Severity of pulmonary disease in infants less than three months with culture confirmed tuberculosis

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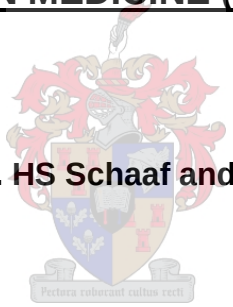

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DECLARATION

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Abstract

Background

Tuberculosis (TB) is a significant health burden among children. Very young infants are particularly at risk for severe pulmonary disease and disseminated forms of TB and the morbidity and mortality is high. There are few studies that address TB disease in infants less than 3 months of age. The aim of this study was to describe various clinical and radiological characteristics of TB in a cohort of infants in this age group.

Methods

This was a retrospective descriptive study of infants less than 3 months of age (<91 days), with a positive culture for *Mycobacterium tuberculosis* on any collected specimen, who presented to Tygerberg Children's Hospital, a tertiary referral hospital in the Western Cape Province (WCP), South Africa (SA) between 1 March 2003 and 30 June 2011.

Results

Seventy-one infants below 3 months of age were included in the study. Sixty-six infants (92%) had pulmonary TB, of which 22/66 (33%) also had extrapulmonary TB; 4 (6%) infants had only extrapulmonary TB. One (1%) infant was only infected with TB. Of the patients with extrapulmonary TB, 54% (14/26) had miliary TB. Six of the 26 (23%) patients (2 confirmed; 4 suspected) had TB meningitis. Of all 71 infants, 27 infants (38%) were human immunodeficiency virus (HIV) exposed and 10 infants (14%) were HIV-infected. Drug-resistant TB was found in 7% (5/71) of the infants.

Cough was the most common presenting symptom, and was found in 41/71 (58%) infants; 29 (41%) infants had loss of weight or failure to gain weight and 24 (34%) infants presented with fever. Respiratory signs were the most common presenting signs. Respiratory distress was a clinical finding in 18/71 (25%) infants, wheezing in 15 (21%) and stridor in 6 (8%) infants. Abdominal distension was found in 6 (8%) patients; 5 (7%) patients had ascites and 5 (7%) had jaundice. Nineteen infants (27%) were classified as having congenital TB.

On chest radiography, 55% (39/71) of the infants had mediastinal lymphadenopathy and large airway compression. Thirty-four (48%) of the 71 infants had features of airway compression as well as bronchopneumonia. Miliary TB was seen in 14 (20%) and cavities were seen in 9 (13%) infants. Twenty-one (54%) of the 39 infants with airway compression underwent bronchoscopy, and 21/39 (54%) infants required lymph node decompression (4 patients who underwent bronchoscopy did not require lymph node decompression; 4 patients who required lymph node decompression did not have a preceding bronchoscopy). Ten (14%) infants died.

Conclusions

Infants under 3 months of age presented with severe pulmonary and also disseminated disease. In areas where there is a high incidence of TB (and HIV), it is important for clinicians to maintain a high index of suspicion of TB disease in young infants, and in so doing to allow earlier diagnosis and treatment. Further studies addressing aspects of TB in very young infants should be undertaken.

Opsomming

Agtergrond

Tuberkulose (TB) is 'n belangrike gesondheidslas in kinders. Baie jong babas het veral 'n risiko vir ernstige longsiekte en verspreide vorms van TB en die morbiditeit en mortaliteit is hoog. Daar is min studies wat TB in babas onder 3 maande oud bespreek. Die doel van hierdie studie was om verskeie kliniese en radiologiese kenmerke van TB in 'n kohort van babas in hierdie ouderdomsgroep te beskryf.

Metodes

Hierdie was 'n retrospektiewe beskrywende studie van babas minder as 3 maande oud (<91 dae) met 'n positiewe kultuur vir *Mycobacterium tuberculosis* van enige ingesamelde monster, wat by Tygerberg Kinderhospitaal, 'n tersiêre verwysingshospitaal in die Wes-Kaap Provinsie (WKP), Suid-Afrika (SA) gepresenteer het tussen 1 Maart 2003 en 30 Junie 2011.

Resultate

Een en sewentig babas onder die ouderdom van 3 maande is ingesluit in die studie. Ses-en-sestig babas (92%) het pulmonale TB gehad, waarvan 22/66 (33%) ook ekstrapulmonale TB gehad het; 4 (6%) babas het slegs ekstrapulmonale TB gehad. Een (1%) baba was slegs TB geïnfekteerd. Van die pasiënte met ekstrapulmonale TB het 54% (14/26) miliêre TB gehad. Ses uit 26 babas (23%; 2 bevestig; 4 vermoedelik) het TB meningitis gehad. Van die 71 babas was 27 (38%) babas aan die menslike immuniteitsgebreksvirus (MIV) blootgestel en 10 babas (14%) was MIV geïnfekteerd. Middelweerstandige TB is in 7% (5/71) van die babas gevind.

Hoes was die mees algemene simptoom waarmee babas gepresenteer het, 41/71 (58%); 29 (41%) babas het gewigsverlies of onvermoë om te gedy gehad en 24 (34%) babas het met koors gepresenteer. Respiratoriese tekens was die mees algemene teken wat voorgekom het. Respiratoriese nood was 'n kliniese bevinding in 18/71 (25%) babas, fluitbors in 15 (21%) en stridor in 6 (8%) babas. Abdominale uitsetting was in 6 (8%) pasiënte gevind; 5 (7%) pasiënte het askites en 5 (7%) het geelsug gehad. Negentien babas (27%) was geklassifiseer as aangebore TB.

Op borskas radiografie het 55% (39/71) van die babas mediastinale limfadenopatie en groot lugweg kompressie gehad. Vier-en-dertig (48%) van die 71 pasiente het kenmerke van lugwegkompressie asook brongopneumonie gehad. Miliêre TB was in 14 (20%) en kaviteite in 9 (13%) babas gesien. Een-en-twintig (54%) van die 39 babas met lugwegkompressie het brongoskopie ondergaan en 21/39 (54%) babas het limfnode dekompressie benodig (4 pasiënte wat brongoskopie ondergaan het, het nie limfnode dekompressie benodig nie; 4 pasiënte wat limfnode dekompressie gehad het, het nie 'n voorafgaande brongoskopie ondergaan nie). Tien (14%) babas het gesterf.

Gevolgtrekkings

Babas jonger as 3 maande oud het met ernstige pulmonale asook verspreide siekte voorgekom. In gebiede waar daar 'n hoë voorkoms van TB (en MIV) is, is dit belangrik vir dokters om 'n hoë indeks van vermoede van TB in jong babas te handhaaf, en sodoende vroeër diagnose en behandeling te verseker. Verdere studies wat aspekte van TB in baie jong babas aanspreek moet onderneem word

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Introduction

Tuberculosis (TB) in childhood represents a significant health burden, despite largely being a preventable disease. In 2014, the World Health Organization (WHO) estimated 1 million incident cases of TB in children worldwide with a case detection rate (CDR) of 36%. The African region accounts for about one third of global cases.[1] The WHO estimates the total number of new TB cases in children less than 15 years of age in South Africa (SA) in 2014 at 31977.[2] According to the 2012 WHO estimates of the TB burden in SA, only 2677 (6.9%) of new cases in children less than 15 years of age were acid-fast bacilli (AFB) microscopy smear-positive; more than 90% of the reported cases in children were AFB smear-negative or unknown.[3] Lack of AFB smear-positivity leads to underestimation of the true burden of childhood TB. This is possibly attributable to low smear-positivity rates in childhood TB disease, incomplete investigation, misdiagnosis (due to similarities with other common diseases in childhood) and/or under-reporting. Some further reasons reported as to why there may be an underestimation of the number of children affected by TB includes: difficulties in accessing healthcare and children treated outside of national treatment programs (NTP). Six percent (n=2327) of the new cases reported in children were extrapulmonary TB,[3] further highlighting the burden of TB in this age group. Child TB cases accounted for 10% of the total number of new and relapsed cases in 2014 with a male to female ratio of 1:3.[2]

The Western Cape Province of South Africa (WCP) had a high incidence of TB of >1,000/100,000 population in 2008.[4] A surveillance study from the WCP found 596 culture-confirmed TB cases in children less than 13 years of age from March 2003 through February 2005 at two pediatric referral hospitals. Of these, 156 (26,2%) children were infants less than 12 months of age at diagnosis, which demonstrates the large burden of TB disease in infants.[5] Infants less than 3 months of age are particularly vulnerable for severe TB disease morbidity and mortality.[4] A study by Hesseling *et al*. in 2009 estimated the incidence of culture-confirmed TB among human immunodeficiency virus (HIV)-infected and uninfected infants (<12 months of age) over a 3-year period in the WCP.[6] Data from 245 infants was collected from 3 referral hospitals in the WCP between 2004 and 2006.[6] The number of TB cases per 100 000 population was 65.9 (57-75) for HIV-uninfected infants and 1596 (115-2132) for HIV-infected infants. Furthermore, pulmonary TB incidence was estimated at 62,5 (53-72) for HIV-uninfected infants and 1505,6 (1075-2023) for HIV-infected infants. Extrapulmonary TB incidence was reported as 22.9 (18-29) for HIV-uninfected infants and 481.8 (257-751) for HIV-infected infants. Disseminated TB incidence was 14.1 (10-18) and 240.9 (87-432) for HIV-uninfected and HIV-infected infants respectively.[6] Although the data presented for HIV-infected infants is before antiretroviral therapy (ART) was routinely initiated in this age group, it clearly indicates the degree of the TB disease burden in infants, and especially in HIV-infected infants who had a 24 times higher risk than HIV-uninfected infants.

There is a paucity of literature describing TB in infants, specifically those under 3 months of age. Epidemiological data for infants less than 3 months of age is scarce and congenital TB is still considered rare, most likely due to missed diagnosis and under-reporting.[4,7,8] There are differences in immune pathogenesis, presentation, and severity of TB disease in young infants compared to older children.[9] Diagnosing TB in this very young age group can be challenging. Some reasons for this include: the presenting symptoms in this age group may be uncharacteristic and vague; tuberculin skin tests are often non-reactive; identifying at-risk infants is difficult as mothers/other household source cases are often not diagnosed with TB.[4,7]

Young age increases the risk for development of disease after infection with *Mycobacterium tuberculosis*. Young children infected before 2 years of age have the greatest risk to progress to TB disease after infection; of these, infants (<12 months) have a 50% chance to develop TB after being infected with *M. tuberculosis* in the absence of preventive measures.[7,10] Furthermore, up to 30% of these infants will develop progressive pulmonary or disseminated forms of TB associated with high morbidity and mortality.[7,10] Before the advent of TB treatment the mortality in infants less than 6 months of age was 55% and in those 1-2 years of age, around 30%.[9] Despite TB treatment, the mortality remains higher for infants with TB than in any other age group.[9]

Tuberculosis in pregnant women represents a substantial health burden and globally, infectious diseases including TB are responsible for around 28% of maternal deaths.[11] Not only does TB in pregnancy pose a significant risk to mothers, but also to their infants who are at risk of unfavourable outcomes including TB disease during early infancy (both congenital TB and postnatally acquired), an increased risk of prematurity, low birth weight, intrauterine growth retardation, and a six-fold increase in perinatal death.[12] A study by Sugarman *et al.,* using data from 217 countries quantifies the burden of TB disease among pregnant women: it was estimated that in 2011 more than 200 000 pregnant women had active TB worldwide with a rate of 2,1 (1,8-2,4) per 1000 pregnant women. More than 70% of cases occurred in Africa and South East Asia.[13] In SA, the rate of TB in pregnant women is estimated at 10,3 (5,4-17,6) per 1000, making up about 4% of the global burden of TB among pregnant women.[13] Pregnant women living with HIV, as well as their infants, are at greater risk of TB compared to HIV uninfected pregnant women. In Africa, the rates of TB disease in HIV-infected pregnant women is 10 times greater than in HIV-uninfected pregnant women, and TB disease increases the risk of both maternal and infant mortality by about 300%.[14] Furthermore, data from India by Gupta et al suggests that dual-infection with HIV and TB in pregnancy is associated with more than double the risk of vertical transmission of HIV to the unborn child.[15] One of the postulated reasons for this increased risk of HIV mother to child transmission (MTCT) includes chronic immune stimulation by TB that in turn leads to increased viral load.[15] Another reason relates to Th-1 down regulation in pregnancy to accommodate the fetus,

which in turn results in pregnant women being vulnerable to TB infection. TB is responsible for strong Th-1 stimulation that may cause an increase in placental inflammation, which is a potential reason for some of the observed adverse fetal outcomes as well as the increased risk of HIV MTCT.[15]

In the era of HIV infection, the risk of infants developing severe and disseminated forms of TB is increased even further. A study conducted in the WCP, South Africa revealed a relative risk of 24 (95% confidence interval [CI], 17-34) for culture-confirmed TB in HIV-infected infants when compared with HIV-uninfected infants.[6] Likely reasons for this were immunosuppression, increased exposure to adults/caregivers with a greater susceptibility to TB and the likelihood that Bacille Calmette-Guérin (BCG) vaccination is less effective in HIV-infected infants.[6]It is also postulated that HIV-exposed uninfected infants are at a higher risk of TB.

It is clear that infants are profoundly vulnerable to TB disease, and especially severe and disseminated forms of TB, which in turn confers a poorer prognosis. Another consideration of TB infection and disease in infants relates to the presenting symptoms that are often uncharacteristic and non-specific thus leading to diagnostic delays. Clinicians need to have a high index of suspicion of TB as a possible diagnosis in high-risk infants, but identifying those infants who are at risk may be problematic in itself, as the source cases are themselves often not diagnosed with TB when the infant presents with symptoms.[16]

We describe the clinical spectrum of disease in infants less than 3 months of age with culture confirmed *M. tuberculosis*, including the clinical presentation, chest radiographic findings, as well as treatment interventions.

Methods

A retrospective, descriptive study including infants below 3 months (<91 days) of age with culture-confirmed TB on any clinical specimen was conducted.

Setting and population

Childhood TB (0-14 years of age) contributed 14% of the total TB burden in 2004 in the WCP, rising to 17.3% in 2008, with an annual notification rate of 407 versus 620 childhood TB cases per 100,000, respectively.[17] (Unpublished data, Western Cape Department of Health) The WCP had a total HIV prevalence of 1.9% in 2005 increasing to 5.0% in 2012.[18]

The infants were identified using a database of prospectively collected *M. tuberculosis* positive culture results for all children <13 years who presented to Tygerberg Children's

Hospital, a tertiary referral hospital serving approximately half of the WCP, South Africa, from 1 March 2003 through 30 June 2011.

All infants below 3 months (91 days) of age (on date of admission to hospital), with a positive culture for *M. tuberculosis* on any collected specimen within the study period were included. Infants with mycobacterial disease caused by *M. bovis* BCG and non-tuberculous mycobacteria were excluded from the study.

Definitions and clinical data collection

Pulmonary TB was defined as a positive culture for *M. tuberculosis* from any respiratory secretions collected (gastric aspirate, tracheal aspirate, bronchoalveolar lavage or induced sputum), or from lung tissue or mediastinal lymph node tissue, together with chest imaging findings in keeping with pulmonary TB.[19]

Severe pulmonary TB was defined as pulmonary TB with nodal large airway compression that includes a range of pathology observed during bronchoscopy, such as extrinsic bronchial compression, caseating lesions, granulomas, polypoid mass lesions and lymph nodes that protrude through mucosal erosions with ulceration. Expansile alveolar opacification, TB bronchopneumonia, multilobar alveolar opacification, cavitation and empyema were also classified as severe pulmonary disease.[20]

Extrapulmonary TB was defined as a positive culture for *M. tuberculosis* from a source external to the respiratory tract, in combination with compatible clinical and or imaging findings. These included mainly TB meningitis, abdominal TB and peripheral lymphadenitis.[19] Extrapulmonary TB was also defined as a positive culture for *M. tuberculosis* obtained from a respiratory secretion sample in combination with clinical and or imaging findings that were compatible with extrapulmonary TB, where other possible causes for the findings had been excluded.[19]

Extrathoracic disease entities such as miliary TB, abdominal TB (TB enteritis, solid organ disease and peritoneal spread), all forms of central nervous system disease (TB meningitis, granulomas, and brain abcesses) and osteo-articular TB were classified as severe disease.[20]

Miliary TB was defined as a positive culture for *M. tuberculosis* from a respiratory specimen together with chest radiographic features compatible with miliary disease.[19]

TB meningitis was defined as a positive culture for *M. tuberculosis* from cerebrospinal fluid (CSF). TB meningitis was suspected if a positive culture was obtained from another source in conjunction with compatible clinical features, CSF chemistry and cell count and/or typical computed tomography (CT) scan brain changes.[21]

Miliary disease, TB meningitis, or disease confirmed through blood culture or bone marrow biopsy combined with compatible signs and symptoms of TB were classified as disseminated TB.[19]

Congenital TB was defined as *M. tuberculosis* transmitted to the fetus in utero or to the infant during birth. Postnatal TB was defined as TB acquired from contact with a source case during the first few weeks of life. Because of difficulties in distinguishing when the infant was infected, congenital and postnatal TB are sometimes referred to in combination as perinatal TB.[4] True congenital TB was described using the revised Cantwell criteria: an infant most likely has congenital TB if the infant has a TB lesion and one or more of the following: (i) presentation within the first week of life, (ii) a primary hepatic complex or caseating hepatic granuloma, (iii) endometrial TB or placental TB infection, or (iv) exclusion of possible postnatally acquired TB by exclusion of TB in other contacts.[22]

Infants diagnosed with TB were treated according to WHO recommendations[23]. For infants with suspected or confirmed pulmonary TB or TB peripheral lymphadenitis, and for infants with all forms of extrapulmonary TB (except TB meningitis and osteoarticular TB), 4 anti-tuberculosis drugs (isoniazid, rifampicin, pyrazinamide and ethambutol) were given daily during the 2-month intensive treatment phase. Isoniazid and rifampicin were given daily for the 4-month continuation phase of treatment. For infants with TB meningitis or osteoarticular TB the WHO recommends prolonging the continuation phase to 10 months. In SA, infants with TB meningitis receive 6 months of rifampicin, isoniazid, pyrazinamide and ethionamide and in those where there is concern regarding clinical progress, the treatment course may be prolonged to 9 months.[24] In the cases of drug-resistant TB, treatment regimens were adapted according to the source case's isolate drug susceptibility pattern if known, or to the infant's isolate drug susceptibility test (DST) result when it became known and treated according to WHO recommendations.[23]

Tuberculin skin testing (TST) was done using the Mantoux test. A positive TST was recorded if the resultant induration measured >=10mm in HIV-uninfected patients and >=5mm in HIV-infected patients.

Lymph node decompression is defined as transthoracic surgical decompression of enlarged mediastinal lymph nodes to relieve airway obstruction. Lymph node decompression was considered urgent if the airway compression was life-threatening and the procedure is performed within 14 days of admission. The operative technique most commonly involves access by a right thoracotomy followed by compression of the right upper lobe to expose the nodes causing airway compression. Cautery is then used to open the nodal capsule and the contents of the node are either curettaged or sucked out. To avoid any damage to

surrounding structures, lymph nodes are not removed.[25]

Demographic, clinical, special investigation and intervention data for each of the patients were obtained retrospectively from 2 established TB databases; the one database included positive *M. tuberculosis* culture data together with demographic and clinical data and the second database included data on bronchoscopies and mediastinal lymph node decompression. Additional data were retrieved from individual patient folders and electronic patients records where necessary.

Chest radiographs were reviewed by an experienced pediatrician (HSS) using a standardized data capture form. The pediatrician was unblinded to patient clinical information. A number of the infants described in this study are also included in other studies describing TB disease in very young children.

TB disease type was classified according to the source of the positive *M. tuberculosis* culture, clinical and radiological (chest radiograph and chest CT scan) findings.

HIV infection was diagnosed based on the WHO case definition of HIV infection in children younger than 18 months of age namely, a positive virological test for HIV or its components (HIV-RNA or DNA or ultra-sensitive HIV p24 antigen), confirmed by a second virological test obtained from a separate determination taken more than 4 weeks after birth. Positive HIV antibody testing is not recommended for confirmatory diagnosis of HIV infection in children until 18 months of age.[26]

The term respiratory distress was not defined by a specific set of criteria, but instead was a clinical descriptor used by the attending clinician and included signs such as tachypnea, chest indrawing and hypoxia requiring oxygen supplementation.

Mycobacteriological culture and drug susceptibility testing (DST)

Mycobacterial culture was done at the National Health Laboratory Service (NHLS) laboratory at Tygerberg Academic Hospital. Primary mycobacterial cultures were performed by inoculation of routine clinical samples into Middlebrook 7H9 broth-based Mycobacterial Growth Indicator Tubes (MGIT960; Becton Dickinson, MD, USA) following a standard protocol for decontamination of the samples. If *M. bovis* BCG was suspected, an RD1 PCR-based assay was used to distinguish between *M. tuberculosis* and *M. bovis* BCG.[27] Prior to August 2008, drug susceptibility testing for isoniazid and rifampicin was done using the phenotypic method. This method was either direct (inoculating drug containing and drug free media directly with a specimen), or indirect (inoculating drug containing media with a pure culture grown from the specimen). Subsequent to this, the genotypic method of drug susceptibility testing is used in children and involves molecular testing of smear-positive samples to detect

genetic mutations associated with antibiotic resistance.[28]

Statistical Analysis

Standard descriptive and non-parametric statistical techniques were used to analyze the data. Medians and interquartile ranges were determined using JMP® Statistical Discovery ™ statistical software. (Developer: Statistical Analysis System (SAS) Institute, Headquarters: North Carolina, United States of America)

Ethical Approval and Consent

The study was approved by the Health Research Ethics Committee of the Faculty of Medicine and Health Sciences, Stellenbosch University. (S14/05/124)
Consent to search patient folders was obtained from the medical director of Tygerberg Hospital. Privacy and confidentiality of included patients was maintained.

Results

Of the 1252 patients <13 years of age with culture-confirmed TB between 1 March 2003 and 30 June 2011, 71 (6%) were under the age of 3 months; of these 71 infants, 43 (61%) were male. The main demographic characteristics as well as the clinical findings of these infants are summarised in table 1.

The median weight for the 71 infants was 3,95kg, with 26 (37%) of the infants having a weight less than the 3rd centile weight-for-age at TB diagnosis. Gestational age and birth weight data was available for 37/71 (52%) infants; 16/37 (43%) infants were born prematurely (<37 weeks gestation) and all of these had a low birth weight (weight < 2,5kg); one of the 37 (3%) infants was term with a birth weight less than 2,5kg. Adjustment of weight-for-age for premature infants according to their corrected gestational age was not performed due to gestational age and birth weight data not being available for almost 50% of the infants.

Sixty-six infants (92%) had pulmonary TB, of which 22/66 (33%) also had extrapulmonary TB; 4 (6%) infants had only extrapulmonary TB. One infant, who had no clinical symptoms of TB, was investigated at birth because the mother had TB during pregnancy. This infant's mother refused isoniazid prophylaxis for the baby as well as treatment for herself. When it was found that the baby had a positive culture for *M. tuberculosis* on a gastric aspirate sample, the patient was recalled and started on treatment.

Nineteen (27%) infants were documented as having congenital TB. Six (32%) of the 19 infants presented within the first week of life; the mothers of 2/19 (11%) of the infants had

endometrial TB and 1 (5%) infant had granulomas and positive acid fast bacilli on liver biopsy. For the remaining 11 infants thought to have congenital TB, data was insufficient to fulfill the revised Cantwell criteria as described in the methods section. Two of these 11 infants presented with ascites, which is a common clinical finding in congenital TB. One infant's mother demised 1 week after birth and one infant's mother was diagnosed with TB in pregnancy but was not treated. The infants of both of these mothers presented at about 2 months of age with severe pulmonary TB and lymph node compression of the large airways requiring decompression of the nodes. Five of the 19 (26%) infants with documented congenital TB died during the course of their hospital admission.

Of the 26 patients with extrapulmonary TB, 14 (54%) had miliary TB (in addition, 2 of the infants with miliary TB had suspected TB meningitis, 1 had abdominal TB and suspected TB meningitis, 3 had abdominal TB alone, 1 had generalized peripheral lymph node TB and 7 infants had no evidence of other extrapulmonary organ involvement). Of the 4 patients who had only extrapulmonary TB, 1 patient had TB meningitis, 1 patient had abdominal TB, 1 had both abdominal TB and TB meningitis, and 1 had cervical lymph node TB. A CSF chemistry and cell count result was only found for 1/6 (17%) of the infants with confirmed or probable TB meningitis.

Twenty-seven (38%) of the 71 of the infants were known to be HIV exposed, of which 14 (52%) received treatment for prevention of mother to child transmission (PMTCT). The adequacy and type of PMTCT was not documented. Ten of the HIV exposed infants tested HIV seropositive by means of PCR; 2 of these 10 received PMTCT, while the remaining 8 (80%) HIV-infected patients had no documentation about whether or not PMTCT was received. Five (50%) of the 10 HIV infected infants were 2 months of age at presentation with TB, 3/10 (30%) infants were 1 month of age and 2/10 (20%) infants were less than 1 month of age at presentation with TB.

No patients were receiving ART prior to admission for TB diagnosis. Nine patients were initiated on ART after the diagnosis of TB was made. For one patient data on ART initiation was not found. Six patients commenced ART within 2 months after the diagnosis of TB, 1 approximately 19 months after diagnosis (defaulted follow up for many months), and for 2 patients the exact time of initiation of ART was not clear from the data available.

Documented source cases were identified in 52/71 (73%) patients. For 42/52 (81%) of the source cases drug susceptibility testing (DST) was unknown. The mother was identified as the source case in 32/52 (62%) cases; in 5 (16%) of these cases the infant was diagnosed with TB before the mother, in 3 (9%) the mother had documented TB during pregnancy, and in one case both mother and baby were diagnosed together. For the remaining maternal

source cases, timing of TB diagnosis was not documented. One (2%) source case had rifampicin-resistant TB.

Four (6%) patients had preventive TB therapy prior to the diagnosis of TB disease; 2 patients received prophylaxis for 2 months, and 1 patient for less than 2 weeks prior to admission and diagnosis. The fourth patient was investigated for TB from birth and received preventive therapy that was later changed to treatment once a positive culture for *M. tuberculosis* was obtained. None of these patients were subsequently diagnosed with drug-resistant TB.

The most common presenting symptom was cough, which was present in 41 (58%) infants; 29 (41%) infants had loss of weight or failure to gain weight and 24 (34%) infants presented with fever. Only 7 (10%) infants presented with cough for >2 weeks, fever and loss of weight/failure to thrive, the triad of symptoms commonly associated with TB.

One infant, who presented with hemoptysis, had a lobectomy for congenital cystic adenomatoid malformation (CCAM) and lung tissue subsequently cultured positive for *M. tuberculosis.*

The most common signs on admission were respiratory signs, with respiratory distress a clinical finding in 18 (25%) infants, wheezing in 15 (21%) and stridor in 6 (8%) infants. Three (4%) infants had apnea episodes and one (1%) infant presented with a cardio-respiratory arrest. This infant was born prematurely at 29 weeks gestation with a birth weight of 1,4kg. He was admitted to intensive care for ventilation after a cardio-respiratory arrest, and was found to have severe nodal airway compression confirmed on chest computed tomography (CT). The infant had lymph node decompression 2 days after admission. The most common gastrointestinal presenting sign was abdominal distension in 6 (8%) patients; 5 (7%) patients had ascites and 5 (7%) patients had jaundice. Six (8%) patients had peripheral lymphadenopathy on presentation (1 generalized and 5 localized). Three infants who had axillary lymphadenopathy had intrathoracic TB, and all 3 had positive cultures for *M. tuberculosis* on gastric aspirates; 1 infant also had abdominal TB. One patient who was diagnosed with TB meningitis presented with meningism and a bulging fontanel. Of the remaining 3 TB meningitis cases, one presented with vomiting, but no other neurological signs were found.

All infants had chest radiographs performed; 39 (55%) showed mediastinal lymphadenopathy, and large airway compression. Thirty-four infants (48%) had features of airway compression as well as bronchopneumonia. Miliary TB was seen in 14 (20%) and cavities were seen in 9 (13%). Five (7%) infants had small pleural effusions on chest radiograph, and 1 (1%) patient had a large effusion clinically found to be an empyema. Seven (10%) chest radiographs were

reported as normal. Of these 7 infants 4 had extrapulmonary TB only, and one infant was infected with TB. The chest radiograph findings are summarised in table 2.

Five infants (7%) had drug-resistant TB; 3 had isoniazid mono-resistance and 2 had rifampicin mono-resistance. One of the patients with rifampicin resistance had a source case (mother) that also had rifampicin-resistant TB. Two of the patients with drug-resistant TB were also HIV-infected. None of the patients with drug-resistant TB died.

Among the 71 infants, 39 (55%) were identified as having airway compression on chest radiography. The characteristics relating to the imaging, bronchoscopy and lymph node decompression of these infants are summarised in table 3. Twenty-eight of 39 (72%) infants had clinical signs of airway compression (wheeze and/or stridor). Twenty-six of 39 (67%) infants had chest CT scans performed, all of which confirmed lymph node compression of the airways. Twenty-one of 39 (54%) infants with airway compression underwent bronchoscopy. In 19/21 (90%) infants the left main bronchus (LMB) was compressed (degree of compression ranged from 50-90%) and bronchus intermedius (BI) was compressed in 19/21 (90%) infants (degree of compression ranged from 75-100%). The trachea was compressed in 13/21 (62%) infants. A lymph node rupturing into the airway was found in 7/21 (33%) infants. One infant desaturated during bronchoscopy, the remaining 20 bronchoscopies were without complication.

Twenty-one of the 39 (54%) infants with airway compression went on to have lymph node decompression by thoracotomy. Of note is that 4 patients had bronchoscopy not followed by lymph node decompression and 4 patients had lymph node decompression that did not have a preceding bronchoscopy. Two of 21 (10%) infants had complications after decompression; one infant developed a bronchopleural fistula and right-sided pneumothorax and 1 infant required re-intubation for recurrence of signs of airway obstruction.

Twenty-seven of 39 (69%) infants who had airway compression received oral glucocorticosteroid treatment in combination with TB therapy. Three of 39 (8%) patients with airway compression had drug-resistant TB; 2 had isoniazid resistance and 1 had rifampicin resistance. The infant with rifampicin resistance and 1 of the infants with isoniazid resistance had lymph node decompression done.

Ten (14%) infants died during admission. Data relating to the cause of death was not found for 3 infants. Two infants did not receive anti-TB therapy before demise. Both of these infants had bronchopneumonia and were ventilated from birth. One infant had contributory candida sepsis (died on day 22 of life) and the other had a pulmonary haemorrhage (died on day 2 of life) as the cause of death. In these cases congenital TB bronchopneumonia was only identified after death. Of the remaining 5 patients, one patient was HIV-infected with stage 4

disease and congenital TB. The infant was found to have miliary TB, suspected TB meningitis, abdominal TB and an abscess on the chest wall. The infant was started on TB therapy 10 days after admission and ART approximately 2 weeks later. This infant demised 5 weeks after admission and the cause of death was hypoxic pneumonia and sepsis. One infant, who was commenced on TB treatment on day 16 of hospitalisation, died of hepatic failure (not antituberculosis drug related) and sepsis 5 weeks after admission, 1 infant died of severe pulmonary TB and airway compression 3 weeks after admission, 1 infant treated on admission for disseminated TB (pulmonary and abdominal TB), required high frequency oscillatory ventilation and died 9 days after admission and the last infant had miliary TB, was commenced on TB treatment on admission, required ventilation and died of multi-organ failure 3 days later. This infant had been given traditional herbal medications prior to admission.

The remaining 61 (86%) patients were alive at discharge from the tertiary institution. Thirty-three (54%) of the infants were known to be well 6 months or more after discharge from the tertiary institution. One (1%) patient had a confirmed recurrence of TB, and was diagnosed with TB of the hip. A further 2 (3%) patients had suspected TB recurrence; 1 patient had a recurrence of a cervical swelling which had previously been culture positive for *M. tuberculosis*. The second patient was diagnosed with pulmonary TB at the age of 2 years.

Discussion

In this study we describe what we believe is the largest cohort of infants less than 3 months with culture-confirmed TB.

Data for infants, in particular those infants less than 3 months of age, is lacking, and few reports address TB burden in this highly vulnerable age group. Our findings in this study are similar in many respects to the findings of a study by Schaaf et al. who described the clinical and radiological features of 38 infants, all of whom were HIV-uninfected and less than 3 months of age from a tertiary hospital in the WCP.[7] The authors demonstrated that, despite the hospital being in an area of high TB burden, there was a median delay of 14 days between symptom onset and diagnosis and treatment initiation. This is likely attributable to the non-specific nature of symptoms and clinical signs of TB in infants.[7] The most common presenting complaint in this cohort was cough and the most prominent respiratory signs were tachypnea, crepitations and bronchial breathing. Around 30% of the infants had respiratory signs of wheezing and more than half of the infants whose chest radiographs were evaluated, had features of large airway obstruction.[7] Seven infants (26%) had miliary tuberculosis on chest radiography, 25 infants (66%) had hepatomegaly and 20 (53%) had splenomegaly, 4 (11%) had TB meningitis indicating that disseminated forms of TB are common in this young

age group. Five (13%) of the infants in the study died due to disseminated TB.[7] None of the infants in this study were HIV-infected (tested by enzyme-linked immunosorbent assay). Also of note is that only 7 infants could be said to have congenital TB infection, thus 31 infants were likely infected postnatally and presented before 3 months of age. Twelve out of 30 mothers evaluated had active TB (7 were unsuspected previously, in 4 the diagnosis of pulmonary TB was known, 1 had confirmed urogenital TB).[7]

A recent Spanish study described 8 patients less than 3 months of age diagnosed with TB between 1978 and 2014 (3 confirmed congenital TB, 3 suspected but unconfirmed congenital TB and 2 postnatally diagnosed TB cases). Three (38%) of the patients developed miliary disease and there was 1 (13%) recorded death. TB culture of gastric aspirates was performed in 7 cases and PCR of gastric aspirates in 3 cases, all of which were positive. A positive TST of >= 10mm was found in 3 (38%) of the patients. The most common presenting symptoms were cough (5; 63%), respiratory distress (3; 38%) and fever (4; 50%). The mother was the source case in 3 (38%) cases. The authors concluded that TB in this age group is rare, difficult to diagnose and severe.[8]

These two studies are the only studies we could find specifically addressing aspects of TB disease in infants less than 3 months of age.

Recognising TB in very young infants is of paramount importance to prevent severe TB disease forms and complications. The nature of TB symptoms in infants, which are often non-specific and compatible with other childhood illnesses and which may even be absent, make diagnosis difficult. In infants the symptoms of TB may be acute, being present for days instead of weeks (chronic), particularly in infants less than 3 months of age.[4]
In our study cough was the most prominent presenting symptom, followed by loss of weight/failure to gain weight and fever. Cough is reported as the most common presenting symptom in the studies of infants less than 3 months of age by Schaaf et al and Del Rosal Rabes et al (described previously in the discussion).[7,8] Cough was also the most prominent symptom in a study by Goussard et al describing pulmonary TB in infants younger than 6 months requiring assisted ventilation.[29]

Classically, a combination of cough for more than 2 weeks duration, fever and documented weight loss/failure to gain weight are seen as important indicators of TB disease. However, in our study only 10% of infants presented with this combination of symptoms. Eighteen percent of the infants presented with cough for < 2 weeks, illustrating that in the less than 3-month age group presenting symptoms are commonly acute in nature. Our study supports the non-specific nature of the symptoms of tuberculosis in infants that has been repeatedly commented on in literature on childhood TB.[4,7,8,29,30] Any infant presenting with respiratory symptoms (acute or chronic) and/or failure to gain weight/loss of weight should be considered

for evaluation of TB especially in those areas where TB prevalence is high. Six percent of the infants in our study presented with chronic diarrhea. In areas of high TB prevalence, TB should be considered in the differential diagnosis of infants with chronic diarrhea.

In a review on the symptoms and signs of 75 infants with perinatal TB by Schaaf et al,[4] prematurity/low birth weight was reported as a common (>40%) occurrence. In our cohort, data was only available for 50% of the patients, of which 43% were premature (<37 weeks gestation) and 46% had low birth weight (<2,5kg).

Respiratory distress was the most common presenting sign of TB in our study, as has been reported in the limited literature on TB in infants.[4,7,8,30] Wheeze and, to a lesser extent stridor, were also common findings. Wheezing as a symptom of airway narrowing by mediastinal lymph nodes is documented in the literature. Schaaf et al. in their study found 13/38 (34%) infants younger than 3 months had wheezing as a respiratory sign, and 15/27 (56%) infants whose chest radiographs were evaluated had features of large airway obstruction.[7] A study by Goussard et al. describes 17 infants (median age of 4 months) who were admitted with respiratory failure due to TB to the paediatric intensive care unit of a tertiary hospital in the WCP of Cape Town, SA.[29] Not one of the 17 infants was suspected to have TB prior to referral for ventilatory support.[29] The most common presentations of respiratory failure in these infants were of large airway obstruction (10; 59%) and extensive alveolar disease (7; 41%).[29] The symptoms were non-specific. The most prominent presenting symptoms were cough (11; 65%), grunting and tachypnea (2; 12%), wheeze (3; 18%) and apnea (1; 6%).[29] Six infants in this study required transthoracic decompression of obstructing mediastinal lymph nodes.[29] Although this study focused on the outcomes of these infants referred for ventilation, it also highlights the severe forms of TB seen in young infants and the common finding of airway compression in this age group. As respiratory distress and wheezing occur as presenting symptoms in a number of infantile infections, there is a need for a high index of suspicion of lymphobronchial TB as a diagnosis in this age group.

In contrast to other reports of perinatal TB, peripheral lymphadenopathy was a clinical finding in only 6 infants. Less than 2% of peripheral lymphadenopathy associated with TB is generalised, the latter is mainly associated with miliary TB.

Hepatosplenomegaly was a common clinical finding in this study as in previous studies. Ascites is a common presenting sign in infants with congenital TB. In our study, ascites was a presenting sign in 7% of the infants under 3 months of age, all of who had congenital TB.

Pulmonary TB alone was the most common form of TB encountered in these infants. A significant proportion of the infants had intrathoracic as well as extrathoracic TB indicating a

more severe form of disease due to dissemination. A small number (4) had only extrapulmonary disease.

A transmission risk of 30-80% exists in infants in close contact with a source case with pulmonary TB. The risk is reported at 60-80% for AFB smear-positive cases, and 30-40% if the source case is AFB smear-negative.[31] Source cases were identified in 73% of infants presenting with symptoms and signs suggestive of TB. As reported by others, the mother was the contact in the majority of cases. A few infants however were receiving prophylaxis prior to admission, implying a delay in diagnosis of the source case or a failure to screen young exposed infants for TB in many cases. For the majority (81%) of source cases DST results were not known. Infants in contact with a drug-resistant TB source case are most likely to be infected with the same resistant TB strain. Knowing the source case strain's DST result allows treatment for infants diagnosed with TB to be tailored to the resistant strain from the outset, preventing possible worsening disease.[32] The management of infants exposed to and diagnosed with TB could be improved if DST results of source cases are known, especially in view of the large number of smear-negative cases amongst the childhood population. This will influence not only TB therapy for diseased infants, but also prophylaxis in the case of infants exposed to drug-resistant forms of TB.

The burden of TB disease is further adversely affected by the HIV epidemic, where TB is a leading killer, and also by various complex social (such as crowding and malnutrition) and economic factors that influence health and the delivery of health care. WHO statistics from 2012 showed that of the TB patients with known HIV status, approximately two thirds were HIV-infected.[3] The incidence rate for HIV-infected TB alone is 631/100 000 population, with a mortality rate of 168/100 000.[3]

In the era of HIV infection, the risk to infants for severe and disseminated forms of TB is increased even further. A study conducted in the WCP revealed a relative risk of 24 for culture-confirmed TB in HIV-infected infants when compared with HIV uninfected infants.[6,33] A large proportion (38%) of our infants were HIV exposed, and about 37% of these subsequently were confirmed to have HIV infection supporting the findings in the literature that HIV-infected and also HIV exposed infants have a higher risk of developing culture-confirmed TB. Two patients are known to have failed the PMTCT program, although the reasons are not clear from the data available.

Apart from immune compromise as seen in diseases such as HIV, immune immaturity related to young age plays an important role in the increased risk for infants to develop TB after infection, especially more severe and disseminated forms of the disease.

In infants TB is a disease in which immaturity of immune pathways leads to inappropriate inflammatory responses to infection.[9] An infant's immune system is shaped by the challenges it faces in the uterus and then subsequently by those to which it is exposed postnatally. The in utero environment restricts pro-inflammatory responses and prevents harmful immune reactions between the mother and fetus. Once the infant leaves this sterile environment however, it enters a world full of bacteria. As colonization with organisms occurs the infant's immune system must adapt to allow it.[9]

Vanden Driessche et al. describe key elements of the immune response to TB as well as the differences in activity seen in infants. Essentially, there is down regulation of immune responses in infants to allow for colonization with beneficial commensals.[9] Some examples of this include diminished chemotaxis and intracellular killing by macrophages, as well as neutrophils, reduced levels and production capacity of TNF, reduced levels of interleukins important in *M.tuberculosis* killing/growth arrest such as IL-1, 12 and 10, as well as differences in $CD4^+$ and $CD8^+$ T cell action.[9] The infant at this stage is thus vulnerable to various infections, including infection with *M. tuberculosis*.[9] Other factors such as BCG vaccination and environmental exposure to mycobacteria may also play a role in shaping the infant's immune system but data regarding this is limited.[9]

The WHO recommends that all infants who are HIV-infected receiver ART irrespective of clinical or immunological stage.[34] Initiation of ART in TB disease is recommended within 2 months of diagnosis of TB.[35] Although this recommendation only became part of the guidelines after the CHER study in 2007 that showed that antiretroviral therapy initiated before 12 weeks of age reduces early mortality in young HIV-infected infants,[36] the majority of the infants in our study were commenced on ART within 2 months of TB diagnosis.

The most common pattern of TB seen radiographically was mediastinal lymphadenopathy and airway compression, which was found in more than half of the patients. Hilar lymphadenopathy and both paratracheal and hilar lymphadenopathy combined, were the most commonly seen. This is similar to findings in a previous study of 38 infants less than 3 months of age, of which 27 chest radiographs were evaluated. 24/37 (88%) had mediastinal lymphadenopathy (majority had enlarged hilar lymph nodes) and 13 (48%) had large airway compression.[7] Findings from this study also reveal that air trapping was the commonest abnormality seen, and occurred in the region of the right lower and middle lobes.[7] Air trapping was only seen in 14% of the infants in our study and, in contrast to previous literature,[7] was seen more commonly in the left lung and bilaterally. Alveolar opacification was also common. This correlates with a previous study describing infants presenting with respiratory failure due to TB in infants less than 6 months of age.[29] Cavities were seen in 9 infants, a finding often only associated with adult type TB.[37] A large number of infants had miliary TB, representing a severe form of TB disease. It is important to note that miliary changes can evolve within days

and that a normal chest radiograph does not exclude miliary disease.[7] One infant presented with an empyema and one with an expansile pneumonia. Interestingly, almost half of the infants with airway compression also had chest radiographic features of pneumonia. Patients with airway compression together with features of pneumonia on chest radiography are more likely to have positive TB cultures. This is thought to be due to a higher bacillary yield in these patients.

Large airway compression by TB mediastinal lymph nodes in children is well described. In a proportion of children life-threatening airway obstruction can result.[25] More than half of the infants in this study had radiographic evidence of airway compression from mediastinal lymph nodes. Seventy-two percent of these infants had clinical signs of airway compression on presentation. One infant presented with a cardiorespiratory arrest. In a large prospective study by Goussard et al. looking at 250 infants and children with TB lymph node airway compression, decompression of lymph nodes was required in 34%.[25]

In our study, 54% with airway compression required surgical decompression. The factors that predisposes some children to have severe airway compression is unknown, but it is well documented that because of the size and compliance of the airways younger children present with more severe airway obstruction.[25,38] Goussard et al. report that 27% of patients required urgent decompression within 2 weeks of presentation due to life threatening compression.[17] In our study 4/21 infants requiring decompression (19%) required urgent decompression within 2 weeks. Complications reported by Goussard et al. related to surgery occurred in 8% of cases.[25] In our infants short-term surgery related complications occurred in 10% of cases. There were no reported serious complications (such as bronchus or vascular/nerve injuries which have been previously reported) or long-term complications. It is possible that this is due to the surgical technique used that does not involve removal of lymph nodes.[25]

In the study by Goussard et al the authors conclude that the best predictor for lymph node decompression was if the degree of compression of both the bronchus intermedius (BI) and the left main bronchus (LMB) was 75% or more, or if the trachea, LMB and BI were significantly compressed.[25] Lymph nodes that ulcerated into the airway did not predict for decompression, and the authors postulate that ulceration of the lymph node may cause spontaneous decompression.[25] In our study, LMB, BI and tracheal compression were the most common sites involved. Seven (33%) infants of those who had nodal decompression had LMB and BI obstruction greater than 75%. Five (24%) infants who had decompressions had compression of the LMB, BI as well as trachea. In a study by Lucas et al. looking at the CT features of children with lymphobronchial TB, the most common sites of airway compression were BI (75%), LMB (64%) and trachea (62%). This group and others have reported that subcarinal nodes are the ones that are most commonly enlarged on chest CT in children with pulmonary TB. This explains the findings of the BI and LMB being the most

commonly seen sites of compression.[39] In our study an equal number of infants had compression of BI when compared to LMB compression. This is in contrast to the findings in previous studies in children where BI is more frequently seen to be compressed when compared to the LMB. This finding may be explained by the increased compliance of the LMB in very young infants compared to older children.

There are varying reports of the mortality from TB at different ages. Before the advent of anti-TB therapy it varied from 55% in infants aged less than 6 months, to 30% in those aged 1-2 years.[40] Since the availability of anti-TB medication, deaths in infants less than 3 months are reported at 13%.[7] Deaths from congenital TB remain very high.[22] Fourteen percent of the infants in our study died before discharge, in keeping with death rates reported for this age group in 1993. This remains an unacceptably high mortality rate. Three of the infants who died had congenital TB, confirming that deaths from this form of TB are common. Two of the 3 infants, one a premature infant with low birth weight and the other a term infant with normal birth weight, presented with respiratory distress at birth requiring assisted ventilation. In these 2 infants TB as a cause for congenital pneumonia was not considered and both demised before the diagnosis of TB was made from culture of routine tracheal aspirates taken in the intensive care unit.

Wiseman et al, propose a framework for classifying the severity and spectrum of TB disease in childhood. This framework is to be used in combination with other risk factors such as HIV disease or other immune suppressive states, nutritional status and age.[20] According the proposed disease classification, expansile pneumonia, alveolar opacification, TB bronchopneumonia and cavitation are seen as severe disease as they represent local complications.[20] As summarized in table 2, a large number of infants had chest radiographic features that classify them as having severe TB disease. Airway compression by mediastinal lymph nodes is classified as severe disease.[20] More than half of the infants in the study had lymphobronchial TB. One infant had an empyema, which with or without acid-fast bacilli, represents a TB complication and is classified as severe disease.[20] All forms of central nervous system disease as well as miliary TB are severe, as they are due to haematogenous spread.[20] TB meningitis (including suspected cases) was found in 8%, and miliary TB was found in 20% of the infants less than 3 months. Solid organ TB and TB of the peritoneum is severe and reflects haematogenous spread, abdominal node rupture into the peritoneal cavity.[20] One infant in our study had proven hepatic TB after biopsy of the liver confirmed acid-fast bacilli.

This study has limitations. Firstly, this was a retrospective study; data relating to prematurity and birth weight was only available for 37/71 patients, and thus weight measurements as taken at admission do not account for this. Information on BCG immunization of the infants was not available thus not reported. Early HIV PCR's were not routinely done during the time

period of the study cohort, and therefore some patients with unknown HIV status may have been HIV-infected. For a significant number of the infants HIV exposure was not known. This information would have been important when considering the role of immune deficiency relating to exposure and the development of TB disease. Because our study only assessed infants with culture-confirmed TB who presented to a provincial referral hospital in the WCP, results may have been biased by selection of a group of infants who most likely have more severe TB disease at presentation. Lastly, data regarding long-term follow up of the infants was only obtained for about half of the patients. Although all but 10 of the patients survived until discharge from the tertiary institute, only data from 33 of them could be found confirming they were alive and well in the long-term.

Conclusions

Tuberculosis remains an important and serious disease affecting all age groups. In countries with high incidences of TB and HIV, children represent a particularly vulnerable group. Data in infants younger than 3 months of age with TB disease is lacking and to our knowledge this is the largest cohort describing TB within this age group. Young infants are at highest risk to develop TB disease after infection and the morbidity and mortality remains high. Recognizing disease in infants less than 3 months of age is difficult and requires a high index of suspicion, as symptoms may be absent or non-specific for TB. These young infants are at risk of more severe disease forms, particularly pulmonary disease, as evidenced by the large number of infants in the study with in particular airway compression, which may be potentially life threatening. Disseminated forms of TB, including miliary TB and TB meningitis are frequent in infants in this age group. Drug-resistant TB is an escalating challenge in the management of TB. Recognizing TB disease in young infants and early diagnosis of source cases together with drug susceptibility testing is necessary to decrease morbidity and mortality. Congenital TB is considered to be uncommon, but this fact has been challenged in the literature as many cases are misdiagnosed or not reported. Infants who are HIV infected and HIV exposed but uninfected have a higher risk of developing TB.

Table 1. Demographic and clinical characteristics of infants less than 3 months (91 days) with culture confirmed TB between 1 March 2003 and 30 June 2011 (n=71)

Characteristics	n (%)	Median	Interquartile Range
Age (days)		69 days	40-79,75 days
Male	43 (61)		
Weight		3,95 kg	2,75-4,55 kg
Weight <3rd centile (weight-for-age)	26 (37)		
Gestational age < 37 weeks; Birth weight < 2,5kg (n=37)*1	16 (43)		
Gestational age > 37 weeks; Birth weight < than 2,5kg (n=37)*1	1 (3)		
Types of TB*2:			
Pulmonary TB	44 (62)		
Extrapulmonary TB	4 (6)		
Pulmonary TB + Extrapulmonary TB	22 (31)		
Sites of Extrapulmonary TB (>1 in some patients): (n=26)			
Miliary	14 (54)		
Abdominal	12 (46)		
Peripheral lymphadenopathy	6 (23)		
TB meningitis confirmed	2 (3)		
TB meningitis suspected	4 (6)		
Other (1 skin, 1 bacteremia, 1 empyema)	3 (4)		
TB drug susceptibility results:			
Drug susceptible	66 (93)		
Isoniazid resistant	3 (4)		
Rifampicin resistant	2 (3)		
Source cases identified:	52 (73)		
Drug susceptible	9 (17)		
Drug resistant	1 (2)		
Unknown resistance	42 (81)		
Mother as source case	32 (62)		
HIV status:			
Infected	10 (14)		
Uninfected	59 (83)		
Unknown	2 (3)		

Exposed • PMTCT • PMTCT unknown Unexposed Exposure unknown	27 (38) 14 (52) 13 (48) 25 (35) 19 (27)		
Antiretroviral therapy: (n=10) After diagnosis of TB Unknown	 9 (90) 1 (10)		
Tuberculin skin tests performed*[3]: Reactive	44 28 (66)		
Preventative TB therapy prior to admission	4 (6)		
Presenting symptoms (some patients >1): Loss of weight/failure to gain weight Cough >2 weeks Fever Cough <2 weeks Night sweats Chronic diarrhea Vomiting Hemoptysis Convulsion Cough + fever + loss of weight	 29 (41) 28 (39) 24 (34) 13 (18) 5 (7) 4 (6) 2 (3) 1 (1) 1 (1) 7 (10)		
Presenting signs (some patients >1): Respiratory distress Wheeze Hepatosplenomegaly Stridor Abdominal distension Peripheral lymphadenopathy Ascites Jaundice Apnea Cardio-respiratory arrest Neurological (meningism, bulging fontanel)	 18 (25) 15 (21) 14 (20) 6 (8) 6 (8) 6 (8) 5 (7) 5 (7) 3 (4) 1 (1) 1 (1)		

<u>Patient outcomes:</u> Deaths before discharge Alive at discharge Number of patients well ≥6 months after discharge (n=61) Admission to TB hospital for inpatient treatment Treatment completion confirmed Recurrence of TB confirmed Recurrence of TB suspected	 10 (14) 61 (86) 33 (54) 6 (8) 24 (34) 1 (1) 2 (3)		
*1 gestational age and birth weight data available for 37/71 patients *2 1 patient was infected withTB *3 2 patients had 2 tuberculin skin tests performed			

TB, tuberculosis; HIV, human immunodeficiency virus; PMTCT, Prevention of Mother to Child Transmission

Table 2. Chest radiographic characteristics of infants less than 3 months (91 days) with culture confirmed TB between 1 March 2003 and 30 June 2011 (n=71)

Characteristics (some patients had more than 1 characteristic)	n (%)
Normal	7 (10)
Airway compression	39 (55)
Mediastinal lymphadenopathy (n=39)	39 (55)
• Paratracheal • Perihilar • Both	4 (10) 18 (46) 17 (44)
Alveolar opacification	38 (54)
Miliary	14 (20)
Air trapping (n=10)	10 (14)
• Right lung • Left lung • Bilateral	2 (20) 4 (40) 4 (40)
Bronchopneumonic opacification	9 (13)
Cavities	9 (13)
Pleural effusion	6 (8)
Collapse	4 (6)
Ghon focus	4 (6)
Expansile pneumonia	1 (1)
Pneumonia alone	18 (25)
Airway compression alone	5 (7)
Airway compression + pneumonia	34 (48)

Table 3. Characteristics of infants less than 3 months with culture confirmed TB between 1 March 2003 and 30 June 2011, who were found to have airway compression on chest radiography (n=39)

Characteristic	n (%)
Clinical signs of airway compression	28 (72)
Imaging:	
Chest radiographs	39 (100)
Chest CT scans	26 (67)
Bronchoscopy:	
Number of patients	21 (54)
Sites of compression (some patients > 1 site):	
• RMB	1 (5)
• LMB	19 (90)
• BI	19 (90)
• Trachea	13 (62)
• Extra-luminal compression	21 (100)
• Gland ruptured into airway	7 (33)
Complications	1 (5)
Follow up bronchoscopy	16 (76)
Lymph node decompression:	
Number of patients	21 (54)
Ventilation before decompression	9 (43)
Ventilation after decompression	14 (67)
Complications	2 (10)
Glucocorticosteroids in addition to TB treatment:	
Yes	27 (69)
No	8 (21)
Unknown	4 (10)
TB resistance:	3 (8)
Isoniazid resistance	2 (67)
Rifampicin resistance	1 (33)
HIV-infected	4 (10)
Deaths (unrelated to bronchoscopy/lymph node decompression)	3 (8)

CT, computed tomography; RMB, right main bronchus; LMB, left main bronchus; BI, bronchus intermedius; TB, tuberculosis; HIV, human immunodeficiency virus

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