22] A newly described paramyxovirus, human metapneumovirus (hMPV), is emerging as a respiratory pathogen second to RSV in children; this has been identified in 11% of South African HIV-uninfected children hospitalised for lower respiratory tract infections.[26,27] This virus produces clinical illness similar to RSV.[26-28] Lack of sensitive assays for diagnosing bacterial pneumonia has led to an underestimation of the importance of bacterial co-infections in children with viral-associated pneumonia. Data from Gambia indicate that mixed bacterial and viral infections may occur in 8 - 40% of cases of childhood pneumonia.[29,30] Recent data from South Africa indicate that in at least 31% of children, viral-associated pneumonia may be due to concurrent infection with *S. pneumoniae* in the absence of vaccination with pneumococcal conjugate vaccines.[26,31]

A broader spectrum of pathogens causes pneumonia in HIV-infected children including Gram-negative pathogens, such as *Escherichia coli* and *Salmonella* spp. as well as *P. jirovecii*.[21,24] While *P. jirovecii* was recognised as a cause of pneumonia in malnourished infants in the 1940s, it has re-emerged as a major pathogen in HIV-infected infants, causing severe pneumonia. Postmortem studies have detected PCP in 16 - 67% of HIV-positive children dying of respiratory illness,[20,32] while in-hospital case-fatality rates for PCP have ranged from 20% to 63%.[17-19] The prevalence of PCP among HIV-infected children hospitalised with pneumonia in Africa has varied from 10% to 49%.[17-19,33] The management of pneumonia in HIV-infected children is further complicated by the presence of complex pneumonia resulting from multiple simultaneous bacterial, viral and fungal infections. In addition, HIV-exposed children may be at increased risk for PCP even if they are HIV-uninfected.[19,34]

Management

Important advances in the management of childhood pneumonia have occurred in the past 50 years, including the development of case management guidelines and production of broad-spectrum, improved antimicrobials with paediatric formulations. In addition, in South Africa in the last decade, improved access to health care for children has resulted from the policy of free care for children and an emphasis on primary health care.

Pneumonia case management was first developed by the World Health Organisation (WHO) as an acute respiratory infection (ARI) guideline and subsequently as part of the Integrated Management of Childhood Illness (IMCI) programme.[35] The pneumonia case-management strategy developed by WHO was based on the assumptions that: (*i*) bacterial pneumonia was largely responsible for ARI mortality in developing countries; (*ii*) antibiotic treatment could reduce case fatality; and (*iii*) a simple algorithm based on clinical signs could reliably detect children with pneumonia. The cornerstone of the ARI case management strategy depends on two key clinical signs – lower chest indrawing and respiratory rate. Based on these signs, children presenting with cough or difficult breathing are categorised into three groups: those with lower chest indrawing are defined as having severe pneumonia, children with tachypnoea are defined as having pneumonia while those without tachypnoea or chest indrawing are considered to have an upper respiratory tract infection. These signs, based initially on work done by Shann *et al.*,[36] have been validated by many subsequent studies and confirmed as having good sensitivity for the diagnosis of pneumonia.[37-39] Children defined as having severe pneumonia require hospital referral, those with pneumonia based on the presence of tachypnoea require oral antibiotics, while those with an upper respiratory tract infection are treated symptomatically.

The use of case-management guidelines for treatment of childhood pneumonia can significantly reduce overall and pneumonia-specific mortality in children.[40,41] A meta-analysis of community-based studies found all-cause mortality was reduced by 27% (95% CI 18 - 35%), 20% (11 - 28%), and 24% (14 - 33%) among neonates, infants, and children 0 - 4 years of age, respectively.[41] In addition, pneumonia-specific mortality was reduced by 42% (22 - 57%), 36% (20 - 48%), and 36% (20 - 49%) among these three groups.[41] These reductions in mortality associated with antibiotic use are consistent with estimates of the proportion of childhood deaths attributable to bacterial pneumonia. The incorporation of ARI case-management guidelines into the IMCI guidelines has provided a more comprehensive approach to diagnosis, prevention and treatment. However, current IMCI guidelines require adaptation to include management of HIV-associated respiratory illness. The IMCI programme has been adapted for use in South Africa and has increasingly become part of the management of children in primary care settings.[42] In addition, South African guidelines for the diagnosis and management of community-acquired pneumonia in children at primary, secondary or tertiary care facilities have recently been published.[43]

The development of paediatric formulations of antibiotics has enabled better therapy in children. Pencillin or ampicillin/amoxicillin remain the cornerstone of effective and rational antibiotic treatment of community-acquired pneumonia in children. Recently, short-course antibiotic therapy was reported to be as effective as conventional 5-day treatment for ambulatory treatment of pneumonia. A study in Pakistan of 2 000 children with pneumonia reported that the clinical efficacy of 3 days of oral amoxicillin (15 mg/kg/dose) was similar to 5 days of therapy.[44] Rates of relapse (1%) and treatment failure (approximately 21%) were similar in both groups. However, these results may not be applicable to HIV-infected children in whom longer duration of therapy may be needed. For severe pneumonia, oral therapy may be effective in children who are able to tolerate oral antibiotics. A multicentre study reported that parenteral pencillin G had similar efficacy to oral amoxicillin for treatment of severe pneumonia.[45]

Despite increasing *in vitro* resistance to beta-lactam antibiotics, favourable pharmacodynamic and pharmacokinetic properties of these antibiotics still make them the treatment of choice when managing pneumonia, even when due to pneumococcal isolates with low or intermediate resistance to the beta-lactam antibiotics.[45,46]

For HIV-infected children hospitalised with severe pneumonia, antibiotic coverage should be broadened to include Gram-negative pathogens.[43] Frequently this involves either the selection of a third-generation cephalosporin or the addition of an aminoglycoside to a beta-lactam antibiotic. Use of macrolides in older children may be required to provide adequate coverage against *Mycoplasma pneumoniae* and *Chlamydia* spp., although the importance of these pathogens in South Africa remains to be elucidated.

In addition, empirical treatment for PCP with co-trimoxazole and corticosteroids should be considered, particularly in HIV-infected infants who are not taking co-trimoxazole prophylaxis or in high HIV prevalence settings in infants with severe pneumonia if their HIV status is unknown.[5,8,43] Although there are no randomised trials of the efficacy of corticosteroids for PCP in children, adult data and paediatric studies using historical controls indicate that timely use of steroids significantly reduces PCP-associated mortality. This however requires further study in Africa, where the risk particularly of cytomegalovirus (CMV)-associated pneumonitis may differ from that in developed countries. Concurrent CMV pneumonitis has been identified in 30 - 40% of postmortem studies in the presence of other causes of respiratory mortality.[20,47]

Mortality from pneumonia is frequently due to hypoxaemia, which can be effectively treated with oxygen. The development of low-flow methods using nasal prongs, nasal catheter or nasopharyngeal catheter has enabled efficient and cost-effective options.[43,48]

Prevention

Effective tools for preventing much of the burden of childhood pneumonia are available. General measures include improved nutrition, micronutrient supplementation with vitamin A and zinc, and attention to indoor environments, particularly avoidance of exposure to passive smoke.[23] Vitamin A supplementation is effective for reducing the severity of respiratory complications of measles[49] but there is no evidence for protection against non-measles pneumonia. Daily prophylactic elemental zinc may substantially reduce the incidence of pneumonia, particularly in malnourished children.[50] A pooled analysis of randomised controlled trials of zinc supplementation in children in developing countries found that zinc-supplemented children had a significant reduction in pneumonia-incidence.[51]

Global immunisation programmes through the Expanded Program of Immunization (EPI) have produced a decline in measles pneumonia and childhood pertussis. Cost is however a major challenge to the adoption of the new generation of childhood conjugate bacterial vaccines into the EPI schedules in developing countries. Furthermore investment is required to ensure that the most vulnerable children have access to vaccines by development of the infrastructure and resources required for a successful immunisation programme. In many African countries coverage even for the EPI programme is poor.[6] In South Africa, relatively high coverage rates for diptheria-pertussis-tetanus (DPT) (94%) and measles (83%) immunisation have been reported.[6] The availability and demonstrated efficacy of new immunisations such as *H. influenzae* type b (Hib)[52-54] and pneumococcal[55-58] conjugate vaccines have great potential to substantially reduce the burden of childhood pneumonia.

Use of the Hib conjugate vaccine may potentially reduce Hib invasive disease by 46 - 93% in vaccine recipients.[53] However, the efficacy of this vaccine for protection against invasive disease is reduced in HIV-infected children not receiving antiretroviral therapy (44% in HIV-infected compared with 96% in uninfected children).[54] South Africa is the only African country which funds, since 1998, the inclusion of Hib conjugate vaccine in its EPI programme. However, the Hib conjugate vaccine has in the past few years become more available in other African countries through donor-funding support. The potential of Hib conjugate vaccine to reduce childhood pneumonia morbidity was first shown in Gambia, where in addition to reducing meningitis and sepsis, vaccination was associated with a 21% reduction in radiologically confirmed pneumonia.[52]

Further potential strides in preventing bacterial pneumonia have been observed with the conjugate pneumococcal vaccines. Unlike the polysaccharide pneumococcal vaccines, which are ineffective in children less than 5 years of age, conjugate pneumococcal vaccines are immunogenic, safe and effective

in children immunised as early as 6 weeks of age onwards. A recent South African trial found that the use of a nine-valent pneumococcal conjugate vaccine reduced invasive pneumococcal disease caused by vaccine serotypes by 65% and 83% in HIV-infected and uninfected children respectively, while the incidence of radiologically confirmed pneumonia was reduced by 13% and 20% in these two groups respectively.[55] Although the efficacy of the conjugate pneumococcal vaccine was lower in HIV-infected compared with uninfected children, the overall burden of pneumonia prevented in HIV-infected children was 9.7-fold greater, mainly because of the higher underlying burden of pneumococcal pneumonia in HIV-infected children.[56] A different formulation of the vaccine, which is more limited in the number of serotypes included in the vaccine to those studied in South Africa, has recently been licensed in South Africa. Because of cost constraints, this vaccine has however not as yet been included in the EPI and hence remains unaccessible to the majority of South African children. The need for advocacy to include a conjugate pneumococcal vaccine into EPIs in developing countries is supported by a study in The Gambia.[57] In addition to reducing the incidence of radiologically confirmed pneumonia by 37%, the vaccine was also found to reduce all-cause childhood mortality by 17%.[57]

Chemoprophylaxis is highly effective for primary prevention of PCP in HIV-infected children, but requires timely identification of HIV-infected infants and infrastructure and resources for implementation. The most effective prophylactic agent is oral trimethoprim-sulphamethoxazole (co-trimoxazole, TMP-SMX), a widely available, well-tolerated and inexpensive drug.[23] A randomised controlled study of TMP-SMX prophylaxis in HIV-infected Zambian children reported that this reduced mortality by 43% and morbidity, including hospitalisation, by 23%.[58] The impact on mortality was noted in children of all ages. As a result of this study, the WHO issued revised guidelines for TMP-SMX prophylaxis, recommending more liberal and widespread use of prophylaxis for HIV-infected children and HIV-exposed infants from 4 - 6 weeks of age.[59] Early identification of HIV-infected infants to initiate this therapy however remains a challenge and probably undermines the potential of this intervention to reduce childhood pneumonia morbidity and mortality in South African children. Similarly, widespread implementation of the WHO guidelines remains a considerable challenge in other sub-Saharan African countries, dependent on timely identification of HIV-infected mothers and their babies.

Prevention of childhood HIV infection by preventing mother-to-child transmission and treatment of HIV-infected children with antiretroviral therapy may prevent much of the morbidity and mortality from HIV-associated pneumonia. The use of antiretroviral therapy in HIV-infected children has dramatically reduced the incidence and severity of pneumonia in the developed world; however, such therapy is currently unaffordable and unavailable to most children in developing countries. Recent rollout of the national antiretroviral programme in South Africa has the potential to reduce HIV-associated pneumonia incidence and severity through the prevention of HIV infection, use of TMP-SMX prophylaxis and treatment of HIV-infected children with antiretroviral therapy. However, in South Africa and other sub-Saharan countries, there remain large operational, cost and educational challenges to expanding the availability of antiretroviral therapy to all children who need it.

References

1. Black RE, Morris SS, Bryce J. Where and why are 10 million children dying every year? *Lancet* 2003; **361:** 2226-2234.
2. Campbell H. Acute respiratory infection: a global challenge. *Arch Dis Child* 1995; **73:** 281-283.
3. Mulholland K. Magnitude of the problem of childhood pneumonia. *Lancet* 1999; 354: 590-592.
4. Williams BG, Gouws E, Boschi-Pinto C, *et al*. Estimates of world-wide distribution of child deaths from acute respiratory infections. *Lancet Infect Dis* 2002; **2:** 25-32.
5. Zar HJ. Pneumonia in HIV-infected and uninfected children in developing countries – epidemiology, clinical features and management. *Curr Opin Pulm Med* 2004; **10:** 176-182.
6. The World Health Organisation Report 2005. **http//www.who.int/whr/en**
7. Zwi KJ, Pettifor JM, Söderlund RN. Paediatric hospital admissions at a South African urban regional hospital: the impact of HIV 1992-1997. *Ann Trop Paed* 1999; **19:** 135-142.
8. Graham SM. HIV and respiratory infections in children. *Curr Opin Pulm Med* 2003: **9:** 215-220.
9. Von Schirnding YE, Yach D, Klein M. Acute respiratory infections as an important cause of childhood deaths in South Africa. *S Afr Med J* 1991; **80:** 79-82.
10. Wyndham CH. Leading causes of death among children under 5 years of age in the various population groups of the RSA in 1970. *S Afr Med J* 1984; **66:** 717-718.
11. Wyndham CH. Trends in the mortality rates for the ten leading causes of death among white, coloured and Asian children under 5 years of age in the RSA, 1968-1977. *S Afr Med J* 1984; **66:** 719-725.
12. Duke T, Mgone CS. Measles: not just another viral exanthem. *Lancet* 2003; **361:** 763-773.
13. UNAIDS. AIDS epidemic update: December 2005 **www.unaids.org**
14. Ikeogu MO, Wolf B, Mathe S. Pulmonary manifestations in HIV seropositivity and malnutrition in Zimbabwe. *Arch Dis Child* 1997; **76:** 124-128.
15. Lucas SB, Peacock CS, Hounnou A, *et al*. Disease in children infected with HIV in Abidjan, Cote d'Ivoire. *BMJ* 1996; **312:** 335-338.
16. Vetter KM, Djomand G, Zadi F, *et al*. Clinical spectrum of human immunodeficiency virus disease in children in a West African city. *Pediatr Infect Dis J* 1996; **15:** 438-442.
17. Zar HJ, Dechaboon A, Hanslo D, *et al*. Pneumocystis carinii pneumonia in South African children infected with human immunodeficiency virus. *Pediatr Infect Dis J* 2000; **19:** 603-607.
18. Graham SM, Mtitimila EI, Kamanga HS, *et al*.The clinical presentation and outcome of Pneumocystis carinii pneumonia in Malawian children. *Lancet* 2000; **355:** 369-373.
19. Ruffini DD, Madhi SA. The high burden of Pneumocystis carinii pneumonia in African HIV-1-infected children hospitalised for severe pneumonia. *AIDS* 2002; **16:** 105-112.
20. Chintu C, Mudenda V, Lucas S, *et al*. Lung disease at necropsy in African children dying from respiratory illnesses: a descriptive necropsy study. *Lancet* 2002: **360:** 985-990.
21. Madhi SA, Petersen K, Madhi A, *et al*. Increased disease burden and antibiotic resistance of bacteria causing severe community-acquired lower respiratory tract infections in human immunodeficiency type 1-infected children. *Clin Infect Dis* 2000; **31:** 170-176.
22. Madhi SA, Schoub B, Simmank K, *et al*. Increased burden of respiratory viral associated severe lower respiratory tract infections in children with human immunodeficiency virus type-1. *J Pediatr* 2000; **137:** 78-84.
23. Zar HJ. Prevention of HIV-associated respiratory disease in developing countries: potential benefits. *Int J Tuberc Lung Dis* 2003: **7:** 820-827
24. Zar HJ, Hanslo D, Tannenbaum E, *et al*. Aetiology and outcome of pneumonia in human immunodeficiency virus-infected children hospitalized in South Africa. *Acta Paediatr* 2001; **90:** 119-125.
25. Jeena PM, Pillay P, Pillay T, *et al*. Impact of HIV-1 co-infection on presentation and hospital-related mortality in children with culture proven pulmonary tuberculosis in Durban, South Africa. *Int J Tuberc Lung Dis* 2002; **6:** 672-678.
26. Madhi SA, Ludewick H, Kuwanda L, *et al*. Pneumococcal coinfection with human metapneumovirus. *J Infect Dis* 2006; **193:** 1236-1243.
27. Madhi SA, Ludewick H, Abed Y, Klugman KP, Boivin G. Human metapneumovirus-associated lower respiratory tract infections among hospitalized HIV-1-infected and HIV-1-uninfected African infants. *Clin Infect Dis* 2003; **37:** 1705-1710.
28. Ijpma FF, Beekhuis D, Cotton MF, *et al*. Human metapneumovirus infection in hospital referred South African children. *J Med Virol* 2004; **73:** 486-493.
29. Forgie IM, O'Neill KP, Lloyd-Evans N, *et al*. Etiology of acute lower respiratory tract infections in Gambian children: I. Acute lower respiratory tract infections in infants presenting at the hospital. *Pediatr Infect Dis J* 1991; **10:** 33-41.
30. Forgie IM, O'Neill KP, Lloyd-Evans N, *et al*. Etiology of acute lower respiratory tract infections in Gambian children: II. Acute lower respiratory tract infection in children ages one to nine years presenting at the hospital. *Pediatr Infect Dis J* 1991; **10:** 42-47.
31. Madhi SA, Klugman KP; Vaccine Trialist Group. A role for *Streptococcus pneumoniae* in virus-associated pneumonia. *Nat Med* 2004; **10:** 811-813.

32. Ansari NA, Kombe AH, Kenyon TA, *et al*. Pathology and causes of death in a series of human immunodeficiency virus-positive and-negative pediatric referral hospital admissions in Botswana. *Pediatr Infect Dis J* 2003; **22:** 43-47.
33. Madhi SA, Cutland C, Ismail K, *et al*. Ineffectiveness of trimethoprim-sulfamethoxazole prophylaxis and the importance of bacterial and viral coinfections in African children with *Pneumocystis carinii* pneumonia. *Clin Infect Dis* 2002; **35:** 1120-1126.
34. McNally LM, Jeena PM, Lalloo U, *et al*. Probable mother to infant transmission of Pneumocystis jiroveci from an HIV-infected woman to her HIV-uninfected infant. *AIDS* 2005; **19:** 1548-1549.
35. Pio A. Standard case management of pneumonia in children in developing countries: the cornerstone of the acute respiratory infection programme. *Bull World Health Organ* 2003; **81:** 298-300.
36. Shann F, Hart K, Thomas D. Acute lower respiratory tract infections in children: possible criteria for selection of patients for antibiotic therapy and hospital admission. *Bull World Health Organ* 1984; **62:** 749-753.
37. Berman S, Simoes EAF, Lanata C. Respiratory rate and pneumonia in infancy. *Arch Dis Child* 1991; **66:** 81-84.
38. Harari M, Shann F, Spooner V, *et al*. Clinical signs of pneumonia in children. *Lancet* 1991: **338:** 928-930.
39. Cherian T, John TJ, Simoes E, *et al*. Evaluation of clinical signs for the diagnosis of acute lower respiratory infection. *Lancet* 1988; **2:** 125-128.
40. Sazawal S, Black RF. Meta-analysis of intervention trials on case-management of pneumonia in community settings. *Lancet* 1992; **340:** 528-533.
41. Sazawal S, Black RE. Pneumonia Case Management Trials Group. Effect of pneumonia case management on mortality in neonates, infants, and preschool children: a meta-analysis of community-based trials. *Lancet Infect Dis* 2003; **3:** 547-556.
42. Chopra M, Patel S, Cloete K, Sanders D, Peterson S. Effect of an IMCI intervention on quality of care across four districts in Cape Town, South Africa. *Arch Dis Child* 2005; **90:** 397-401.
43. Zar HJ, Jeena P, Argent A, Gie R, Madhi S. Diagnosis and management of community acquired pneumonia in childhood – South African Thoracic Society Guidelines. *S Afr Med J* 2005; **95:** 977-990.
44. Pakistan Multicentre Amoxycillin Short Course Therapy (MASCOT) pneumonia study group. Clinical efficacy of 3 days versus 5 days of oral amoxicillin for treatment of childhood pneumonia: a multicentre double-blind trial. *Lancet* 2002; **360:** 835-841.
45. Addo-Yobo E, Chisaka N, Hassan M, *et al*. Oral amoxicillin versus injectable penicillin for severe pneumonia in children aged 3 to 59 months: a randomised multicentre equivalency study. *Lancet* 2004; **364:** 1141-1148.
46. Tan TQ. Antibiotic resistant infections due to *Streptococcus pneumoniae:* impact on therapeutic options and clinical outcome. *Curr Opin Infect Dis* 2003; **16:** 271-277.
47. Jeena PM, Coovadia HM, Chrystal V. *Pneumocystis carinii* and cytomegalovirus infections in severely ill, HIV-infected African infants. *Ann Trop Paediatr* 1996; **16:** 361-368.
48. Muhe L, Webert M. Oxygen delivery to children with hypoxaemia in small hospitals in developing countries. *Int J Tuberc Lung Dis* 2001; **5:** 527-532.
49. Hussey GD, Klein M. A randomized controlled trial of vitamin A in children with severe measles. *N Engl J Med* 1990; **323:** 160-164.
50. Bhandari N, Bahl R, Taneja S, *et al*. Effect of routine zinc supplementation on pneumonia in children aged 6 months to 3 years: randomised controlled trial in an urban slum. *BMJ* 2002; **324:** 1358.
51. Bhutta ZA, Black RE, Brown KH, *et al*. Prevention of diarrhea and pneumonia by zinc supplementation in children in developing countries: pooled analysis of randomized controlled trials. Zinc Investigators' Collaborative Group. *J Pediatr* 1999; **135:** 689-697.
52. Mulholland K, Hilton S, Adegbola R, *et al*. Randomised trial of *Haemophilus influenzae* type-b tetanus protein conjugate vaccine for prevention of pneumonia and meningitis in Gambian infants. *Lancet* 1997; **349:** 1191-1197.
53. Swingler G, Fransman D, Hussey G. Conjugate vaccines for preventing *Haemophilus influenzae* type b infections. *Cochrane Database Syst Rev* 2003; **4:** CD001729.
54. Madhi SA, Petersen K, Khoosal M, *et al*. Reduced effectiveness of *Haemophilus influenzae* type b conjugate vaccine in children with a high prevalence of human immunodeficiency virus type 1 infection. *Pediatr Infect Dis J* 2002; **21:** 315-321.
55. Klugman KP, Madhi SA, Huebner RE, *et al*. A trial of 9-valent pneumococcal conjugate vaccine in children with and without HIV infection. *N Engl J Med* 2003: **349:** 1341-1348.
56. Madhi SA, Kuwanda L, Cutland C, Klugman KP. The impact of a 9-valent pneumococcal conjugate vaccine on the public health burden of pneumonia in HIV-infected and -uninfected children. *Clin Infect Dis* 2005; **40:** 1511-1518.
57. Cutts FT, Zaman SM, Enwere G, *et al*. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. *Lancet* 2005; **365:** 1139-1146.
58. Chintu PC, Bhat G, Walker A, *et al*. Co-trimoxazole as prophylaxis against opportunistic infections in HIV-infected Zambian children (CHAP): a double-blind randomised placebo-controlled trial. *Lancet* 2004; **364:** 1865-1871.
59. Guidelines for co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults in resource-limited settings. Recommendations for a public health approach. WHO 2006. **http/www.who.int/hiv/pub/guidelines/ctx**. (last accessed 8 August 2006).

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PRACTICE REVIEW

The Allergy Clinic: 50 years

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Establishment and development

There has been an allergy clinic at Red Cross Children's Hospital from the day that the doors opened 50 years ago. This may not appear surprising given the prevalence of allergic conditions in children, but even today few major teaching hospitals in South Africa have paediatric allergy clinics – this despite the recent International Study of Asthma and Allergies in Children (ISAAC) which ranked South Africa twelfth in prevalence out of the 56 countries surveyed.[1]

Dr Lorn Shore, who had trained in allergy at St Mary's Hospital in London, was instrumental in establishing the clinic. He developed an extensive knowledge of local allergens and developed and adapted skin-prick test solutions for these allergens. He collaborated closely with scientists at the Bencard Allergy Unit in the UK producing locally relevant pollen allergens. He established that few, if any, indigenous tree and weed pollens were allergenic and that allergenic pollens were largely derived from imported trees such as oaks and planes. Invasive species in the Western Cape such as the Port Jackson and pine trees were non-allergenic.

Shore was a most astute clinician. At several postgraduate lectures he described the typical progression of allergic conditions from atopic eczema to asthma in infants and young children which he called 'standing in the queue for asthma'. This phenomemon is now known as the 'atopic march' and is the subject of worldwide interest and research. He was a pioneer in the field of sublingual immunotherapy in children, which he used with great success. There has been intense international interest and research recently into this method of immunotherapy now known as SLIT.

Shore was a personal friend of Roger Altounyan, the discoverer of cromoglycate, the first preventative medication used in asthma treatment. Cromoglycate had an enormous impact on asthma research leading to the recognition of the inflammatory nature of the condition. Shore took part in the first studies of the use of cromoglycate in children and was later to be involved in the first international studies on the use of the pioneer inhaled corticosteroid, beclomethasone, in children.

Shore observed that beta$_2$-agonists, notably fenoterol, could be absorbed from the buccal mucous membrane in children, resulting in effective bronchodilatation. He developed a simple clinical test to determine wheezing in infants and young children, which he called the 'squeeze test'. This test involved a slight squeeze of the infant's chest while auscultating during expiration.

In 1971 the first full-time consultant was appointed to the Allergy Clinic when Eugene Weinberg returned from a Fellowship in Paediatric Allergy in the USA. Allergy clinical services and research expanded rapidly and the clinic soon gained national and international recognition. Initial research was devoted to aerobiological studies of allergenic pollens and fungi in Cape Town, which continues to this day under the supervision of Dilys Berman. Sampling techniques established the major importance of house-dust mites as indoor allergens in Cape Town. Early studies on the use of a wide-range of important drugs used in allergy and asthma treatment were conducted. Among these were non-sedating antihistamines, inhaled corticosteroids, cromolyns, beta-agonists, theophyllines and anticholinergics. Reports of the findings of these studies appeared in national and international peer-reviewed publications.

Weinberg's clinical research interests were directed at developing appropriate diagnostic and treatment methods for children with asthma and allergies. The recognition that few Xhosa children were attending the Allergy Clinic in the early years despite forming a significant part of Cape Town's population, led to the prevalence studies that have been a feature of research in this unit. Urban-rural comparative studies on asthma prevalence in Xhosa children[2] have led to important findings regarding factors responsible for the rapid increase in asthma prevalence in children.

In 2001 the Allergy Clinic moved to superb premises in the new specialist outpatients building. For the first time consultants could work in individual offices and an excellent treatment room, patient waiting area, education room, laboratory and nurses office became available.

Cas Motala was appointed as the second fulltime consultant in the clinic in 1988 and took over as head of the clinic when Eugene Weinberg retired in 2004.

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Allergy training and research

The Allergy Clinic at Red Cross Children's Hospital was the first of its kind in southern Africa to provide postgraduate training in allergy to senior paediatric registrars – to date, seventeen paediatric registrars have been trained. This training post in allergy is highly sought after in view of the importance of allergic conditions in paediatric practice, particularly in the diagnosis and management of asthma, allergic rhinitis, food allergies, drug allergies, atopic dermatitis and chronic urticaria. The clinic also provides training in venom immunotherapy and more unusual allergic and immunological diseases including mastocytosis and hereditary angioedema.

Special attention is focused on history taking, aerobiology, allergy diagnostic tests (skin-prick tests, *in vitro* allergy tests, lung function tests, food challenges) and the principles of management in allergy (environmental control, elimination diets, pharmacotherapy, immunotherapy, patient education). Specific training is also provided for evaluation and management of anaphylaxis.

In addition to 'clinical' training, the registrars learn research methodology (including writing grant proposals, seeking ethical approval, designing studies, conducting research, statistical analysis, presentation of data at congresses and writing papers). The projects are either stand-alone studies or undertaken in collaboration with other units at the hospital e.g. Paediatric Pulmonology and Dietetics departments, Allergology Unit (Groote Schuur Hospital) and the UCT Lung Institute. Many projects have been successfully completed and published either as theses or papers.

One of the notable projects was the development and evaluation of low-cost spacer devices for inhaled asthma therapy.[3,4] The impact of these studies has enabled the use of inhaled therapy for asthmatic children and adults in poorly resourced areas. Spacer devices are now widely used in under-resourced areas and have become the standard of care for delivery of inhaled asthma medicines in many parts of South Africa. Recommendations for making and use of this device appear in the South African Guideline for Treatment of Childhood Asthma,[5] in the National Guidelines of Integrated Management of Childhood Illness (IMCI) and have been included in international guidelines for asthma treatment including those produced by the World Health Organisation (WHO) and the Global Initiative for Asthma (GINA).

Other key studies conducted at the clinic include: (*i*) the role of *Staphylococcus aureus* in eczema; (*ii*) genetic and environmental influences on cord blood serum IgE and an atopic sensitisation in infancy; (*iii*) the requirements for hydration in children with acute asthma; (*iv*) continuous monitoring of aerobiology data in the Western Cape; (*v*) strategies for treatment of house-dust mite allergy; (*vi*) cytokine profiles in Xhosa children with atopic asthma; (*vii*) prevalence of latex allergy in health care workers; and (*viii*) autoantibodies in children with chronic urticaria.

Future role

The estimated prevalence of allergy and asthma in the paediatric population of South Africa is between 10% and 15% but is expected to rise with increasing urbanisation.[6] Advances in the understanding, diagnosis, prevention and treatment of allergy are increasing exponentially. Therefore, it is very likely that South Africa will need a greater work-force with expertise in allergy to manage these disorders. Opportunities for allergy training in South Africa remain limited and allergy is still not recognised as a specialty. In line with the current emphasis on a 'primary health care approach' in our country, it is essential to integrate primary and secondary/tertiary care for allergy and asthma.

To meet some of these challenges, we have identified five strategic and key issues to shape the future of the clinic and the discipline of allergy in sub-Saharan Africa: (*i*) promoting education and information of allergy and asthma at undergraduate and post graduate levels; (*ii*) strengthening links with primary and secondary level care facilities and providing outreach support for management of allergy and asthma; (*iii*) fostering and dissemination of locally relevant allergy research; (*iv*) building strategic alliances with other institutions (national and continental departments who share a common interest (e.g. pulmonology, dermatology and otolaryngology) in the areas of education, training and research; and (*v*) motivation for recognition of paediatric allergy as a subspecialty by the Health Professions Council of South Africa.

References

1. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 1998; **351**: 1225-1232.
2. Van Niekerk C, Shore L, Weinberg EG. The house dust mite and childhood asthma in the Cape Peninsula. *S Afr Med J* 1977; **25**: 75-78.
3. Zar HJ, Brown G, Donson H, Brathwaite N, Mann MD, Weinberg EG. Home-made spacers for bronchodilator therapy in children with acute asthma: a randomised trial. *Lancet* 1999: **354**; 979-982.
4. Zar HJ, Weinberg EG, Binns HJ, Gallie F, Mann MD. Lung deposition of aerosol – a comparison of different spacers. *Arch Dis Child* 2000; **82**: 495-498.
5. Motala C, Kling S, Gie R, et al. Guideline for management of chronic asthma in children - 2000 update. *S Afr Med J* 2000; **90** (5 Part 2): 524-537.
6. Zar HJ, Ehrlich RI, Weinberg EG. The rising prevalence of asthma, allergic rhinitis and atopic eczema in African adolescents from 1995 to 2002. *Current Allergy & Clinical Immunology* 2004; **17**: 140.

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PRACTICE REVIEW

Sydenham's chorea – clinical and therapeutic update 320 years down the line

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Post-streptococcal neuropsychiatric movement disorders (PNM) were first described in the Middle Ages, but today more than 300 years later, confusion remains surrounding the terminology, treatment and monitoring of these conditions.

Rheumatic fever is currently the major cause of acquired heart disease among children in South Africa.[1] The incidence of acute rheumatic fever (ARF) and rheumatic heart disease (RHD) is not declining. Recent figures quote the incidence of rheumatic fever as 0.6 - 0.7/1 000 population in the USA and Japan compared with 15 - 21/1 000 population in Asia and Africa.[2] In a study conducted in 1975 in Soweto, South Africa, 12 050 schoolchildren were examined and 19.2/1 000 had rheumatic heart disease.[3] A 2002 report from a cardiology workshop highlighted the belief among clinicians that South Africa is currently in the midst of a rheumatic fever epidemic.[4,5] Sydenham's chorea (SC) is a major manifestation of ARF. Accordingly, in the South African context when PNMs are diagnosed, treatment strategies must always include the prevention of RHD.

History

The term chorea originates from the Greek word 'khoreia', which translates as 'the act of dancing'. Paracelsus (1416) used the term chorea to describe the frenzied, hysterical movements of religious fanatics who visited healing shrines of St Vitus during the Middle Ages (St Vitus dance/chorea major), 'the emphasis here is hysterical'. In 1686 (320 years ago) Thomas Sydenham noted that chorea was occasionally associated with arthritis. He realised that chorea was organ-based and used the term chorea minor or Sydenham's chorea (SC).

In 1894, William Osler noted the behavioural component that has features of obsessive-compulsive disorder (OCD). He observed that some patients with chorea minor had a certain 'perseverativeness of behaviour'.

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In 1980, Susan Swedo described the first 50 cases of paediatric auto-immune neuropyschiatric disorders associated with streptococcus (PANDAS).[6]

In 2003 Dale *et al*.[7] described a spectrum of poststreptococcal auto-immune basal ganglia disorders. Group A beta-haemolytic streptococcus (GABHS) is linked to a number of autoimmune conditions (Table I).[7, 8]

Pathogenesis of the auto-immune response

A GABHS infection in a susceptible host leads to an abnormal immune response. A marker called the D8/17 marker is a monoclonal antibody, directed against a polymorphic protein on the surface of B-lymphocytes. This marker is present in over 90% of patients with ARF and in 85% of patients with PANDAS, but it is not found in healthy controls.[9,10] A single (limited) study has been performed in South Africa to establish the usefulness of this marker to identify susceptible hosts and its expression in South African populations *per se*.[11] It was postulated that these susceptible hosts produced abnormal antibodies, which attached to epitopes in the heart, leading to a pancarditis, or in the basal ganglia, resulting in conditions such as SC and PANDAS.[9,10]

Clinical features of Sydenham's chorea (SC)

SC is a neuropsychiatric disorder; the clinical features include both neurological abnormalities (choreatic movements,

Table I. Conditions associated with poststreptococcal autoimmune disorders

- SC
- PANDAS
- Tourette's disorder
- Chronic tic disorder
- ADEM
- Dystonia
- Myoclonus
- Anorexia nervosa

SC = Sydenham's chorea; PANDAS = paediatric auto-immune neuropsychiatric disorders associated with sttreptococcus; ADEM = acute disseminated encephalomyelitis.

weakness and hypotonia) and psychiatric disorders (such as emotional lability, hyperactivity, distractibility, obsessions and compulsions).[12] These abnormalities lead to inability to perform normal activities of daily living (ADL) including eating, talking, dressing, writing, walking, learning and socialising, and thus impact negatively on the child's quality of life. Although SC is typically described as benign and self-limiting,[13] our experience at the Rheumatic Fever Clinic (RFC) at Red Cross Children's Hospital (RCCH) is that at best it lasts for 6 months but more usually it has a relapsing course for up to 2 years, or at worst it may evolve into a chronic movement disorder.[14] The hypotonia and weakness range in severity from mild to severe, where it is termed chorea mollis[15] and may be confused with a stroke.

The clinical features of chorea were classified by Aaron *et al*.[16] as minimal, mild, moderate and severe: minimal – elicited on examination; mild – patient aware of chorea but no ADL affected; moderate – can ambulate and some ADL limited; severe – cannot ambulate, many ADL limited. This classification while useful does not take into account the impact of the psychiatric component on daily functioning. (We are currently formulating a rating scale which will include these parameters.)

SC abounds with a variety of clinical signs such as hippus, milkmaids, grip, piano-playing movements, pronator sign and many more. These too should be harnessed into a standardised scale, which would facilitate objective monitoring of the progression of the illness.

Results of studies performed during the first half of the 20th century established the tenet that only pharyngeal infection with group A streptococcus causes ARF.[13] Carapetis *et al*.[13] have recently challenged this concept. They have hypothesised that 'in tropical countries with a high prevalence of both pyoderma and rheumatic heart disease, skin infections caused by group A streptococcus have a priming role or even cause acute rheumatic fever, either directly or by subsequent infection of the throat'.[13] We must take cognisance of this; treatment of streptococcal skin infections at a primary health care level is recommended.

Physiology of poststreptococcal neuropyschiatric movement disorders

Motor movements, attention and emotions all result from a complex interaction of neurotransmitters in the basal ganglia, limbic systems and pre-frontal cortex.[17] Gamma-amino butyric acid, dopamine, noradrenaline and serotonin all play a role. Dopamine is particularly important in the control of motor movements. Excess dopamine results in hyperactivity, jerks and stereotyped movements.

Medications that act on the dopamine system include haloperidol and pimozide which block dopamine receptors, clonidine which increases pre-frontal lobe dopamine, L-dopa which increases dopamine levels and methylphenidate which stimulates dopamine neurones.

Explanation of clinical features of SC

The clinical presentation of SC consists of two syndromes in one disorder: (*i*) a tic or movement syndrome which results from overactivity of dopamine neurones; and (*ii*) a pre-frontal lobe syndrome which results from underactivity of dopamine neurones and which is also influenced by serotonin and nor-adrenaline. The pre-frontal lobe syndrome manifests as inability to pay attention, emotional lability, impulsivity and thoughtless actions.[17]

Neuropsychiatric movement disorders are influenced by dopamine, nor-adrenaline and serotonin. A dopamine-driven system would function as follows: Antibodies attach to epitopes in the basal ganglia, which results in decreased dopamine activity in the ventral tegmental area. This in turn results in decreased dopamine activity in the frontal lobe. This leads to disinhibition of subcortical structures, which leads to attention deficit disorder (ADD), impulsivity, learning difficulties and hyperactivity.

The decreased dopamine in the ventral tegmental area also leads to increased sensitivity of dopamine receptors in the striatum, leading to abnormal motor movements. In addition, the disinhibition effect leads to increased sensitivity of dopamine receptors. This concept of disinhibition is a key factor.[17]

Greater understanding of these behaviour trends in SC should follow from current studies being undertaken by the Department of Psychiatry, University of Stellenbosch and Rheumatic Fever Clinic, University of Cape Town, reviewing neuropyschiatric sequelae of affected patients early (at 6 months) and long term (2 - 12 years).

The Rheumatic Fever Clinic (RFC)

This clinic was established in the early 1970s by Dr Hyam Joffe (then head of cardiology at RCCH), housed in the pre-fab buildings of the old outpatient department. Currently 10 - 12 'old' cases are booked weekly and an average of 3 - 4 new referrals are received per month. These figures have not changed over the years, but the attendance rate has improved with patients keeping appointments and often phoning to reschedule when necessary. The goals of the clinic include empowering these young people to understand and take charge of their own illness, and facilitating transfer to an adult unit when indicated. With this end in mind a special Adolescent Rheumatic Fever Clinic will operate once-monthly from May 2006. It is hoped that these young people will become advocates and counsellors to create an awareness of rheumatic fever and its consequences. A database of attendees at the RFC is kept to facilitate improved data collection from developing countries.[13]

The clinical impact of the disorder

A study of patients diagnosed with SC and followed up at the RFC at RCCH identified significant data.[14] SC occurs with equal incidence in males and females. All the patients at the RFC are of indigenous African ancestry or mixed ancestry. The majority of the children live in poverty. Carditis and emotional lability were diagnosed in more than half of the study group. Pre-chorea behaviour changes and learning difficulties were noted by educators who referred the children to a health professional. Over two-thirds of the group had a poor outcome, as defined by the persistence of SC for 2 years, relapses and recurrences or a chronic adverse outcome. Mean duration of symptoms in SC has previously been reported as 6.2 months.[18]

In our cohort 12 patients had a chronic adverse outcome and of these 5 evolved into Tourette's disorder, 6 evolved into PANDAS and 1 developed chronic learning difficulties. Many of these patients had a significant family history of OCD, RHD, learning difficulties, behaviour problems, substance abuse and/or tic disorders.

Certain risk factors were associated with a poor outcome: (*i*) pre-movement behaviour disorders and learning difficulties; (*ii*) males; (*iii*) mixed ancestry; (*iv*) significant family history; (*v*) failure to complete 10 days of penicillin treatment and hospitalisation/bed rest. The age of onset and severity of chorea had no effect on the outcome.

Contrary to other reports, PANDAS was strongly associated with cardiac complications and required penicillin prophylaxis.[19]

To date, at the RFC, therapeutic efforts have been limited to palliation of the motor movements using neuroleptic agents such as haloperidol. In our study haloperidol seldom completely suppressed the movements, nor did it shorten the course of the illness; furthermore it has potential adverse effects of considerable concern.[12,14]

Treatment and management of SC

Treatment of SC is based on four principles:

1. The first tenet of treatment is to eliminate the streptococcus at a primary, secondary and tertiary level. To achieve this end the key factor is the elimination of poverty. More practicable strategies involve the adequate treatment of throat and skin infections, with a 10-day course of penicillin when SC is newly diagnosed, followed by long-term penicillin prophylaxis. Behavioural and emotional changes may precede the movement disorders, in a previously well child.[12,16]

2. Treatment of movement disorders. Therapeutic efforts are limited to palliation of the movement disorders. Haloperidol is frequently used because of its dopaminergic effect as described above. In the South African context it is the drug of choice because it is affordable and readily available at a primary health care level. It has serious potential side-effects, e.g. tardive dyskinesia. In a study conducted at the RFC 25 out of 39 patients on haloperidol reported side-effects severe enough to cause the physician or parent to discontinue treatment or reduce the dose.[14] Other medications which have been used to control the movements include, pimozide, clonidine, valproic acid, carbamazepine and phenobarbitone.[12,20,21]

As a result we have formulated a guideline for the treatment of SC at our centre (Table II).

3. Immunomodulatory interventions include: (*i*) steroids; (*ii*) intravenous immunoglobulins; and (*iii*) plasma exchange.

Patients may benefit from treatment with steroids; controlled clinical trials are indicated to explore this further.[12,14]

Table II. Guidelines for management of Sydenham's chorea

Movement disorder
Acute phase
Penicillin V K 500 mg 12-hourly po or 250 mg 6 hourly for 10 days
Haloperidol start low – go slow
0.025 mg/kg/day orally in divided doses gradually increasing to a maximum of 0.05 mg/kg/day. Balance benefits with side-effects
After 1 month if no improvement in activities of daily living discuss other treatment options with consultant (e.g. pimozide)
Chronic phase
Prophylactic penicillin
Haloperidol or pimozide as above. Continue treatment until patient has been symptom-free for 3 months, then tail slowly
Comorbid conditions
Family intervention: supportive family psychotherapy
Educational intervention; contact teacher and school psychologist
Social intervention; apply for social support grant with yearly medical reassessment of need
Notify all cases of Sydenham's chorea

ETHICS

Why are some South African children with Down syndrome not being offered cardiac surgery?

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About 1 in 1 000 children has Down syndrome. Extra chromosomal material results in a myriad of potential problems for the affected individual. About 40% of Down syndrome children will have cardiac abnormalities, ranging from the simple arterial duct to the complex atrioventricular septal defect. Virtually all these defects are amenable to surgical correction and extended survival is possible. In South Africa many of these children do not undergo cardiac surgery.

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In all provinces in South Africa specialist medical services are under threat. Many of these services are perceived as being expensive and serving patients with limited outcomes. Resource constraints (in particular nursing shortages and budgetary limitations) have forced specialists to examine their practices and curtail those practices that offer low yield at high financial cost. The recently published 'head injury' protocols are a good example of such a relook.[1] Denying ventilatory support to premature infants weighing less than 900 g is another example of a policy designed to reassign resources to those who might achieve a better outcome.

All cardiac surgical units within the State sector in South Africa are affected by these resource constraints. The long waiting lists for surgery are the most obvious manifestation of these limitations. For children with congenital heart disease, a longer waiting period may mean the difference between low-risk and high-risk (and more expensive) surgery. At worst, the wait may make safe surgery impossible.

Prioritising patients within waiting lists is not an easy task. We have some experience with at least three approaches to shortening lists:

1. Increasing resources (even for a short period of time, as happened during 2000 in the Western Cape) helps to shorten the list. 'Fairness' can be achieved within a hospital setting by rotation of priorities – cardiac patients this year, tonsillectomy patients next year and so on.

2. The use of more expensive devices may allow non-surgical treatment of simpler lesions in the catheterisation laboratories rather than in the operating theatre. (While the cost of closing an atrial septal defect with a closure device may exceed the cost of the same procedure surgically in the setting of a developing country,[2] the opening of an operating space for a child with tetralogy of Fallot may offset that extra cost, in terms of future hospitalisations and morbidity).

3. Careful reorganisation of the list, which involves a thorough re-analysis of the indications for surgery and postulated outcome for each patient. It may require the wisdom of Solomon to deny surgery to patients who are perceived as benefiting less from surgery than others.

With our profession's basic commitment to preserve life for all who seek our help, selecting any patients who will not be helped is an ethical minefield. The only criterion that stands even a chance of being a 'fair' or 'just' basis for selection is the likelihood of long-term medical benefit from the care provided. There is no ethical ground for choosing on the grounds of long-term contribution to society or any other assessment of 'worth'. But how do we assess the likelihood of long-term medical benefit? Personal moral judgements (of social worth and promise) inevitably cloud assessments of medical benefit. This seems at least in part to be the problem with certain patients being refused cardiac surgery.

The 'Baby Ronnie' episode brought the (sincere) attempts of one province to shorten the waiting list of children waiting for cardiac surgery into the limelight. Baby Ronnie was flown at great cost to a private facility in the Cape when he was denied cardiac surgery in the State sector in another province.[3]

What made Baby Ronnie different from any other child with the same congenital heart defect? He was born with Down syndrome.

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The scope of the problem of children with Down syndrome and congenital heart defects

About 1 in 1 000 children has Down syndrome (most commonly due to trisomy 21).[4] The extra chromosomal material results in a myriad of potential problems for the affected individual. About 40% of Down syndrome children will have cardiac abnormalities ranging from the simple arterial duct to the atrioventricular septal defect.[5] Virtually all defects are amenable to surgical correction and extended survival is possible.

The majority of children with Down syndrome and congenital heart defects (60%) will have simpler defects such as ventricular septal defects, tetralogy of Fallot or patent arterial ducts. In our opinion there are no medical reasons that make Down syndrome patients with these particular defects less likely to benefit from surgery than their counterparts with a normal karyotype.

The other 40% of patients with Down syndrome and a heart abnormality will have an atrioventricular septal defect, which is a far more complex lesion. This abnormality in essence involves the presence of a large gap in the walls between both atria and ventricles and abnormal atrioventricular valves. (These patients have a common atrioventricular valve instead of true 'mitral' and 'tricuspid' valves.[6]) Repair of the atrioventricular defect is a significant challenge for the surgeon.

If repair of atrioventricular septal defects is delayed beyond the first year of life, irreversible pulmonary vascular changes may ensue as a consequence of the high-pressure left to right shunt. Surgery may then no longer be possible.[7] After the first year of life, if they survive congestive cardiac failure and repeated chest infections, unoperated children enter a 'honeymoon period' as they develop irreversible pulmonary hypertension. They then succumb in their third decade from right heart failure or the consequences of persistent cyanosis.

Patients with Down syndrome also have other associated abnormalities such as mid-face hypoplasia and airway obstruction that increase their propensity to develop accelerated pulmonary hypertension.[8] For these reasons, there is a perception that cardiac surgery in these patients is more hazardous and associated with a higher morbidity and mortality. This perception is incorrect.

Reasons given for not operating on Down syndrome children with an atrioventricular septal defect

Poor surgical results

In an article published in the early 1980s Bull and colleagues[9] argued that not offering surgery to Down syndrome patients with an atrioventricular septal defect resulted in equivalent survival to the surgical option. Despite cogent arguments, their ideas were highly controversial at the time. The article was published in *The Lancet* after having been rejected by the *New England Journal of Medicine*.[10]

Improvements in surgical outcome have resulted in their conclusions becoming obsolete. The life expectancy of patients with Down syndrome has doubled since the 1970s largely as a consequence of treatment of these heart lesions.[11] Most USA and UK centres would claim 30-day mortality figures of less than 5% for correction of an atrioventricular septal defect in a patient with Down syndrome.[12]

There is no reason why South African surgical centres cannot achieve equivalent surgical results (Table I). At Red Cross Children's Hospital, the mortality for isolated complete atrioventricular canal repair was 6.9% (4 of 58, of whom 44 had Down syndrome).[13]

Limited lifespan and early dementia of patients with Down syndrome

The lifespan of a person with Down syndrome is less than that of a person with a normal karyotype.[11] Nevertheless, the patient may reach an advanced age. In societies with resources, 13% of patients with Down syndrome reach the age of 60 years.[14]

Intellectual handicap is universal in individuals with Down syndrome and most children will face institutionalisation as adults. Up to 50% of patients with Down syndrome will show

Table I. Five years' experience at Red Cross Children's Hospital, comparing selected procedures with Stark *et al.

	Red Cross: 1 unit, 5 years		UK: 5 units, 1 year	
Operation	Number	Mortality (%)	Number	Mortality (%)
All operations	1 334	5.1	1 378	4.0
Isolated VSD	162	1.2	168	0.6
Fallot's tetralogy	115	3.5	88	2.3
Switch (simple TGA)	15	6.7	67	0
Complete AVSD	58	7	55	3.6

*Reproduced from: Hewitson *et al.*[13]
VSD = ventricular septial defect; TGA = transposition of the great arteries; AVSD = atrioventricular septal defect.

signs of Alzheimer's disease by the age of 50.[15] Recent data suggest that the diagnosis of dementia in these individuals is difficult and late-onset hypothyroidism as well as depression as a consequence of the death of a caregiver may cause a 'pseudodementia'.[16]

For some, sheltered employment will be possible. For all affected individuals, however, the intangible elements that make up 'quality of life' will nevertheless be present in abundance.[17]

Does not fixing a cardiac defect save money?

The patient with a significant defect is likely to suffer from cardiac failure and repeated chest infections. The 'honeymoon' period alluded to previously may take a year to develop with symptoms and signs of congestion gradually decreasing unless the patient succumbs prior to this time. Each episode of pneumonia might result in a hospital admission. Each illness may be associated with time away from work for the child's parents. The cost of an admission to hospital may rapidly start to offset money saved by not repairing a defect (see article by Roussot *et al*.[18] in this edition of the journal).

The patient with severe pulmonary hypertension is said to be relatively free from symptoms until the 2nd or 3rd decade.[9] The end of their lives is associated with worsening dyspnoea and cyanosis and life-threatening dysrhythmias; in our experience, the last few years of these adolescent children's lives are often miserable.

How many Down syndrome patients are there?

Only 8% of patients with congenital heart disease have Down syndrome (i.e. on the average surgical waiting list only 8 of every 100 patients should have Down syndrome). Therefore not performing surgery on these patients will represent only an 8% decrease in waiting lists. (If simpler lesions are corrected and atrioventricular septal defects are not, a 'saving' of 3 - 4% on a list will be achieved.)

What are the rights of patients with Down syndrome?

The rights to basic health care are guaranteed to all South Africans as a constitutional right.[19] The definition of what constitutes 'basic health care' is open to interpretation. In South African law, the Soobramoney case is cited as a legal definition of basic health care and has been used to justify withholding super specialist services.[20]

It could be argued that an expensive operation that 'guarantees' a long survival is also effective and basic health care when the costs are defrayed over a long time period. For example, the chances of surviving for more than 30 years after repair of tetralogy of Fallot are excellent.[21]

The challenge to health care planners is not only to make sure that no one succumbs from a simple pneumonia but also to ensure that the patient with congenital heart disease from Mafikeng has a similar chance to the patient from Cape Town to receive the surgery that will extend his/her life. The patients who benefit from so-called 'ivory tower' medicine do not come from a different country to the patient who dies when gastroenteritis is not treated properly.

Is it unethical not to offer surgery to South African patients with Down syndrome?

Distribution of medical care on the basis of lifespan, quality of life, or contribution to society is a slippery slope towards denying care to many other patients, such as severe burns or oncology patients to mention only two. Why should Down syndrome be singled out?

In an elegant article in the *British Medical Journal*, Savulescu[22] argues that medical practitioners are used to rationing resources. Furthermore, limiting available treatments with some benefit in favour of treatments benefiting more people to a greater degree may not be illegal despite being unethical, provided decisions taken to limit medical care are taken in consensus and that the process is transparent. In addition, the decision to limit access to a particular resource should be considered for reversal should circumstances change.

The reasons for not offering surgery to children with Down syndrome and congenital heart defects – never working, intellectual impairment, and the 'stealing' of surgery from potentially productive individuals – need to be carefully examined. In a country with 30% unemployment, 'not being employable in the open market' is a somewhat soft reason to deny surgery. In addition, the right of mentally handicapped individuals to work is protected under basic labour laws![23]

When we reject a child's candidacy for surgery because he has a low IQ, then we have allowed judgements of social worth and promise to masquerade as questions of the likelihood of long-term medical benefits.

It is disconcerting that within major urban centres there are units in the public sector hospitals which feel that they are not able to offer surgery to patients with atrioventricular septal defects and Down syndrome existing cheek-by-jowl with centres in the private sector where such children are offered surgery because they have parents with sufficient financial resources.

Conclusion

The history of the South African medical establishment is tainted by less than perfect decisions taken for political and/or financial expediency. The decision to restrict a service or withhold a particular service must be taken against a backdrop

of idealism and striving to obtain the maximum good rather than as a reaction to political or economic pressure. In the 'supermarket' of medicine, super-specialists are the 'loss leaders'. They enhance the quality of the entire system and this benefits not the health economist but the patient.

Given scarcity of resources and in the face of the need to make tragic choices about how to deal with long waiting lists, what can we do? The first thing is to be truthful: acknowledge the limits and scarcities we face to both our patients and the public. There is a reticence to speak openly in the media about the health services in crisis because it puts health politicians in a bad light. But public money is being spent on a public service about which we must be transparent. Such transparency implies a readiness to admit that there are limits to what we can do, but also that we will not turn our backs on basic patient rights.

The problems that beset South African cardiac surgery (which can be summarised as 'too few operations for too many patients with too few nurses') may in our opinion be better dealt with by reviewing our practices as a whole rather than denying surgery to one group of children with an easily identifiable genetic abnormality.

References

1. Benatar SR, Fleischer TE, Peter JC, Pope A, Taylor A. Treatment of head injuries in the public sector in South Africa. *S Afr Med J* 2000; **90:** 790-793.
2. Vida VL, Barnoya J, O'Connell M, Leon-Wyss J, Larrazabal LA, Castaneda AR. Surgical versus percutaneous occlusion of ostium secundum atrial septal defects: results and cost-effective considerations in a low-income country. *J Am Coll Cardiol* 2006; 17; **47:** 326-331.
3. Smetherham J. Down's syndrome baby on the mend after heart op. *The Star* (Johannesburg) 5 February 2002.
4. Boughman JA, Neill CA, Ferencz C, Loffredo CA. The genetics of congenital heart disease. In: Ferencz C, Rubin JD, Loffredo CA, Magee CA, eds. *Epidemiology of Congenital Heart Disease. The Baltimore-Washington Infant Study 1981-1989*. Mount Kisco, New York: Futura, 1993: 123-167.
5. Freeman SB, Taft LF, Dooley KJ, *et al*. Population-based study of congenital heart defects in Down syndrome. *Am J Med Genet* 1998; **80:** 213-217.
6. Anderson R, Ho SY, Falcao S, Daliento L, Rigby ML. The diagnostic features of atrioventricular septal defect with common atrioventricular junction. *Cardiol Young* 1998; **8:** 33-49.
7. Clapp S, Perry BL, Farooki ZO, *et al*. Down's syndrome, complete atrioventricular canal, and pulmonary vascular obstructive disease. *J Thorac Cardiovasc Surg* 1990; **100:** 115-121.
8. Cooney TP, Thurlbeck WM. Pulmonary hypoplasia in Down's syndrome. *N Engl J Med* 1982; **307:** 1170-1173.
9. Bull C, Rigby ML, Shinebourne EA. Should management of complete atrioventricular canal defect be influenced by coexistent Down syndrome? *Lancet* 1985; **i:** 1147-1149.
10. Shinebourne E, Carvalho J. Atrioventricular septal defect and Down's syndrome. British Council Paediatric Cardiology Course, London. 9-16 March 1994.
11. Yang Q, Rasmussen S, Friedman J. Mortality associated with Down's syndrome in the USA from 1983 to 1997: a population-based study. *Lancet* 2002; **359:** 1019-1025.
12. Hanley FL, Fenton KN, Jonas RA, et al. Surgical repair of complete atrioventricular canal defects in infancy: twenty year trends. *J Thorac Cardiovasc Surg* 1993; **106:** 387-394.
13. Hewitson J, Brink J, Zilla P. The challenge of pediatric cardiac services in the developing world. *Semin Thorac Cardiovasc Surg* 2002; **14:** 340-345.
14. Baird A, Sadovnick A. Life expectancy in Down syndrome adults. *Lancet* 1988; ii: 1354-1356.
15. Menendez M. Down syndrome, Alzheimer's disease and seizures. *Brain Dev* 2005; **27:** 246-252.
16. Roizen N, Patterson D. Down's syndrome. *Lancet* 2003; **361:** 1281-1289.
17. Alderson P. Down's syndrome: cost, quality and value of life. *Soc Sci Med* 2001; **53:** 627-638.
18. Roussot MA, Lawrenson JB, Hewitson J, Smart R, de Decker HP. Is cardiac surgery warranted in children with Down syndrome? A case-controlled review. *S Afr Med J* 2006; **96:** 924-930 (this issue).
19. *Constitution of the Republic of South Africa 1996* Chapter 2 Section 27.
20. *Soobramoney v. Minister of Health*, KwaZulu-Natal CCT32/97.
21. Murphy JG, Gersh BJ, Mair DD, *et al*. Long-term outcome in patients undergoing surgical repair of tetralogy of Fallot. *N Engl J Med*. 1993; **329:** 593-599.
22. Savulescu J Resources, Down's syndrome, and cardiac surgery. *BMJ* 2001; **322:** 875-876.
23. South African Parliament. Employment Equity Act No. 55 of 1998.

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Given the postulated auto-immune pathophysiology of SC, intravenous immunoglobulins may shorten the duration of the illness by resulting in the cessation of the auto-immune-mediated process involving the basal ganglia.[10,12] Before this expensive intervention can be recommended in a developing country, its safety and efficacy in the South African population needs to be established. A study is currently under way at the RCCH.

Plasma exchange is not performed for SC in South Africa.

4. Supportive strategies. Family, school and community counselling is indicated. In situations of dire poverty we recommend application for a care dependency grant, with review after 2 years, when it is to be hoped that the patient's symptoms will have improved. Ongoing education to encourage secondary penicillin prophylaxis and education in the community to create an awareness of the condition is an essential aspect of treatment. It is also important to educate traditional healers to become advocates for prevention of RHD. In our experience they are often the first health professionals consulted when parents are suddenly presented with a child whose personality changes overnight! Implementation of the awareness, surveillance, advocacy, prevention (ASAP) programme to control rheumatic fever and RHD in Africa is mandatory.[22]

Future interventions

There is an increased expression of the D8/17 marker in patients with rheumatic heart disease and PANDAS.[9,10,23] If this marker could identify, at presentation, those patients at risk of bad outcome of SC, they would be the population to benefit from early intervention with immunoglobulins. A study investigating this possibility is about to begin at RCCH.

Long-term outcome of SC

There are reports of continued morbidity after the cessation of the chorea, with subsequent psychopathology and cognitive defects.[12,14] Assessment of neuropsychiatric and neuropsychological manifestations of SC 2 - 12 years after initial diagnosis is currently being studied by the Department of Psychiatry, University of Stellenbosch, and RFC, University of Cape Town.

It would be useful to develop tools to objectively monitor the neurological and psychiatric outcomes of SC. Standardised clinical rating scales and SPECT (single photon emission computed tomographic scanning) appear to be useful. These tools are being investigated at RCCH.

Conclusion

ARF and SC with their chronic sequelae, RHD and chronic neuropsychiatric movement disorders, remain serious public health problems in South Africa. Implementation of the recently formulated ASAP programme is mandatory to prevent first attacks of rheumatic fever. Primary and secondary health services are important in this regard.[22] However, in order to prevent, monitor and treat the devastating complications of ARF tertiary services are necessary.

Current research at the RFC at RCCH has improved our understanding of SC, but as some questions are answered so new questions arise. One such question is whether there is any possibility that the streptococcal infection and antibody production act as triggers to unmask an underlying neuropsychiatirc disorder rather than causing it via a destructive auto-immune process? We at RCCH are committed to continued research to prevent, monitor, treat and decrease complications in this disease first described 320 years ago.

References

1. Mayosi BM, Commerford BJ, Levetan BN. Anticoagulation for prosthetic valves during pregnancy. *Clin Cardiol* 1996: **19:** 921.
2. Brice EAW, Commerford PJ. Rheumatic heart disease: prevention and acute treatment. *Evidence-based Cardiology* 1998; **46:** 787-779.
3. McLaren MJ, Hawkins DM, Koornhof HJ, *et al*. Epidemiology of rheumatic heart disease in black school children of Soweto, Johannesburg. *BMJ* 1975; **3:** 474-478.
4. Report on the Paediatric Cardiology Workshop. Modernisation of tertiary care services. Strand, South Africa, 26-27 September 2002. **http://www.doh.gov.za/mts/reports/cardiology01.html**
5. Robertson KA, Volmink JA, Mayosi BM. Lack of adherence to the national guidelines on the prevention of rheumatic fever. *S Afr Med J* 2005; **95:** 52-56.
6. Susan SE, Leonard HL, Garvey M. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 Cases. *Am J Psychiatry* 1998; **155:** 264-271.
7. Dale RC, Heyman I, Surtees RAH. Dyskinesias and associated psychiatric disorders following streptococcal infections. *Arch Dis Child* 2004; **89:** 604-610.
8. Van Toorn R, Weyers HH, Schoeman JF. Distinguishing PANDAS from Sydenham's chorea: case report and literature review. *European Journal of Paediatric Neurology* 2004; **8:** 211-216.
9. Swedo SE, Leonard HL, Mittelman BB, *et al*. Identification of children with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections by a marker associated with rheumatic fever. *Am J Psychiatry* 1997; **154:**110-112.
10. Bottas A, Richter MA. Paediatric autoimmune neuropyshciatric disorders associated with streptococcal infections (PANDAS). *Pediatric Infect Dis J* 2002; **21:** 67-71.
11. Niehaus DJH, Knowles JA, Stein DJ, *et al*. D8/17marker in OCD and trichotillomania. *SAMJ* 1999; **89:** 755-756.
12. Garvey M, Swedo SE. Sydenham's chorea clinical and therapeutic update. Horaud *et al*., eds. *Streptococci and the Host*. New York: Plenum Press, 1997: 115-120.
13. Carapetis JR. Acute rheumatic fever (Seminar). *Lancet* 2005; **366:** 255-268.
14. Walker KG, Lawrenson J, Wilmshurst JM. Neuropsychiatric movement disorders following streptococcal infection. *Developmental Medicine and Child Neurology* 2005; **47:** 771-775.
15. Garvey MA, Asbahr FR. Sydenham chorea. In: Guerrini R, Aicardi J, Andermann F, Hallett M, eds. *Epilepsy and Movement Disorders*. Boston: Cambridge University Press, 2002: 359-378.
16. Aaron AM, Freeman JM, Carter S. The natural history of Sydenham's chorea. *Am J Med* 1965; **88:** 83-93.
17. Comings DE. *Tourette Syndrome and Human Behaviour*, 3rd ed. Duarte, California: Hope Press, 1994: 51-52.
18. Swedo SE. A model for childhood autoimmune neuropsychiatric disorders. Grand rounds at the Clinical Center of the National Institute of Health. *JAMA* 1994; **272:** 1788-1790.
19. Kurlan R, Kaplan EL. The paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) etiology for tics and obsessive-compulsive symptoms: hypothesis or entity? Practical considerations for the clinician. *Pediatrics* 2004; **113:** 883-886.
20. Daoud AS, Zaki M, Shakir R, al-Saleh Q. Effectiveness of sodium valproate in the treatment of Sydenham's chorea. *Neurology* 1990; **40:** 1140-1141.
21. Edgar TS. Oral pharmacotherapy of childhood movement disorders. *J Child Neurol* 2005; **18:** 840-849.
22. Robertson KA, Volmink JA, Mayosi BM. Towards a uniform plan for the control of rheumatic fever and rheumatic heart disease in Africa - the Awareness Surveillance Advocacy Prevention (ASAP) Programme. *S Afr Med J* 2006; **96:** 241-245.
23. Garvey MA, Gied J, Swedo SE. PANDAS: The search for environmental triggers of pediatric neuropyschiatric disorders: lessons from rheumatic fever. *J Child Neurol* 1998; **13:** 413-421.

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