Diagnosis and treatment of common infectious diseases in severely ill sub-Saharan African patients
Bos, J.C.

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Chapter 4

Pharmacokinetics of antibiotics in sub-Saharan African patient populations: a systematic review

Bos JC, van Hest RM, Prins JM

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Abstract

**Background** In sub-Saharan Africa (SSA), severe febrile illness accounts for a large majority of medical admissions. SSA patients may also suffer from cachexia and organ dysfunction resulting from tuberculosis, hepatitis B and hypertension. It is hard to tell how these conditions influence the pharmacokinetics (PK) of antibiotics in this population. The aim of this systematic review was to summarize antibiotic PK data of SSA adult patient populations in order to clarify whether inappropriate drug concentrations, which may also lead to antimicrobial resistance, are likely to occur.

**Methods** An electronic search was conducted in Ovid MEDLINE, Embase and the African Index Medicus collecting studies from 1946 to May 2016. Reviewers independently selected studies reporting outcome data on volume of distribution (V), clearance and half-life. Relevant information was abstracted and quality assessed.

**Results** Twelve studies were selected, addressing 6 antibiotic classes. There were 6 studies on fluoroquinolones and 1 on β-lactam antibiotics. 9/12 originated from South Africa and 6 of those dealt with ICU populations. The quality of most studies was low. Studies on amikacin, teicoplanin and ertapenem (n=4) displayed a pattern of a large V with low drug concentrations. Fluoroquinolone PK changes were less prominent and more diverse while the probability of pharmacodynamic (PD) target attainment was low for the treatment of TB in South Africa. Interindividual variability of V was high for 10/12 studies.

**Conclusion** Antibiotic PK data of SSA adult patient populations are scarce, but disease-induced inappropriate drug concentrations do occur. Data from non-ICU, severely ill patients, as well as β-lactam data are particularly lacking, whereas β-lactam antibiotics are commonly used, and typically vulnerable to disease-induced PK changes. Studies investigating PK/PD of β-lactam antibiotics in severely ill, adult SSA populations are needed to improve local antibiotic dosing strategies.
Introduction
Infectious diseases are the leading cause of death in low-income countries and in patients with severe infections, inappropriate empirical antibiotic therapy has been found to increase 30-day and in-hospital mortality.\textsuperscript{1-3} The appropriateness of antibiotic treatment has been mostly reviewed in terms of timeliness of initiation and optimization of empirical drug choices, while exercising standard dosing regimens. In patient groups at high risk for pathophysiological changes however, an increasing amount of attention is being paid to altered antibiotic pharmacokinetics (PK) and its consequences for adequate systemic drug exposure.\textsuperscript{4} In sepsis patients for example, changes in volume of distribution (V), protein binding and drug clearance (CL) may change the total drug concentration and make it hard to predict the unbound drug concentration. Furthermore, such changes may give rise to sub-optimal drug exposure, inability to attain pharmacodynamic (PD) targets and, potentially, to adverse clinical outcome.\textsuperscript{4,5}

In sub-Saharan Africa (SSA), advanced HIV disease still accounts for a large majority of medical admissions despite the scale-up of antiretroviral therapy. Severe febrile disease or sepsis, frequently caused by bacterial pathogens, can be found in up to 60% of in-patients and mortality is especially high when adequate empirical antimicrobial treatment and fluid resuscitation is not provided.\textsuperscript{6,7} Sepsis may very well not be the only condition with the potential to change PK of antibiotics in SSA patients, as highly prevalent chronic diseases such as tuberculosis (TB), hepatitis B, diabetes mellitus and hypertension may cause pre-existing cachexia and liver and kidney dysfunction, respectively.\textsuperscript{8,9} Even though sepsis could affect a SSA patient’s PK of antibiotics in ways that have been described in other patient populations, it is hard to tell if and how a potential combination of conditions would influence PK in this population. What is clear is that underexposure to antibiotics may pose a threat to a patient’s health as well as to public health, as it is known to contribute to the emergence of antimicrobial resistance, a phenomenon that is already highly prevalent in South Africa as well as in other SSA countries.\textsuperscript{10,11}

Unfortunately, clinical data concerning the PK of antibiotics in SSA populations are scarce, especially for adults. In view of the above, we performed a systematic review looking for clinical studies addressing PK of antibiotics used for the treatment of bacterial infections in adult SSA patients. The aim of this review was to summarize and interpret available relevant data and to discuss potential implications for treatment and research.
Methods

Search strategy

We performed a systematic literature search of relevant electronic databases, including Ovid MEDLINE, Embase and the African Index Medicus with an experienced clinical librarian, based on pre-defined objectives and eligibility criteria. Firstly, databases were searched for all studies addressing PK of antibiotics in SSA patient populations that had been published from 1946 until 10 May 2016, while applying the search terms and limits as presented in Table 1. Because the African Index Medicus database is relatively small that does not allow searches with more than three search terms at the same time, we searched it consecutively with different sensitive search terms after which a broad yield was screened for eligibility using title and abstract. A country’s designation to the SSA region was based on the United Nation Statistics Division’s grouping list. The primary search results were imported into a database (EndNote, Thomson Reuters, Philadelphia, PA, USA) and duplicate studies were removed.

Table 1. Search terms Ovid MEDLINE, Embase and the African Index Medicus (10 May 2016).

<table>
<thead>
<tr>
<th>#</th>
<th>search term</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>Ovid MEDLINE, Embase</strong> (in title, abstract, keyword heading word, OR registry number)</td>
</tr>
<tr>
<td></td>
<td>(Africa south of the Sahara) OR (sub-Saharan) OR Sahara OR (central Africa) OR sSA countries by name OR (developing countries) OR (resource-poor) OR (low-income countr*)</td>
</tr>
<tr>
<td>2</td>
<td>pharmacokinetics OR PK OR (volume of distribution) OR clearance OR elimination OR (half-life) OR (drug level) OR (serum or plasma) concentration) OR Cmax OR (area under the curve) OR AUC OR absorption OR pharmacodynamics OR PD OR (PK/PD) OR (population pharmacokinetics) OR PKP</td>
</tr>
<tr>
<td>3</td>
<td>(anti-bacterial agents) OR antibiotic* OR antibiotic classes by name</td>
</tr>
<tr>
<td>4</td>
<td>#1 AND #2 AND #3</td>
</tr>
<tr>
<td>5</td>
<td>animals OR not humans</td>
</tr>
<tr>
<td>6</td>
<td>#4 NOT #5</td>
</tr>
<tr>
<td></td>
<td><strong>African Index Medicus</strong> (as keyword)</td>
</tr>
<tr>
<td></td>
<td>pharmacokinetic, concentration, drug level, volume of distribution, clearance, half-life, (antimicrobial OR antibiotic OR anti-bacterial)</td>
</tr>
</tbody>
</table>

The Ovid MEDLINE and Embase search was executed as a composite search (#6), whereas the African Index Medicus search was executed while applying all named search terms consecutively.

One author (JCB) screened all titles and abstracts that would potentially meet the eligibility criteria and two other authors (JMP, RvH) each independently screened 10% of the primary search results. We allowed a 2.5% margin of difference between
screening authors to occur without a need to repeat the screening procedure. Within margin-differences of opinion were resolved by discussion. The full text articles of all potentially relevant studies were retrieved and subsequently assessed for quality and risk of bias by two authors. Reference lists of eligible articles were screened as well.

**Eligibility criteria**
Studies were eligible for assessment of antibiotic PK evidence when they reported SSA adult patient data on non-dose dependent PK parameters (V; half life: t½; CL). Adult was defined as age ≥18 years and individual study participants were considered to be patients whenever the antibiotic of study was used for the treatment of a specified disease. We excluded papers involving healthy volunteers and papers reporting on ill-defined mixed paediatric/adult patient groups. Eligible studies had to be investigating PK of antimicrobial drugs that are primarily indicated for the treatment of bacterial disease and we therefore also considered studies investigating fluoroquinolones as part of TB treatment regimens. The following publication languages were allowed: English, German, French, Portuguese, Spanish and Dutch. We excluded narrative reviews, discussion papers, conference papers, letters to the editor and editorials, as well as studies investigating the prophylactic and peri-operative use of antimicrobial drugs. To map out the number of records identified, included and excluded, as well as the reasons for exclusion, the PRISMA flow diagram was used.¹⁴

**Data extraction and quality assessment**
Pre-defined PK outcomes were extracted and summarized in a standard format alongside other study information necessary for the study assessment. Summary measures and measures of spread were used as presented by the authors. Summary measures of V were expressed as volume per kilogram. All information was extracted by one author (JCB) and fully checked for accuracy by the other authors (JMP, RvH). Discrepancies were resolved through discussion. The risk of bias of each included study with regard to the generation of our pre-defined outcomes V, t½ and CL was assessed independently by the screening author (JCB) as well as by one of the other authors (JMP, RvH) using an adapted version of the Newcastle-Ottawa Quality Assessment Scale (NOS) for non-randomized studies and the Cochrane risk of bias tool for RCTs.¹⁵,¹⁶ Non-randomized studies could score points (stars) on three dimensions: selection (max. 4 points/stars), comparability (max. 1 point/star) and outcome (max. 3 points/stars; table 2). The NOS score was considered high when above the median score of 4 (≥5) and low when ≤4. We did not seek to examine an alternative clinical management strategy or intervention based on a pre-defined focused clinical question and we did therefore not rate the quality of pooled
scientific evidence coming from our selection of studies with the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.17

Results

Search results

Our systematic search identified 1584 papers after removal of duplicates (Figure 1). After screening of titles and abstracts, 31 potentially relevant studies were selected for full-text screening. Ultimately, 12 papers remained for qualitative analysis. The main reason for exclusion was not providing any of the pre-defined outcome data.

Figure 1. PRISMA flow diagram of clinical studies.14

Our predefined outcomes were generated through non-randomized (observational) study designs in 11/12 cases. One study was a clinical trial with a crossover design. There were no studies designed to compare patient populations from different geographical origin or race and the majority of studies (9/12) originated from South Africa, six of which had been performed on ICUs. There were six studies on fluoroquinolones, two on aminoglycosides, one on a glycopeptide, and one a β-
lactam antibiotic. Dapsone and chloramphenicol were each also represented with one study. The publication language was English for all studies.

**Assessment of risk of bias**

Quality scores of included cross-sectional studies ranged from 2-7, with a median score of 4. The majority of cross-sectional studies (6/11) was assessed to have a high risk of bias and was therefore considered to be of low quality with regard to the predefined outcomes (Table 2). Low scores mostly resulted from shortcomings in the selection, description and representativeness of the study populations. The only clinical trial was assessed to have a high risk of bias (high risk of allocation concealment and detection bias).

**PK pre-defined outcomes**

*Aminoglycosides:* Two studies investigated PK of amikacin in South African ICU populations with gram-negative sepsis. In the only study with >1 patient the mean V was 0.41 L/kg and considered larger than in healthy volunteers (HV), using a normal value of 0.24 L/kg. There was a positive correlation between the APACHE II score and V.\(^\text{18}\) In the other study, describing one patient’s course of PK parameters over time, V and t\(^{1/2}\) were found to be variable, while increasing further as the patient’s condition worsened.\(^\text{19}\)

*Fluoroquinolones:* Six studies described PK of four different fluoroquinolones, all of which were studies originating from South Africa, although two studies involved one or more study sites in other SSA countries. A majority of studies (4/6) investigated pulmonary TB outpatients in a population pharmacokinetic (PPK) design during standardized oral TB treatment (including a rifamycin) and two studies dealt with sepsis patients using intravenous formulations of ciprofloxacin. In the first of the two sepsis studies on ciprofloxacin, the estimated mean V ranged from 1.2-1.4 L/kg on different study days while the mean CL was 0.4 l/h/kg on all study days.\(^\text{20}\) In the second study, the geometric mean V ranged from 1.3-1.6 L/kg and the mean CL from 0.3-0.4 L/h/kg.\(^\text{21}\) Both sepsis studies considered the observed mean V to be normal or smaller compared with HV, with the first of the two studies using a V normal value of 2.0 l/kg. In the only study with ofloxacin, Monte Carlo simulations using the estimated V of 1.7 L/kg and CL of 3.8 L/h/kg demonstrated that the use of 800 mg q24h is expected to be too low for the treatment of South African pulmonary TB patients when the MIC range of *Mycobacterium tuberculosis* for ofloxacin is 0.5-8 mg/L.\(^\text{22}\) Doubling the dose would increase the probability of target attainment (PTA) to 0.77. Two PPK studies with South African and Zimbabwean pulmonary TB populations rendered an estimated moxifloxacin V of 3.0 and 3.8 L/kg and a CL of 8.5 and 10.6 L/h/kg.\(^\text{23,24}\) One study comparing the PTA of moxifloxacin...
and that of ofloxacin using another study’s parameter estimates and models, concluded that current dosing of both ofloxacin and moxifloxacin was likely to be too low for the treatment of drug-resistant TB in the target population. In the one study on gatifloxacin in pulmonary TB patients, the investigators found that the use of a gatifloxacin dose of 400mg q24h would not achieve sufficient steady state free drug exposure, based on Monte Carlo simulations with a model based on an estimated V of 2.6 L/kg and a CL of 11.3 L/h.

Glycopeptides: One South African paper investigated the PK of total and free teicoplanin in chronic gram-positive bone/joint infection in patients with hypoalbuminemia. The median teicoplanin bound fraction was lower than in HV and found to lie between 66-81% over a time period of 4 days. The estimated V was larger than normal with 2.2 L/kg for total teicoplanin and 2.5 L/kg for free teicoplanin. Serum creatinine and albumin concentrations were found to impact the free drug concentration, while the total drug concentration did not. There was a high interindividual variability of V and CL.

β-lactams: The PK of total and free ertapenem was investigated in a paper from South Africa among ICU patients with severe gram-negative infection, low albumin concentrations and normal renal function. Study results showed a mean total V of 0.98 L/kg and a CL of 12 L/h/kg, according to the authors, both substantially higher than those observed in HV, using referred normal values of 0.11 L/kg and 0.4 L/h/kg, respectively. As for free ertapenem, V and CL were 1.5 L/kg and 19 L/h/kg respectively, which is about 1.5 times as large as the V and CL of total ertapenem. The calculated median time of the unbound ertapenem concentration > MIC of 1 mg/L (= clinical breakpoint Enterobacteriaceae) was 14.7 h, but the unbound plasma concentration of 3/8 patients was >1 mg/L for only 11-34% of the dosing interval. The study found a high variability for all non-dose dependent PK parameters.

Dapsone: In a study with Nigerian leprosy patients, investigators found that rifampicin significantly reduced the t½ of dapsone based on drug concentration measurements three and thirty days after the administration of 600 mg rifampicin.

Chloramphenicol: Chloramphenicol had a t½ of 3.5 h and 3.6 h, with and without concomitant use of oral paracetamol respectively, in a small Zimbabwean outpatient clinic study with pneumonia and typhoid patients.
The study found a high variability for all non-dose dependent PK parameters. The calculated median time of the unbound ertapenem concentration > MIC of 1 concentration of 3/8 patients was >1 mg/L for only 11-34% of the dosing interval. The unbound plasma respectively, which is about 1.5 times as large as the V and CL of total ertapenem. As for free ertapenem, V and CL were 1.5 L/kg and 19 L/h/kg than those observed in HV, using referred normal values of 0.11 L/kg and 0.4 L/h/kg.

Chloramphenicol: Dapsone: Glycopeptides: β-lactams: Gatifloxacin: Ofloxacin: Teicoplanin:

Table 2. Quality assessment summary.

<table>
<thead>
<tr>
<th>CROSS-SECTIONAL STUDIES</th>
<th>Sample selection criteria</th>
<th>Comparability</th>
<th>Outcome &amp; evaluation</th>
<th>Summary score/8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mark, 1993\textsuperscript{18}</td>
<td>★</td>
<td>-</td>
<td>★</td>
<td>☠</td>
</tr>
<tr>
<td>Botha, 1996\textsuperscript{19}</td>
<td>-</td>
<td>-</td>
<td>★</td>
<td>-</td>
</tr>
<tr>
<td>Lipman, 1998\textsuperscript{20}</td>
<td>★★</td>
<td>★★</td>
<td>★</td>
<td>-</td>
</tr>
<tr>
<td>Gous, 2005\textsuperscript{21}</td>
<td>★★</td>
<td>-</td>
<td>★</td>
<td>-</td>
</tr>
<tr>
<td>Chigutsa, 2012\textsuperscript{22}</td>
<td>-</td>
<td>★★</td>
<td>★</td>
<td>-</td>
</tr>
<tr>
<td>Zvada, 2012\textsuperscript{23}</td>
<td>-</td>
<td>-</td>
<td>★</td>
<td>-</td>
</tr>
<tr>
<td>Zvada, 2014\textsuperscript{24}</td>
<td>-</td>
<td>-</td>
<td>★</td>
<td>-</td>
</tr>
<tr>
<td>Smythe, 2013\textsuperscript{25}</td>
<td>-</td>
<td>-</td>
<td>★</td>
<td>-</td>
</tr>
<tr>
<td>Brink, 2015\textsuperscript{26}</td>
<td>-</td>
<td>★</td>
<td>★</td>
<td>-</td>
</tr>
<tr>
<td>Pieters, 1998\textsuperscript{27}</td>
<td>-</td>
<td>★</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Brink, 2008\textsuperscript{28}</td>
<td>-</td>
<td>★</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CLINICAL TRIALS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stein, 1989\textsuperscript{29}</td>
<td>Risk of bias</td>
<td>high</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cross-sectional studies: score in points (stars) based on risk of bias in generation of outcome variables, and assessment criteria, using a modified version of Newcastle-Ottawa Scale for non-randomised studies. Clinical trial: score using the Cochrane Collaboration’s tool for assessing risk of bias in randomized trials.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Setting</th>
<th>Disease Selection</th>
<th>Design</th>
<th>Study drug</th>
<th>Sample size</th>
<th>V (l/kg)</th>
<th>CL (l/h/kg)</th>
<th>t½ (h)</th>
<th>Conclusions</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marik et al, 1993</td>
<td>South Africa</td>
<td>ICU</td>
<td>Gram-negative sepsis</td>
<td>cross-sectional</td>
<td>amikacin</td>
<td>42</td>
<td>0.41</td>
<td>0.13</td>
<td>2.42</td>
<td>V large compared to HV</td>
<td>5/8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Serum creatinine ≤120 μmol/l</td>
<td>non-compartmental analysis</td>
<td></td>
<td></td>
<td>(0.24-0.62)*</td>
<td></td>
<td></td>
<td>APACHE II score positively correlated with V (r=0.7; p&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>Botha et al, 1996</td>
<td>South Africa</td>
<td>ICU</td>
<td>Gram-negative respiratory infection after head trauma</td>
<td>cross-sectional</td>
<td>amikacin</td>
<td>1</td>
<td>0.46</td>
<td>0.13</td>
<td>2.42</td>
<td>V and t½ increased as patient’s condition worsened</td>
<td>2/8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PK in steady state</td>
<td>PK after loading dose</td>
<td></td>
<td></td>
<td>(0.25-0.61)*</td>
<td></td>
<td></td>
<td>Low Cmax, Cmin with high variability over time</td>
<td></td>
</tr>
<tr>
<td>Lipman et al, 1998</td>
<td>South Africa</td>
<td>ICU</td>
<td>Non-abdominal nosocomial severe sepsis</td>
<td>cross-sectional</td>
<td>ciprofloxacin</td>
<td>18</td>
<td>1.4 ± 0.3</td>
<td>0.4 ± 0.2</td>
<td>3.9 ± 1.7</td>
<td>V small and CL low compared with HV; high V variability</td>
<td>7/8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PK after first dose &amp; in steady state</td>
<td>400mg q8h iv</td>
<td></td>
<td></td>
<td>(2 day 0):</td>
<td>(0.25-0.61)*</td>
<td>(1.73-5.29)*</td>
<td>Cmax/MIC &gt;8 &amp; AUC/MIC &gt;100 for microorganisms with MIC&lt;0.5mg/l</td>
<td></td>
</tr>
<tr>
<td>Gous et al, 2005</td>
<td>South Africa</td>
<td>ICU</td>
<td>abdominal (a) &amp; other sepsis (b)</td>
<td>cross-sectional</td>
<td>ciprofloxacin</td>
<td>22/18</td>
<td>a: 1.3 ± 1.2</td>
<td>0.4 ± 1.6</td>
<td>3.4 ± 1.6</td>
<td>V normal-small compared with HV; no V change over time</td>
<td>6/8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PK after first dose &amp; in steady state</td>
<td>non-compartmental analysis</td>
<td></td>
<td></td>
<td>b: 1.3 ± 1.3</td>
<td>0.4 ± 1.5</td>
<td>3.3 ± 1.3</td>
<td>No significant V difference between abdominal- and other sepsis groups (p&gt;0.05)</td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Continued.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Setting Selection</th>
<th>Disease</th>
<th>Study Design</th>
<th>Study drug Dose</th>
<th>Sample size</th>
<th>Study drug</th>
<th>V (l/kg)</th>
<th>CL (l/h/kg)</th>
<th>t½ (h)</th>
<th>Conclusions</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiguta et al, 2012</td>
<td>South Africa, hospital</td>
<td>cross-sectional</td>
<td>MDR-TB</td>
<td>PPK</td>
<td>ofloxacin</td>
<td>65</td>
<td></td>
<td>central: 5 1.1 (30%)</td>
<td>CL: 5 3.7/68ml/min (26%)</td>
<td>7.8 (5)</td>
<td>ofloxacin 800mg q24h PTA low: 0.45 (PD target: f AUC/MIC ≥100 &amp; MIC range 0.5-8.0 mg/l)</td>
<td>6/8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Monte Carlo</td>
<td>800 mg q24h orally</td>
<td></td>
<td></td>
<td>peripheral: 5 0.6 (-)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>simulations</td>
<td>PK in steady state</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zvada et al, 2012</td>
<td>South Africa</td>
<td>in/out-patient not indicated</td>
<td>PTB</td>
<td>PPK</td>
<td>moxifloxacin</td>
<td>28</td>
<td></td>
<td>central: 2.2 (-)</td>
<td>CL: 8.5 (13%)</td>
<td>9.2 (-)</td>
<td>High dose rifapentin increased moxifloxacin CL by 8% without changing moxifloxacin exposure</td>
<td>4/8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PK in steady state continuation phase &amp; after single dose</td>
<td></td>
<td></td>
<td>peripheral: 0.8 (-)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Zvada et al, 2014</td>
<td>South Africa &amp; Zimbabwe</td>
<td>in/out-patient not indicated</td>
<td>PTB</td>
<td>PPK</td>
<td>moxifloxacin</td>
<td>241</td>
<td></td>
<td>central: 2.1 (-)</td>
<td>CL: 10.6 (19%)</td>
<td>-</td>
<td>PTA moxifloxacin substantially higher than PTA ofloxacin</td>
<td>4/8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Monte Carlo</td>
<td>400mg once weekly with 1200mg rifapentin/400mg twice weekly with 900mg rifapentin orally</td>
<td></td>
<td></td>
<td>peripheral: 1.7 (-)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>simulations</td>
<td>PK in steady state</td>
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<td></td>
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</tr>
<tr>
<td>Smythe et al, 2013</td>
<td>South Africa, Senegal, Guinea, Benin</td>
<td>outpatient clinic</td>
<td>PTB</td>
<td>PPK</td>
<td>gatifloxacin</td>
<td>169</td>
<td></td>
<td>CL: 6.2 (33%)</td>
<td></td>
<td>-</td>
<td>gatifloxacin exposure declined after multiple doses</td>
<td>4/8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Monte Carlo</td>
<td>400mg q24h orally</td>
<td></td>
<td></td>
<td>CL: 5.1 (33%)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>simulations with external MTB MICs</td>
<td>PK in steady state</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

...continued...
<table>
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<tr>
<th>Study</th>
<th>Country</th>
<th>Setting</th>
<th>Disease</th>
<th>Selection</th>
<th>Design</th>
<th>Study drug</th>
<th>Sample size</th>
<th>V (l/kg)</th>
<th>CL (l/h/kg)</th>
<th>t½ (h)</th>
<th>Conclusions</th>
<th>Quality score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brink et al, 2015</td>
<td>South Africa</td>
<td>hospital</td>
<td>chronic, deep seated Gram-negative bone/joint infection &amp; hypoalbuminemia</td>
<td>cross-sectional analysis</td>
<td>teicoplanin 12mg/kg q24h iv with loading dose 12mg/kg q12h on day 1</td>
<td>10</td>
<td>total: 2.2 (1.3-4.1)</td>
<td>total: 7.0 (6.8-9.8)</td>
<td>free: 2.5 (2.4-2.5)</td>
<td>free: 38.6</td>
<td>High IIV free drug fraction Higher free fractions with lower albumin concentrations</td>
<td>5/8</td>
</tr>
<tr>
<td>Pieters et al, 1988</td>
<td>Nigeria</td>
<td>outpatient clinic</td>
<td>leprosy</td>
<td>cross-sectional analysis</td>
<td>dapsone 100mg q24h orally co-use rifampicin 600 mg orally, once monthly</td>
<td>23</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Total drug concentration could not predict free drug concentration. Free PD target achieved</td>
<td>3/8</td>
</tr>
<tr>
<td>Stein et al, 1989</td>
<td>Zimbabwe</td>
<td>outpatient clinic</td>
<td>anaerobic lung infection or typhoid</td>
<td>non-compartmental analysis</td>
<td>chloramphenicol 500mg q6h orally</td>
<td>2x5</td>
<td>-</td>
<td>-</td>
<td>pmol +: 3.6 ± 1.8</td>
<td>pmol -: 3.5 ± 1.7</td>
<td>t½ not prolonged by co-use paracetamol (p=0.08)</td>
<td>4/8</td>
</tr>
</tbody>
</table>
### Table 3. Continued.

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<tr>
<th>Study</th>
<th>Country</th>
<th>Setting</th>
<th>Disease Selection</th>
<th>Design</th>
<th>Study drug</th>
<th>Dose</th>
<th>Sample size</th>
<th>V (l/kg)</th>
<th>CL (l/h/kg)</th>
<th>t½ (h)</th>
<th>Conclusions</th>
<th>Quality score</th>
</tr>
</thead>
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<tr>
<td>Brink et al, 2008</td>
<td>South Africa</td>
<td>ICU</td>
<td>severe Gram-negative sepsis</td>
<td>cross-sectional</td>
<td>ertapenem</td>
<td>1g q24h iv</td>
<td>8</td>
<td>total: 0.98 ± 1.4</td>
<td>total: 12.0 ± 18</td>
<td>5.7 ± 4.9</td>
<td>Total V large compared with HV and other critically ill patients</td>
<td>4/8</td>
</tr>
</tbody>
</table>

Predefined outcomes expressed as means ± standard deviation (SD), unless mentioned otherwise (footnotes). HV: healthy volunteers; RSE: relative standard error; CT: clinical trial; MTB: Mycobacterium tuberculosis; PTA: probability of target attainment; PTB: pulmonary TB; MDR-TB: multi-drug resistant TB; CL: renal clearance; CLNR: non-renal clearance; *: predefined outcomes expressed as means (range); ‡: predefined outcomes expressed as geometric mean (geometric SD); §: predefined outcomes expressed as typical value (population variability in RSE (%)); ¶¶: predefined outcomes expressed as median (IQR).
Discussion
This review summarizes non-dose-dependent antibiotic PK data from twelve clinical studies with adult SSA patients, for six different classes of antimicrobial drugs. The body of evidence is limited, heterogeneous and most of the research was executed in South African (ICU) patient populations, while non-ICU, in-hospital research from other SSA countries was merely absent. Among our selection of papers, there were no studies that had been specifically designed to investigate the PK of antimicrobial drugs in SSA patient populations in comparison with non-SSA populations. The selection of studies on amikacin, teicoplanin and ertapenem displayed a general pattern of an increased V with low drug concentrations. PK parameter changes of fluoroquinolones tended to be less prominent and more diverse. The probability of drug class specific pharmacodynamic (PD) target attainment of fluoroquinolones was low for the treatment of TB in South Africa. There was a scarcity of data regarding the use of β-lactams. A substantial number of studies involving severely ill patients reported a high interindividual variability of V of the study drug involved.

Severe illness, and sepsis in particular, causes several pathophysiological changes that may affect PK of antimicrobial drugs: an increased extracellular volume can lead to an increased V and hypoalbuminaemia may lead to a significantly higher free drug fraction, while augmented renal clearance, renal insufficiency and hepatic metabolic dysfunction may cause increased or impaired drug CL. Hydrophilic drugs with renal CL, such as aminoglycosides, are particularly sensitive to changes in extracellular volume, while drugs that are highly bound to protein (>90%) such as teicoplanin and some of the β-lactams, including ceftriaxone and ertapenem, are particularly sensitive to changes in the concentration of the binding protein. At the same time, large interindividual differences in PK of antibiotics in critically ill patients have been reported. Consequently, the use of standard drug doses in critically ill patients can lead to inadequately low or high plasma drug concentrations.

The aminoglycoside outcomes in our selection of studies on gram-negative infection/sepsis showed a normal to increased V, while CL and t½ varied, depending on the level of illness and organ dysfunction and this seems to compare well with the outcomes of a Spanish and an American modelling study with critically ill patients. Botha et al. also concluded that their patient’s peak amikacin concentrations were too low. Although this study was only reporting the results of one patient, it does fit results from studies from other parts of the world showing that PK alterations in sepsis patients may necessitate the use of higher daily doses to attain the specified PD targets.
The single study in our review on highly protein-bound β-lactams investigated the PK of total and unbound ertapenem in patients with severe, gram-negative infection. The patients’ (total) V of 0.98 L/kg was larger than the V of HV (0.11 L/kg) and of other critically ill patients. It is also in accordance with what can be expected on the basis of the drug’s PK properties, as well as with results from a German study in critically ill patients with ventilator-associated pneumonia. Also here, the authors mentioned the potential inability of the free drug concentration to reach specific PD targets.

A comparable phenomenon could be seen with our selected study on teicoplanin in patients with chronic gram-positive bone infection and hypoalbuminaemia, where the investigators found an increased V compared to normal values (0.7-1.4 L/kg). The free fraction of teicoplanin increased with lower albumin concentrations and in a multiple regression model, plasma creatinine and albumin concentrations, and not the total drug concentration, were found to significantly impact the free drug concentration. Although free teicoplanin trough concentration appeared to remain above what is for some the calculated PD target of 1-2 mg/L, the target total plasma trough concentration of 20 mg/L was not achieved. Teicoplanin is a 90-95% protein-bound glycopeptide and investigations into the PK of this drug in a hospital population without hypoalbuminaemia and in a Japanese patient population with sepsis have shown similar PK alterations, with normal to increased V, and low initial plasma total teicoplanin concentrations necessitating higher loading doses for up to four days, with the dosing interval depending on the estimated glomerular filtration rate.

Although to a lesser extent, PK of fluoroquinolones can be altered by severe illness too, even though this class of drugs has different PK properties: fluoroquinolones are more lipophilic drugs with low protein binding that tend to have a relatively large V. Our review’s studies on the use of ofloxacin, moxifloxacin and gatifloxacin as part of TB treatment regimens generally found normal to increased V, and these findings appear to be in line with V results from two Asian studies and one American study among TB patients. However, the V found in the two papers on ciprofloxacin in ICU patients with sepsis were found to be normal to smaller than in HV. 22,25 Although fluoroquinolone HV normal values seem to have quite a wide range from 1.2-2.7 L/kg to 2-3 L/kg for ciprofloxacin, and from 2L/kg to 1.7-2.7 L/kg for moxifloxacin, depending on the source consulted, a normal to small V was also observed in a number of ciprofloxacin and moxifloxacin studies with sepsis patients from other parts of the world. It is not clear whether these findings represent a real difference in the direction of Vd change between the TB and the sepsis patient populations. In the case of the TB populations, the occurrence of...
lower plasma drug concentrations resulting from rifamycin-induced phase II hepatic drug metabolism with increased drug elimination could be interpreted as a larger $V$, and for the sepsis populations, impaired renal and hepatic function with subsequent lower drug elimination could be interpreted as a smaller $V$. An illustration of the same relationship can be found in the results of a study that found the ciprofloxacin $V$ in sepsis patients to be significantly lower than in healthy volunteers with a tendency to decrease further with a decreasing estimated glomerular filtration rate.\textsuperscript{45}

Interestingly, our fluoroquinolone studies with TB patients as well as the ones with sepsis patients reported a potential inability to reach PD targets for infections with ‘non-susceptible’ microorganisms when using normal to high doses of the study drug.

Chloramphenicol is a lipophilic drug with moderate protein binding of 50-60%. It has a large $V$ and a large fraction of the drug undergoes metabolism before tubular secretion. The $t_{1/2}$ as mentioned in the study of Stein et al with non-severely ill patients in Zimbabwe, some of whom with typhoid, comes close to what is generally believed to be the normal $t_{1/2}$ in HV, namely 1.6-3.3 h.\textsuperscript{29,41} A Nepalese study among severely ill patients with enteric fever found a steady state $V$ close to normal of 1.2 L/kg and a $t_{1/2}$ of about 3 hours.\textsuperscript{46} The methodologically weak study on the use of dapsone, another lipophilic drug that is metabolized by the liver with 70-90% protein binding, only reported $t_{1/2}$ information in relation to rifampicin use and the results seemed to match normal values.\textsuperscript{28,34}

The overall picture arising from this review’s study results in comparison with reports from other parts of the world is that the directions of effects of (severe) illness on PK of antimicrobial drugs appear to be similar, including the occurrence of high interindividual PK variability. As was demonstrated in the PD results of our studies on fluoroquinolones and the $\beta$-lactam ertapenem, the probability of drug class specific PD target attainment may be too low for the treatment of specified disease in that population. Even though fluoroquinolones and carbapenems are unlikely first-line antibiotics for the empiric treatment of severe febrile illness in SSA,\textsuperscript{47} clinical data suggesting an inability to reach pre-defined treatment goals and difficulty to predict individual drug concentrations are worrisome, especially since an increasing number of reports emphasizes the need for higher PD targets for the severely ill.\textsuperscript{48,49} Furthermore, recent in-vitro research has shown that an even higher exposure to antibiotics may be needed to minimize the development of de novo resistance.\textsuperscript{50}

All of this is of particular importance to resource poor SSA settings, and to southern African settings in particular. Over the last two decades, health institutions in the region have witnessed an impressive influx of chronically HIV-infected patients with
presumptive community-acquired bloodstream infections or sepsis, with non-
typhoidal salmonellae, Streptococcus pneumonia, Escherichia coli and
Staphylococcus aureus being the most important bacterial pathogens
encountered.6,7,51 Indications of existing underexposure to antibiotics combined with
the need for stricter treatment goals for large numbers of severely ill patients should
therefore be taken seriously, especially since it is quite clear that antimicrobial
resistance is existing and on the rise in SSA.11 Investing in the generation of
antibiotic PK data may be one of the solutions to save commonly used, cheap
antibiotics for the empiric treatment of bloodstream infections, such as benzyl-
penicillin and ceftriaxone, from becoming obsolete.50 In order to improve local
dosing strategies, such research should go hand in hand with obtaining local
microbiological surveillance data.52

The conclusions that can be drawn from our review’s summarized evidence are
clearly limited by the overall scarcity of appropriate data and the high proportion of
studies with low quality scores based on the risk of bias. The body of evidence may
be further biased by the fact that most studies were executed in South Africa and in
ICU settings, suggesting an underrepresentation of more resource-poor, non-ICU, in-patient populations in TB/HIV high endemic settings, in which a combination of
acute and chronic disease-driven changes may influence PK of antibiotics.
Underrepresentation of such patient populations could lead to a misinterpretation of
the direction and an underestimation of the magnitude of PK alterations. We did
also not encounter studies on the commonly used β-lactam antibiotics benzyl-
penicillin, ampicillin and ceftriaxone, whereas several non-SSA studies on β-lactams
in ICU populations have found that there is significant β-lactam PK variability and
that standard empiric dosing may lead to sub-therapeutic antibiotic concentrations,
depending on the PD targets used.53

**Conclusion**

This review highlights the existing scarcity of data concerning PK of antibiotics in
(severely ill) SSA adult patient populations and factors influencing it. Available data
seem to indicate that the type of disease-induced PK alterations are in agreement with
what can be expected on the basis of information from comparable European,
American and Asian patient populations, including a high interindividual variability.
However, data concerning severely ill patient populations from resource-poor, non-
ICU settings, as well as β-lactam data are particularly lacking, whereas these
antibiotics are among the most widely used antibiotics for the empiric in-hospital
treatment of severe febrile disease and sepsis, while being particularly vulnerable to
disease-induced PK changes. This could mean that large, severely ill (TB/HIV
infected) patient populations are at risk for added, avoidable morbidity and
mortality as a result of underexposure to antibiotics, a phenomenon that is known to fuel the emergence of antimicrobial resistance.

**Recommendation**

Clinical studies investigating PK and PD of β-lactam antibiotics in geographically different, severely ill, SSA adult in-hospital populations are needed to improve guidance on local antibiotic dosing strategies. This should preferably go hand in hand with intensified local microbiological surveillance that would render up to date ranges of MICs of bacterial pathogens most frequently causing severe febrile illness/sepsis in the SSA region.

**Acknowledgments**

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References


