Diagnosis and treatment of common infectious diseases in severely ill sub-Saharan African patients
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Chapter 8

Summary and concluding remarks
Summary

Chapter 2 In this cross-sectional study of medical records, we studied the hospital tuberculosis (TB) diagnostic process for adult patients with presumptive TB to investigate whether it matched with the 2007 WHO recommendations for the diagnosis and treatment of smear-negative pulmonary and extra-pulmonary TB in HIV prevalent and resource-poor settings. The results clearly show that recommended basic steps in this process were lacking for a large majority of patients with presumptive TB, and that for very few patients with presumptive TB a TB diagnosis was confirmed. One of the most important findings was that sputum smear microscopy was requested for only 93/234 (40%) patients with presumptive TB, and that only 59/234 (25%) actually received a result, of which 8/59 (14%) had a positive result. Out of the 8 patients with a positive result, only 6 patients received TB treatment. Seventy patients with presumptive TB (30%) died during hospital stay. As there are reports from other SSA countries reporting on similar flaws in the TB diagnostic process, this is clearly a problem that is neither limited to one hospital, nor to one country.

In Chapter 3 we investigated S. pneumoniae susceptibility to penicillin, erythromycin and co-trimoxazole in an adult patient population with pneumococcal pneumonia. In a cross-sectional setup, we collected sputum samples for culture and susceptibility testing from patients presenting in the hospital with pneumococcal pneumonia. Diagnosis was made on the basis of a combination of clinical symptoms, chest radiography, presence of pneumococcal antigens in urine and sputum culture. Forty-one patients with a probable or definitive diagnosis rendered 15 pneumococcal strains with susceptibility results assessed by disc diffusion as well as e-test. Twenty percent of these strains (3/15) had an MIC >0.5 mg/L (0.75 mg/L) for penicillin. Co-trimoxazole resistance, as measured by disc diffusion, was found in 7/16 (44%) of pneumococcal strains and all strains were susceptible to erythromycin.

Chapter 4 Based on data from non-SSA intensive care unit (ICU) patients with sepsis, one could hypothesize that non-ICU severely ill patients in SSA hospitals, a large proportion of which is thought to suffer from severe infection or sepsis, could be at risk for changes in the pharmacokinetics of antibiotic drugs. Such changes could potentially lead to underexposure to antibiotics and the emergence of antimicrobial resistance, something which can be detrimental to an individual patient’s health as well as public health. β-lactams are vulnerable to such pharmacokinetic changes, as they are hydrophilic drugs with predominant renal clearance. In preparation of a large population pharmacokinetic study among non-ICU, severely ill SSA hospitalized patients, we performed a systematic review screening different databases for the presence of studies focusing on the
pharmacokinetics of antibiotics in SSA adult patients. We could include only 12 studies, addressing six different classes of antibiotics. Only one study dealt with pharmacokinetics of a β-lactam antibiotic drug, namely ertapenem. A majority (9/12) studies originated from South Africa, and within this selection, six had investigated ICU patients. Four studies, including the one on ertapenem, reported the occurrence of inappropriately low plasma concentrations in the presence of a large volume of distribution. The quality of most selected studies was low. We concluded that there is a severe lack of adult clinical pharmacokinetic SSA data on antibiotics and that studies on β-lactams are especially needed.

**Chapter 5** In this chapter we describe the first part of a larger population pharmacokinetic (PPK) study of antibiotics, investigating the variability and its sources of the pharmacokinetics of the β-lactam ceftriaxone in a severely ill adult SSA hospital population. Ceftriaxone is a broad-spectrum antibiotic drug that is often used for the empiric treatment of severe infection and sepsis. We built a PPK model based on observed unbound and total plasma concentrations of 88 patients and simulated unbound ceftriaxone time-concentration profiles for different patient and dosing scenarios so that probabilities of pharmacodynamic target attainment could be estimated. The binding of ceftriaxone to albumin followed a non-linear pattern and patient’s creatinine clearance was the main source of unbound ceftriaxone pharmacokinetic variability. The simulations implied that patients are at substantial risk for underexposure to unbound ceftriaxone when using the commonly used 1g twice-daily ceftriaxone regimen, especially when applying the increasingly recommended, more stringent pharmacodynamic targets for severely ill/septic patients, and when their kidney function is intact. The use of a 2 g once-daily regimen was projected to lead to an even higher risk of underexposure.

**Chapter 6** This chapter contains the second part of the PPK study on antibiotics, investigating the pharmacokinetics of benzylpenicillin, a small-spectrum β-lactam antibiotic that is most frequently used for the treatment of pneumococcal disease. This time, we built a PPK model based on observed total plasma concentrations from 112 severely ill hospital patients, and simulated unbound time-concentration profiles using an estimate of the unbound benzylpenicillin fraction based on a random sample of unbound concentrations. Also for benzylpenicillin, creatinine clearance turned out to be the main source of pharmacokinetic variability. The simulations demonstrated that the patients in our study population are at high risk for underexposure to unbound benzylpenicillin when using commonly prescribed dosing regimens, such as 3 million IU four times daily, especially when the causative agent has intermediate susceptibility for benzylpenicillin. Again, the risk was higher for patients with a normal kidney function. Applying the stringent pharmacodynamic
targets for severely ill/septic patients, where the unbound plasma concentration needs to stay above the minimal inhibitory concentration throughout the dosing interval, rendered low probabilities of pharmacodynamic target attainment. Based on these outcomes, we suggested that in situations where a microbiological diagnosis cannot be made, where continuous drug infusion is not feasible, and local patient population factors and health care system restraints. Although substantial inadequacies found in our studies are likely to be explained by a combination of infectious diseases in a hospital setting in Mozambique are inadequate. The interval, rendered low probabilities of pharmacodynamic target attainment. Based this thesis illustrates that important aspects of diagnosis and treatment of common paracetamol, and that for a large group of severely ill SSA patients the paracetamol prescription, and an estimated high prevalence of renal and kidney dysfunction. We selected 76 patients who were already participating in the PPK study on antibiotics and had 225 plasma concentration samples at our disposal. There were no toxic concentrations, but we did find the large majority of plasma concentrations to be sub-therapeutic or below the level of quantification. We concluded that routine oral dosing practices are likely to lead to underexposure to paracetamol, and that for a large group of severely ill SSA patients the paracetamol palliative goals are probably not attained. We suppose that our findings can be explained by a combination of altered pharmacokinetics and shortcomings in the efficiency of oral drug dispensing procedures.

Chapter 7 In this chapter, we report population plasma concentration data of paracetamol in an effort to get an idea of the occurrence of therapeutic, sub-therapeutic and toxic plasma concentrations in severely ill patients with an oral paracetamol prescription, and an estimated high prevalence of renal and kidney dysfunction. We selected 76 patients who were already participating in the PPK study on antibiotics and had 225 plasma concentration samples at our disposal. There were no toxic concentrations, but we did find the large majority of plasma concentrations to be sub-therapeutic or below the level of quantification. We concluded that routine oral dosing practices are likely to lead to underexposure to paracetamol, and that for a large group of severely ill SSA patients the paracetamol palliative goals are probably not attained. We suppose that our findings can be explained by a combination of altered pharmacokinetics and shortcomings in the efficiency of oral drug dispensing procedures.

Concluding remarks
This thesis illustrates that important aspects of diagnosis and treatment of common infectious diseases in a hospital setting in Mozambique are inadequate. The inadequacies found in our studies are likely to be explained by a combination of patient population factors and health care system restraints. Although substantial differences may exist between hospitals and between countries, studies from other SSA low-income countries with colliding HIV and TB epidemics have shown that the sort of inadequacies we observed are neither unique to one hospital, nor to one country. The study results and the underlying issues raised provide starting points for change and ideas for further research.

The tuberculosis diagnostic trajectory
Our study showed that the implementation of a seemingly simple WHO algorithm concerning the estimated most important cause of hospital morbidity and mortality, failed, even though the recommended necessary testing infrastructure was available. Although our study did not specifically look into the reasons behind the unsuccessful implementation, we can conclude from our study’s results that a large part of the explanation lies in the flawed first steps of the diagnostic trajectory,
namely the requesting and reporting of locally available microbiological tests and their results. In circumstances with a continuous high influx of severely ill patients, diagnostic tests are still largely depending on the collection of relatively hard to retrieve bodily materials such as sputum, pleural fluid and lymph node aspirates, for which both a health care worker’s time and dedicated effort, as well as a patient’s close cooperation are needed.

Another conclusion is that chest-radiograph results, even when suggestive of active TB, do not seem to influence TB diagnosis and treatment decision-making in circumstances where there is no microbiologically confirmed diagnosis. Chest radiography is also a labour intensive procedure, as severely ill patients usually need to be transported to the radiology department and subsequently instructed and moved into position. Apart from the practical infrastructural issues with chest radiography, the interpretation of chest radiography results is subject to a high intra- and inter-reader variability, while the WHO guideline recommendations fail to clearly state what is, and what is not likely to be consistent with active TB. The same guideline also provides little guidance on how to approach a patient with presumptive extra-pulmonary TB. It is our experience that knowledge about the epidemiology and diagnostics of extra-pulmonary TB among health care workers is poor.

Over the last decade, new TB diagnostic techniques, such as nucleic acid amplification with Xpert® MTB/RIF assays, and the point of care detection of lipoarabinomannan in urine, have started to offer the possibility of a more rapid TB diagnosis with increased sensitivity and specificity. The former is mostly used as an ‘add-on’ diagnostic test. The latter urine-based technique seems to be lacking sensitivity for routine clinical use. Both tests continue to depend on relatively labour intensive collection of bodily material. Interestingly, a recent evaluation of Xpert MTB/RIF implementation data from 18 countries showed that the utilization of this assay is still low, even though most participating countries and sites had access to the test.

Our study is not the only SSA study to find substantial flaws in the implementation of a hospital TB diagnostic trajectory, which suggests a set of explanations that is strongly related to local restraints. In view of the above, we suppose that the difficulties involved in the implementation of a TB diagnostic guideline may lie in a combined lack of appropriate health care worker knowledge and motivation, and limited practical feasibility of guideline recommendations, despite the fact that they were specifically designed for use in resource constrained settings with a high HIV prevalence. We therefore recommend placing more emphasis on sustained training.
and supervision efforts of health care workers, as well as on continuous re-evaluation of guideline feasibility and of the effectiveness of implementation strategies. Taking a high patient load as well as a supposed current sub-standard level of knowledge and skills among health care workers into account, ideally, guideline recommendations would consist of a series of easy and unambiguous clinical steps that leave little room for doubt.

Supported by work from other researchers, we want to make a plea for local capacity building for front-end operational research, where the focus lies on how policy change affects daily clinical practice and patient outcome on the SSA hospital work floor. Such research should ideally also look into how different hospital staff communicate and collaborate when caring for patients.

**Antibiotic dosing and antimicrobial resistance**

Antimicrobial resistance is increasing worldwide, and SSA is certainly no exception in this respect, although existing data from the region, including data concerning the susceptibility of common pathogens are scarce. Existing data do however appear to draw a picture of the presence of antimicrobial resistance across the region, affecting a wide array of pathogens commonly causing febrile disease. At the same time, it is becoming increasingly clear that proper antibiotic dosing is not only important from a patient’s perspective, but also from a public health perspective, as inappropriate dosing may facilitate the emergence of antimicrobial resistance. Inappropriate dosing is more likely to happen when disease induced pharmacokinetic changes occur that influence a patient’s antibiotic exposure.

SSA is in a particularly difficult position, as there is a scarcity of antimicrobial resistance and antibiotic pharmacokinetic data, in the presence of a large patient population potentially at high risk for disease-induced pharmacokinetic changes. Our PPK studies’ results confirm that this is a true cause for concern, and that further action needs to be taken to improve patient care and to preserve existing commonly used antibiotics for use. We feel that more PK data are needed for different SSA hospital settings and that clinical trials should be performed in the SSA context that would look at the probability of target attainment with different dosing regimens. Such trials would best be performed using locally derived MICs of the pathogens most frequently causing febrile disease, such as *S. pneumoniae*, *E. coli* and non-typhoidal salmonellae. In the meantime, we do not recommend using a 2 g once daily ceftriaxone-dosing regimen. As for the small-spectrum β-lactam benzylpenicillin, the appropriateness of use for severely ill patients in a SSA hospital setting, with and without a microbiological diagnosis should become a topic for discussion among health professionals and policy makers.
Paracetamol plasma concentrations
In any hospital around the world, paracetamol is probably one of the most frequently prescribed drugs, if not THE most frequently prescribed one. The second largest hospital in Mozambique is probably no different in that respect, as there is a high density of patients that could potentially benefit from pain and fever reduction. We recommend to evaluate hospital oral drug dispensing procedures and the actual ingestion of tablets by patients, as erroneous oral drug dispensing and a severely ill patient’s limited capacity to actually ingest a tablet without help may have contributed to the alarmingly low plasma concentrations observed. At the same time, position induced delayed oral drug absorption and severe disease driven changes in systemic drug distribution should be investigated as well through PK studies. Getting more clarity about the background of our findings and acting accordingly may not only have positive consequences for the degree of palliation with paracetamol, but also for the probability of plasma target attainment of the frequently prescribed oral fixed dose drug combination for the treatment of tuberculosis.

HIV
This thesis did not look into HIV infection as such, but it is clear that for the patient population described in this thesis, all of the above will only make sense if a concerted, interdisciplinary, motivated and sustained effort is made to link all HIV infected people to care, to put them on antiretroviral treatment and keep them on it. We are together. Estamos juntos.
References


