Tuberculosis in South and Central Africa

Understanding epidemiology - Improving diagnosis and management

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Chapter 11

Summary, Conclusion and Future Perspectives
SUMMARY AND CONCLUSIONS

In this thesis epidemiologic, diagnostic and management aspects of tuberculosis were studied in two African countries where tuberculosis accounts for considerable morbidity and mortality. At the time of research only few retrospective reports and WHO estimates were available on tuberculosis control in Gabon and systematic data were urgently needed as a basis for targeted improvement of diagnosis and management of tuberculosis. The research on tuberculosis epidemiology in Gabon collated the first systematic data on local epidemiology including HIV-coinfection, childhood tuberculosis, drug resistant tuberculosis, and treatment outcome. The work in South Africa retrospectively and prospectively assessed extrapulmonary tuberculosis in children by means of ultrasound, thereby at the time providing epidemiologic data on extra-pulmonary tuberculosis in children and evaluating point-of-care ultrasound as novel tool for improving diagnosis of childhood tuberculosis. The hypothesis was that a considerable number of children would have features of extra-pulmonary tuberculosis and that point-of-care ultrasound would be a valuable tool to improve timely diagnosis of childhood tuberculosis. The studies on caregivers’ practices for treatment of childhood tuberculosis in South Africa, on availability of antituberculosis first-line and second-line drugs in Gabon, and the review on bedaquiline as a novel drug for drug resistant tuberculosis explored important issues for tuberculosis management.

In Section I of this thesis two studies that contributed to a better understanding of local tuberculosis epidemiology in Lambaréné, Gabon, were described. In chapter 2 data from a one year retrospective evaluation of the paediatric tuberculosis register from the Albert Schweitzer Hospital in Lambaréné was presented. Due to the small sample size and the retrospective study design these data were limited in their generalizability. However, these data from 62 paediatric cases constituted the first published data on childhood tuberculosis from this geographic area and identified major deficiencies in tuberculosis management and control. Most importantly, in children with tuberculosis HIV status was not systematically assessed for, microbiological confirmation was not strived for, treatment completion rate was low, and loss to follow-up and mortality rates were high.

In chapter 3 findings of a prospective cohort study on 201 tuberculosis patients diagnosed and cared for in Lambaréné were described. This study, the first of that kind in the country, revealed that the 42% tuberculosis/HIV co-infection was higher than estimated and unfortunately compatible with a virtually absent integrated tuberculosis/HIV care. Furthermore, this study provided the first data on drug resistance showing that multi-drug resistant tuberculosis was present in 31% of retreatment cases and thereby a threatening reality in that region. Moreover, this study documented an unacceptably low treatment success rate of 53% and unacceptably high mortality rate of 25% in tuberculosis/HIV co-infected patients.
Section II of this thesis focused on improving diagnosis of tuberculosis disease in children. Children are more susceptible to develop disseminated forms of tuberculosis disease and extra-pulmonary tuberculosis is more common than in adults. In chapter 4 sonographic features of abdominal tuberculosis in 102 children with pulmonary tuberculosis who underwent abdominal ultrasound were evaluated. The study found that many children with pulmonary tuberculosis had abdominal lymphadenopathy and splenic microabscesses on ultrasound, both sonographic features compatible with tuberculosis. In terms of possible additive value of ultrasound in the diagnostic work-up of childhood tuberculosis the study found that 13 (40%) of the 32 children with microbiologically unconfirmed tuberculosis and with a chest x ray not suggestive or inconclusive for tuberculosis, had sonographic abdominal lymphadenopathy and/or splenic microabscesses supporting the diagnosis of tuberculosis. A further finding of this study was the significant association of splenic microabscesses with HIV infection. Findings of this study supported the hypothesis of a prospective study that point-of-care ultrasound is a useful additional tool for diagnosis of tuberculosis in children. The findings also have implications for treatment, as extrapulmonary tuberculosis should be treated with four drugs rather than three, which is recommended for uncomplicated pulmonary tuberculosis.

Chapter 5 is a contribution to a “minisymposium” entitled “Outreach in pediatric radiology” published by the journal “Pediatric Radiology” in 2014 comprising commentaries from paediatric radiologists engaged in imaging outreach activities in resource sparse settings. The challenges for diagnosing childhood tuberculosis were summarized, the experiences of point-of-care ultrasound for diagnosis of extra-pulmonary tuberculosis in adults were outlined, and the potential perspectives and research questions for point-of-care ultrasound in children with tuberculosis were discussed.

Chapter 6 was published as editorial in the South African Medical Journal. The editorial highlighted the different new imaging approaches for improving diagnosis of childhood tuberculosis. Besides delineating the potential benefits of focused sonography in children, mediastinal ultrasound for detection of tuberculosis related mediastinal lymphadenopathy in children was highlighted, and, a novel limited MRI protocol under investigation for intrathoracic tuberculosis was described. The potential for teleradiology was also addressed.

The experiences and findings of the prospective study investigating a focused ultrasound protocol for extrapulmonary tuberculosis in 232 children with presumptive pulmonary tuberculosis were presented in chapter 7. Children presenting with suspected pulmonary tuberculosis at a tertiary care hospital in Cape Town, South Africa, and enrolled in an ongoing larger diagnostic cohort study evaluating novel tuberculosis diagnostic tools underwent point-of-care ultrasound at presentation and at follow-up. In this cohort, comprising 17% HIV-infected children, we found that children
with confirmed or unconfirmed tuberculosis had a higher prevalence of sonographic features of extrapulmonary tuberculosis than children with unlikely tuberculosis. Abdominal lymphadenopathy and splenic microabscesses were both more likely in children with HIV-infection, but only splenic microabscesses correlated significantly with tuberculosis disease. In children without treatment issues sonographic findings had mostly resolved three month after treatment initiation; in contrast, in children with sonographic features persisting beyond three months after treatment initiation inappropriate tuberculosis treatment was predominantly identified. Compliance with beside ultrasound examination and visualization of the upper abdomen was good for most children. In summary, this was the first study evaluating point-of-care ultrasound for extrapulmonary tuberculosis in children and a high prevalence of sonographic features compatible with extrapulmonary tuberculosis in HIV-infected and HIV-uninfected children was found. Although an overall positive point-of-care ultrasound was associated with tuberculosis, most individual sonographic features were not associated with tuberculosis. In summary, bedside ultrasound was feasible and detected sonographic features compatible with tuberculosis in many children, interpretation of ultrasound findings at presentation must be made critically, and sonographic follow-up appears useful to assess treatment response.

Studies presented in Section III of this thesis addressed potential targets for improving treatment-related management of tuberculosis. During the early phase of tuberculosis research in Gabon presented in chapter 3 health care staff was repeatedly told by tuberculosis patients that drug stock forced them to interrupt tuberculosis treatment or to buy tuberculosis drugs out of their pockets. Also, tuberculosis patients in need for second-line drugs were faced by the absence of an institutional infrastructure providing drugs for drug-resistant tuberculosis. This prompted a survey on availability of and access to antituberculous drugs in Gabon of which the results are presented in chapter 8. Through semi-structured interviews drug shop vendors, pharmacists and health care workers confirmed stock outs of first-line tuberculosis drugs and the need of tuberculosis patients to purchase their tuberculosis treatment. All health care workers interviewed knew patients in need of second-line tuberculosis medication but in the private sector only a small selection of drugs with second-line antituberculous activity was available for purchase.

Drug resistant tuberculosis is of particular concern within the ongoing efforts on tuberculosis control. Access to diagnostic and treatment infrastructure is still often poor in many settings and for a long time new antituberculous drug candidates fell through clinical development. In chapter 9 a comprehensive review on bedaquiline, a novel drug for multidrug resistant tuberculosis, was presented. Bedaquiline had received fast-track approval by the US FDA in 2012 and by the European Commission in 2014. The review includes preclinical and clinical development data as well as early
experiences of compassionate use/early access which had not been reviewed before. Until that time several case series on a total of 45 patients receiving bedaquiline for compassionate use had been published. Overall compassionate use of bedaquiline showed high efficacy in patients with a broad variety of pre-medication history and did not show any new safety concerns. The review concluded that bedaquiline is highly efficacious in the treatment of multidrug resistant tuberculosis, that clinical experience was still limited warranting data from extended Phase III and IV studies, and that its use must be guided carefully to preserve its unique benefits.

Compliant intake of antituberculous regimen over six months is challenging even in adults, but is particularly challenging in pediatric patients as they are dependent on their caregiver for regular administration. Furthermore unavailability of paediatric fixed-drug combinations as well as child-friendly formulations and regimen increase the risk for inadequate antituberculous treatment in children. In chapter 10 the results of a prospective survey among caregivers of 253 children treated for tuberculosis were described, to better understand caregivers’ practices and preceptions on treatment of childhood tuberculosis. Several issues with treatment were identified; administration of tuberculosis drugs differed substantially from recommended practice, children were not weighed so that dosage could be adjusted, most caregivers crushed, dissolved or mixed tablets with beverages or food, and medication was given after meals – all potentially contributing to sub-therapeutic drug levels.

In summary, work of this thesis focusing on investigation of local tuberculosis epidemiology in Gabon, a country ranking among the top ten countries on the WHO ranking list for tuberculosis incidence, found low successful tuberculosis treatment outcome, high mortality in HIV-coinfected tuberculosis patients, and prevalent multi-drug resistant tuberculosis in re-treatment patients. The studies were performed as part of the activities for establishing a tuberculosis laboratory and clinical platform to address research questions and to improve routine tuberculosis diagnostic and treatment capacity. The research contributed to reduce the knowledge gap on tuberculosis epidemiology and care on the ground and formed the basis to understand local tuberculosis control needs and to improve local tuberculosis care and national tuberculosis care.

In conclusion, work of this thesis focusing on improving tuberculosis diagnosis and care in children found that clinician performed bedside ultrasound was a useful and feasible imaging approach during the diagnostic work-up and during follow-up of children with presumptive pulmonary tuberculosis and that tuberculosis treatment practice differed substantially from recommendations in South Africa. Findings of the studies suggested that point-of-care ultrasound could contribute to timely diagnosis of childhood tuberculosis and to monitoring treatment response and that caregivers’ treatment administration practices could be optimized.
Impact of this research and perspectives for future work

The scientific tuberculosis work in Lambaréné, including the studies of this thesis, exemplifies successful development of tuberculosis diagnostic and treatment capacity in a Central African country, demonstrating that nuclei of capacity development can make a difference on a larger, even country-wide scale.

Since the conduct of the studies in Gabon special attention has been directed at establishing a strong collaboration with the Gabonese Ministry of Health to promote uptake of tuberculosis epidemiology data and provide expert mentorship to the National Tuberculosis Program. The endeavors proved instrumental for the fruitful elaboration of a Global Fund Tuberculosis concept note and for a temporary designation of the tuberculosis laboratory in Lambaréné as reference laboratory until set-up and transition to national partners (Massinga-Loembe et al. publication in preparation). In 2016, the tuberculosis laboratory in Lambaréné was granted the status of privately owned public utility by the Gabonese state; a partnership model which contributed to increase Gabon’s attractiveness for international donors, accelerating the national tuberculosis control agenda (Massinga-Loembe et al. publication in preparation).

Furthermore, in the field molecular analyses including samples from our study revealed that almost three quarter of the local multidrug resistant strains grouped into one cluster of strains. To break the chain of transmission of that outbreak strain and prevent further spreading, a molecular test assay to rapidly identify patients infected with the outbreak strain was implemented (Massinga-Loembe et al. publication in preparation). Also the tuberculosis laboratory infrastructure supported setting up of multidrug resistant tuberculosis management units within national hospitals, piloting a short duration regimen in line with the recent WHO endorsement (Massinga-Loembe et al. publication in preparation). Preliminary local data from the first patients treated for multidrug resistant tuberculosis in Lambaréné indicate that a 9-month regimen leads to sustained clinical improvement and culture negativity; however, cost and logistical hurdles remain high and challenging (Massinga-Loembe et al. publication in preparation).

Besides the continuous evaluation and improvement of tuberculosis care and control, perspectives for future tuberculosis work in Gabon include further investigations of local particularities that may impact local tuberculosis control. In Gabon parasitic diseases are highly prevalent and parasitic diseases have been reported to impact on tuberculosis immune response in co-infected patients [71]; studies evaluating parasitic co-infections in tuberculosis patients in Gabon and the possible effects of antiparasitic treatment on tuberculosis outcome are warranted. Studies on interactions of tuberculosis and other local risk factors, such as diabetes mellitus or substance use, have not yet been conducted in Gabon but could crucially impact on tuberculosis control. The Gabonese population is a particularly mobile population and travelling...
during antituberculous treatment can considerably affect treatment adherence and follow-up. Therefore, development of treatment distribution and follow-up strategies adapted to local population characteristics are urgently needed. We saw that tuberculosis patients presented late implying long periods of infectiousness before treatment initiation; optimal approaches to improve early case detection are yet to be developed. Last but not least particularly challenging forms of tuberculosis such as microbiology negative, HIV-associated and extrapulmonary tuberculosis appear to be underdiagnosed in the resource-limited setting of Lambaréné; diagnostic algorithms, e.g. including point-of-care sonography, are to be set-up to enhance timely diagnosis and treatment. Beyond locally centred aspects of tuberculosis control also investigations that contribute to improvement of overall tuberculosis control such as conduct of diagnostic or clinical trials assessing novel diagnostic tools, drug or vaccine candidates, or regimens should be increasingly on the agenda.

In the light of the increasing appreciation and deployment of point-of-care ultrasound applications in adult and paediatric patients, the findings of our paediatric ultrasound studies in childhood tuberculosis constitute first guidance on how to interprete and use sonographic features within a diagnostic tuberculosis work-up in children. However, the studies constitute a starting point for the evidence-based use of bedside ultrasound in childhood tuberculosis and many questions remain that require further investigation. These include the performance of point-of-care ultrasound in further cohorts including children that present at the primary care level where diagnostic infrastructure is most limited and including children that are suspected of any form of tuberculosis and in- and outpatient settings. The optimal placement of point-of-care ultrasound within a diagnostic tuberculosis workup needs to be defined to maximize sensitivity and specific. A modification and simplification of the point-of-care protocol to include scans with a high yield should also be considered and evaluated. Last but not least, implementation studies need to define the optimal training and roll out strategies to broaden access to qualitative point-of-care ultrasound for children presenting with presumptive tuberculosis. As interpretation of sonographic findings depends also on local tuberculosis prevalence, utility point-of-care ultrasound for children in epidemiologic settings where tuberculosis is less prevalent also needs investigation before deployment. Furthermore, other point-of-care ultrasound protocols assessing other aspects of childhood tuberculosis, i.e. mediastinal sonography [72] or lung ultrasound in children with presumptive tuberculosis (Heuvelings et al. manuscript submitted for publication), could also contribute to improve time diagnosis of childhood tuberculosis.
REFERENCES
