Title: Role of therapeutic drug monitoring in pulmonary infections: use and potential for expanded use of dried blood spot samples

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Role of TDM in pulmonary infections: use and potential for expanded use of dried blood spot samples.

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Summary

Respiratory tract infections are among the most common infections in men. We reviewed literature to document their pharmacological treatments, and the extent to which TDM is needed during treatment. We subsequently examined potential use of dried blood spots as sample procedure for TDM. TDM was found to be an important component of clinical care for many (but not all) pulmonary infections. For gentamicin, linezolid, voriconazole and posaconazole dried blood spot methods and their use in TDM were already evident in literature. For glycopeptides, beta-lactam antibiotics and fluoroquinolones it was determined that development of a DBS method could be useful. This review identifies specific antibiotics for which development of DBS methods could support the optimization of treatment of pulmonary infections.

Key terms:

- Pharmacokinetics: how the body affects a specific drug after administration through the mechanisms of absorption and distribution, as well as metabolism and the excretion of the drug.
- Dried blood spot: microvolume sampling technique collecting whole blood spots on a filter paper card for analysis.
- Therapeutic drug monitoring: individualization of drug dosage by maintaining plasma or blood drug concentrations within a targeted therapeutic range to ensure efficacy and prevent side effects.
- Pulmonary infections: number of infectious diseases involving the respiratory tract.
- Pharmacokinetic drug-drug interactions: A drug interaction is a situation in which a another drug when both are administered together affects the activity of a drug by alterations in

the pharmacokinetics of the drug, such as alterations in the absorption, distribution, metabolism, and excretion of a drug.

- PK/PD: relationship between the pharmacokinetics and pharmacological effect of a drug.

Introduction

Respiratory tract infections are among the most common infections in men. The range of respiratory tract infections can vary from a upper respiratory tract infection e.g. sinusitis to lower respiratory tract infections e.g. community acquired pneumonia (CAP) respectively in immune competent patients but also severe pulmonary infections in immune compromised patients and patients with (non)-cystic fibrosis bronchiectasis ((non-)CF BE). Lower respiratory tract infections are common diseases for both general practitioners and medical specialists like pulmonary physicians and infectious diseases (ID)-physicians. Pulmonary infections in immune compromised patients are more complicated and less common and therefore mostly treated by pulmonary physicians and ID-physicians.

Morbidity and mortality rates among patients with pulmonary infections can be high especially in immune compromised patients . The causative micro-organism may differ in immune competent patients or in immune compromised patients [1-6]. Therefore the empirical antibiotic regimen differs between these categories of patients. Antibiotic treatment for CAP is guided by mortality risk scores, like the pneumonia severity index or the CURB65 score [7, 8]. In patients with an underlying disease, like non-CF BE, the local immune system might be impaired, giving way to infections caused by micro-organisms that are generally non-pathogenic in immunocompetent patients, requiring different antibiotic strategies [9, 10]. The most common bacteria causing CAP in immunocompetent patients are *Streptococcus pneumoniae, Haemophilus influenzae and Mycoplasma pneumoniae followed by less frequent causative micro-organisms like Staphylococcus aureus, Legionella species, Chlamydiophila pneumonia, Coxiella burnetii* and *Bordetella pertussis*. Lower respiratory infections in patients with COPD are also frequently caused by the common causative micro-organisms in immunocompetent patients, but also by other bacteria such as *Moraxella catarrhalis* and

Pseudomonas aeruginosa [10]. Non-tuberculous mycobacteria can cause pulmonary infections in patients with COPD as well, as holds true for immunocompromised patients [11-13], who also can contract infections with less common bacteria like *Proteus mirabilis, Klebsiella pneumoniae, Escherichia coli, Actinomyces species, Nocardia species* and *Acinetobacter baumannii* and fungal infections (*Aspergillus species*) [1, 5, 6, 10]. *Pseudomonas aeruginosa* or *Burkholderia cepacia* can cause deterioration of lung function in patients with either CF BE or non-CF BE [2, 4, 9].

Luckily, physicians have an extensive antimicrobial armamentarium to treat patients with pulmonary infections caused by this plethora of microorganisms, according to national and international treatment guidelines. However, emergence of drug resistance and economical reasons challenges physicians to select an effective and cheap antimicrobial drug with the narrowest antimicrobial spectrum for the particular infection. Once the appropriate drug is selected, physicians will use guidelines, summary of product characteristics, peer-reviewed literature and patient's characteristics to determine the dosage of the selected drug. The goal is to prescribe the drug in a dose that is likely to be effective in the majority of patients with the narrowest possible spectrum, an acceptable range of side effects and at the lowest costs.

However, in daily practice the registered dose or the dose recommended in general guidelines will not always result in clinical cure. For instance, several studies have shown that critically ill patients tend to respond differently to standard dosed drugs [14]. Altered organ function or changes in body composition may change pharmacokinetics (PK) in these individuals. In addition, drug-drug interactions are a well-known source of variability of drug concentrations, especially in patients receiving multiple antimicrobial drugs for co-infections, like HIV patients suffering from a range of pulmonary infections [15]. Obviously, variability in PK, can have a grave impact on PK / pharmacodynamics (PD) of antimicrobial drugs. PK/PD parameters for antimicrobial drugs - i.e. the

maximum concentration (Cmax) in relation to minimal inhibitory concentration (MIC), area under the concentration – time curve (AUC) in relation to MIC, and time above MIC - describe the correlation between the concentration of the drug in relation to the susceptibility of the pathogen [16]. In severely ill patients, drug exposure has been observed to be lower than in patients who are less ill. If such a patient is also infected with a less susceptible isolate the PK/PD ratio might be too low and might not exceed target values [17]. Therefore, it seems plausible that patients with severe infectious diseases would benefit most from individualized dosing based on drug concentration monitoring or therapeutic drug monitoring (TDM).

For TDM often plasma or serum is used as matrix to determine the concentration of the antimicrobial drug. However, conventional blood sampling using vena puncture is not always feasible. Alternative sampling strategies have been evaluated and dried blood spot (DBS) sampling has been increasingly applied for optimizing drug dosages in patients with pulmonary infectious diseases [18]. Feasibility of TDM using DBS has been demonstrated for drugs used in many different infectious diseases, such as HIV and malaria [19, 20]. DBS is popular for its well-known advantages like minimal invasive sampling, sample stability and small blood volume. In general, a DBS sample consists of a peripheral blood sample obtained by a finger prick. Ideally, it resembles the venous blood concentration.

Before DBS can be applied in daily practice, an analytical and clinical validation has to be performed. The analytical validation has to take into account the linearity, accuracy and precision, recovery, matrix effect, sample stability, type of DBS-card, and punch size of the analytical method. During the subsequent clinical validation, the concentrations of a particular drug in the DBS samples are compared to the plasma or blood concentrations obtained at the same time point [21]. Important factors regarding the procedure are environmental factors like temperature and humidity as these

may have a detrimental effect on the sample stability. In addition, spot size is important for the analytical procedure. Especially, in case of non-capillary sampling (punching part of the spot) the spot size may differ depending on the correct performance of the procedure performed by the patient or healthcare professional. During the DBS sampling it is important to spot a single free falling drop of blood on the DBS card for each spot. Touching the DBS cards with the pricked finger will affect the formation of the blood spot and may create DBS that are too small for partial spot analysis. This incorrect performance of the DBS procedure will negatively affect the DBS analysis results. Measuring the haematocrit value during clinical validation enables to correct for the influence of blood spreading on the DBS-card [22]. So to summarize, a clinical validation of a DBS application should take into account the haematocrit variability and concentration range within the intended population along with all the environmental circumstances.

To facilitate pulmonary physicians and ID physicians and those providing analytical and TDM services to optimize treatment of pulmonary infections, this article provides a comprehensive overview of published literature. More specifically, our aim is to present an overview of the value of TDM for drugs used to treat pulmonary infections and the usefulness of DBS sampling when performing TDM. Furthermore, our aim is to describe the DBS methods for these drugs that are already known from literature. Finally, we aim to prioritize future development of novel DBS methods of drugs used to treat pulmonary infections that are currently not available.

Methods

Applicability of DBS for drugs used in pulmonary infections

In order to attain our first goal of giving an overview of TDM of drugs to treat pulmonary infections, we started by selecting microorganisms that cause these infections. For our review, we limited the pulmonary infections in our search to those that are caused by common airway pathogens. These pathogens can be found in most guidelines for the treatment of pulmonary infections (for example in the guidelines of the Infectious Diseases Society of America, IDSA) and were determined in consultation with a pulmonologist. The following bacterial species were selected (in random order): *Streptococcus pneumoniae, Streptococcus anginosus, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus, Pseudomonas aeruginosae, Legionella species, Mycoplasma pneumoniae, Chlamydia psittaci, Chlamydophila pneumoniae, Coxiella burnetii, Bordetella pertussis, Proteus mirabilis, Klebsiella pneumoniae, Escherichia coli, Burkholderia cepacia Actinomyces species, Nocardia species and Acinetobacter baumannii.* We also selected *Mycobacterium tuberculosis.* Besides bacteria mentioned above, fungi and viruses also cause pulmonary infections. Therefore, we selected *Aspergillus*, a mold capable of causing pulmonary infections in immunocompromised patients. We selected the following common viruses: influenza (common flu), para influenza, rhino virus, human meta pneumonia virus and rhino synovial virus. We also selected the following less common viruses: cytomegalovirus, herpes simplex and adenovirus.

After finalizing the list of common airway pathogens, the anti-infective drugs that are active against these pathogens were retrieved from commonly available antimicrobial guidelines (for example IDSA guidelines and guidelines from the American Thoracic society). We selected antibiotic,

antifungal and antiviral drugs that are readily available in most countries. We only included drugs that could be used for systemic treatment, i.e. intravenous or oral formulations, according to their summary of product characteristics. Antimicrobial drugs that are nebulized or inhaled as dry powder are only applied for local therapy in the lung resulting in reduction in colonization or are given as prophylaxis. DBS will not likely be used for these treatment strategies.

Of these selected drugs, we presented an overview of several parameters in order to determine whether DBS, facilitating drug concentration guided dosing, might be useful. Therefore we determined the need for dose adjustment in renal or hepatic impairment, the impact of interactions on the PK of the drugs and the relevance of TDM in general. A number of PubMed searches were conducted using the following keywords: names of the selected drugs AND pharmacokinetics, pharmacodynamics, PK/PD, interactions, therapeutic drug monitoring, TDM, renal impairment or hepatic impairment. The duration of treatment was estimated, based on treatment duration used in pulmonary infections. Treatment duration exceeding two weeks was considered to be long term treatment.

Available DBS methods for drugs used in the treatment of pulmonary infections

After selecting drugs for which DBS could be useful, we searched PubMed for articles about DBS analytical methods for the antimicrobial drugs used in pulmonary infections. We expanded this search by including immunosuppressive drugs (cyclosporine, tacrolimus, everolimus, sirolimus and mycophenolate). To our opinion this expansion of the search could be useful because the patients using immunosuppressive drugs are often prone to pulmonary infections. In addition, these patients

may already be familiar with DBS sampling (some laboratories might already use DBS in TDM of immunosuppressive drugs) and the DBS analysis could be extended with the antimicrobial drugs discussed in this review. We searched for articles with the names of the selected drugs AND dried blood spot testing OR dried blood spot OR DBS. Only articles about DBS methods in humans for the selected drugs were included. Articles about other drugs, dried plasma spots (DPS), DBS in animals and articles that did not describe DBS sampling were excluded. From the retrieved articles we extracted information about the analytical method, type of DBS card, type of spot, extraction method, haematocrit effects and correction, stability of the sample, linear range and clinical validation of the analytical method.

Feasibility of developing DBS methods for drugs used in pulmonary infections

For some antimicrobial drugs no DBS method could be retrieved from literature. However, for these drugs a DBS method could be of clinical use. Therefore a feasibility assessment was performed. To determine the lowest level of quantification that the DBS method should be able to measure, we verified the summary of product characteristics of the drugs for information on the expected trough concentrations. For the drugs for which this information was not stated, a PubMed search was performed using the names of the drugs and the terms pharmacokinetics, single dose, volunteers and human. We searched for publications describing the pharmacokinetics in healthy volunteers after a single dose and derived the minimal concentration of this drug. Subsequently PubMed was searched for published methods of analysis for these drugs in human plasma, serum or whole blood. The search was restricted to analytical procedures using liquid chromatography tandem mass spectrometry (LC-MS/MS) because of the required sensitivity for DBS analysis. Out of the publications found, we selected one analysis method per drug. To determine if these methods were

237 suitable for DBS we derived the concentration range, the extraction method and the stability

238 information.

239

Results

Applicability of DBS for drugs used in pulmonary infections

In table 1, an overview of the drugs used in pulmonary infections is presented. This overview indicates whether a DBS analysis technique would be useful for these drugs. We selected drugs for which TDM is relevant based on the need for dose adjustments in renal or hepatic impairment, pharmacokinetic interactions and duration of treatment. Multiple drugs are excreted renally and need dose adjustment in patients with renal impairment. For drugs undergoing metabolism in the liver, dose adjustments may be required in patients with impaired hepatic function. Several drugs are metabolized trough Cytochrome P450 (CYP) enzymes, which can lead to interactions when combined with drugs or other substances that induce or inhibit these enzymes. Moreover, for several CYP enzymes, the genetic background strongly determines activity (e.g. CYP2D6) [23]. In all these situations, TDM can be relevant, either in a group of patients or in individual cases. Because of increasing antibiotic resistance, TDM is more important to guarantee therapeutic blood levels of these drugs.

Advantages of DBS in pulmonary infections

In the following, we will describe whether or not DBS can be useful for the different groups of drugs used for the treatment of pulmonary infections. In general, DBS could be useful for different settings, in a small hospital, in the outpatient setting or for neonates. Small hospitals will not likely have an in-house laboratory that is able to measure plasma or serum concentrations of these drugs. DBS will simplify transportation of the sample so that dry ice cooled shipment of plasma or serum samples to a reference laboratory will not be necessary. In cases where the patient is treated at home, either with oral drugs or with parenteral drugs, DBS can be convenient for the patient. The patient can sample at home with or without help of the home care nurse and send the sample to the laboratory. In neonates, DBS sampling can be helpful because of the very small amount of blood needed. When considering DBS, it is important to take the increased turnaround time into account. Drying time of the DBS sample, shipment by mail and sample processing of a DBS sample may increase turnaround time. When feedback on the concentration of the sample is urgent, DBS is less suitable. For routine TDM checks, or less urgent questions, DBS could be very practical.

Beta-lactam antibiotics

For beta-lactam antibiotics it has been shown that dose adjustment is recommended for most drugs in patients with renal impairment, especially when combined with β-lactamase inhibitors [24-30]. These drugs are not extensively metabolised by liver enzymes and therefore dose adjustments in patients with hepatic impairment are not required. Caution is required when using clavulanic acid in patients with hepatic impairment [31]. Because of their lack of metabolism by the CYP450 isoenzym system, there are no important drug-drug interactions with drugs inducing or inhibiting these enzymes that influence the pharmacokinetic profile of the beta-lactam antibiotics [24, 28, 32]. Drugs

influencing the renal clearance of beta-lactam antibiotics could influence their pharmacokinetic profile, but the beta-lactam antibiotics have a wide therapeutic index [32]. Based on their safety and their consistent PK profile, beta-lactam antimicrobial drugs are not often subjected to TDM. However, in critically ill patients it is recommended to perform TDM to prevent sub-therapeutic or toxic blood concentrations, because of the altered kinetic parameters in these patients [33]. For critically ill patients, DBS sampling could be useful, but only in hospitals without a local laboratory. The only advantage would be stability of the sample and lower costs for transportation. The advantage of sampling would be of less importance because multiple blood samples are taken frequently from critically ill patients. TDM will generally not be required in outpatients because they are treated for community acquired infections which are normally susceptible to standard dosing and the treatment courses are generally short. DBS will therefore be of limited value in these cases.

Tetracyclines

For tetracycline antibiotics, TDM is not described in literature. Duration of treatment with these drugs is often short (one or two weeks). Dose adjustments are normally not required for tetracyclines in patients with renal (except for tetracycline) or hepatic impairment [25, 34]. Tetracyclines do have important drug-drug interactions related to their absorption or their metabolism that influence the plasma levels of tetracyclines [35, 36]. It is advised to switch to another antibiotic in these cases or not to take these drugs at the same time to make sure the absorption of the tetracycline is not affected [35]. Because there is no need for TDM, DBS will not be useful for tetracycline antibiotics.

Fluoroquinolones

Fluoroquinolones are used for a multitude of lung infections. Ciprofloxacin is used in more common infections, while moxifloxacin is used for infections caused by less common or resistant pathogens, for example *Mycobacterium tuberculosis*. Most fluoroquinolones need dose adjustments in patients with decreased renal function [25, 37-39]. These drugs are not extensively metabolised in the liver, so no dose adjustments are required for patients with impaired liver function [37, 40]. The plasma levels of the fluoroquinolones can be altered by drugs that influence the P-gp activity [36]. Furthermore, absorption can be reduced when the drugs are administered together with cations [41]. In most infections, the treatment duration with fluoroquinolones is short, but tuberculosis (TB) patients are treated for a long period of time [41]. Especially in multidrug-resistant tuberculosis and in cystic fibrosis patients or patients treated for hospital acquired pneumonia, TDM can be important [32, 38, 41, 42]. DBS can be of great advantage in these situations because these patients can be treated at home. Patients could be able to sample at home and send the DBS card to the laboratory. The physician can monitor the treatment from a distance.

Aminoglycosides

TDM for aminoglycosides is widely accepted because of their small therapeutic range and their toxicity profile [43]. Dose adjustments for aminoglycosides are required in patients with impaired renal function [44]. Also, when aminoglycosides are administered together with drugs that influence their renal clearance, the kinetics of the aminoglycosides will change and the plasma concentration of the drugs needs to be monitored [32]. Aminoglycosides do not undergo hepatic metabolism and therefore dose adjustment in patients with hepatic impairment is not required [44, 45]. Sometimes, patients can be treated at home with an aminoglycoside, for example patients with cystic fibrosis or

patients that need long term treatment with aminoglycosides. TDM usually requires a Cmax and a trough concentration [43]. DBS can be very helpful in these cases because sampling can be performed before and after the infusion at the patient's home. DBS can simplify logistics of sampling for aminoglycosides.

Macrolides

Treatment with macrolides can be both short term and long term [46]. Macrolides can be used for treatment of infection but also for prophylaxis in patients with CF (azithromycin) or tuberculosis (clarithromycin). For clarithromycin, dose adjustments are recommended for patients with impaired renal function [46]. The macrolide plasma concentration is influenced by drugs that inhibit or induce CYP3A4 [36, 47]. Normally, standard dosing is accepted for macrolides because of their wide therapeutic index, therefore TDM is not recommended [32]. However, in special populations like patients with TB, TDM of clarithromycin is recommended to prevent subtherapeutic plasma concentrations [48]. DBS can be useful for TDM of clarithromycin in TB patients.

Rifamycines

Rifamycin treatment courses are long, varying from weeks to months. The plasma concentration of these drugs is influenced by many drug-drug interactions, furthermore the absorption of rifampicin is variable and influenced by both food and drugs [49, 50]. Rifampicin is metabolised by the liver, and therefore dose adjustment is recommended in patients with hepatic impairment [49]. In specific populations like patients with TB, TDM is recommended for these drugs to ensure therapeutic plasma concentrations [51]. For outpatient use, or use of rifamycines in a smaller hospitals without

abilities to analyse rifamycin samples, DBS can be useful. Also for patients treated with oral rifamycines, sampling would be less painful using DBS.

Glycopeptides

Glycopeptides are most often used in hospitals because they are administered intravenously. These drugs are not extensively metabolised, but are subject to renal elimination and dose adjustment for patients with renal impairment is necessary [43, 52]. Because of their lack of hepatic metabolism, there are no important drug-drug interactions that influence the pharmacokinetic profile of the glycopeptides [32, 53]. Only drugs that influence the renal clearance can influence the plasma concentration of glycopeptides [32, 53]. TDM is highly recommended for vancomycin, because of its small therapeutic index and toxicity profile [43]. For teicoplanin TDM is recommended in special populations, to ensure therapeutic plasma concentrations; toxicity is less important for teicoplanin (except for high dosing) [43, 53]. For both vancomycin and teicoplanin DBS can be useful. In hospitals without a local laboratory DBS could improve sample logistics and reduce costs. For outpatient use, regular check of effectivity and toxicity of glycopeptides would be possible wih little inconvenience for the patient.

Lincosamides

For clindamycin, dose adjustments are not required for patients with impaired renal functions [25]. Neither are there important drug-drug interactions that influence the plasma concentrations of this drug [54]. TDM is not recommended in literature. There is no importance to develop a DBS method for this group of drugs.

Oxazolidinones

Oxazolidinones are important drugs in the treatment of TB. Patients are treated with these drugs for a long period of time. The drugs are susceptible to interactions with food or drugs influencing P-gp [55, 56]. In special populations it is recommended to perform TDM for these drugs because of their toxicity profile [51, 55]. DBS can be useful in these cases. Especially for outpatients DBS could be convenient, and lower transportation costs.

Other microbial agents

For TB drugs like ethambutol, isoniazid, pyrazinamide and clofazimine it is recommended to perform TDM [51, 55]. Patients are treated with these drugs for a long period of time. Also dose adjustments are required for some of these drugs in patients with impaired renal function [46]. For these patients, DBS can improve the ease of sampling, especially in outpatient settings.

TDM for protionamide, thioacetazone and metronidazole has not been described in literature. For these drugs, dose adjustments are not required in patients with impaired renal function, nor are there important drug interaction mechanisms that influence the plasma concentration of these drugs [46]. DBS will not be relevant for these drugs.

Cotrimoxazole is eliminated through the kidneys [57, 58]. It can be used both short and long term. Usually treatment with cotrimoxazole is short term. Long term treatment is used especially in TB patients or transplantation patients. In critically ill patients, TDM could be useful because of the toxicity profile of cotrimoxazole at high doses and to guarantee therapeutic plasma concentrations [57]. In these cases DBS can be useful in small hospitals. The dosing for outpatient use will be lower

(more susceptible organisms of prophylactic use) and therefore the risk of toxicity is decreased. In these cases TDM and therefore DBS would not be important.

The new marketed drugs for the treatment of TB, delamanid and bedaquiline, are both metabolised by CYP isoenzymes (delamanid less then bedaquiline) [59]. Because of the comedication used in patients treated with these drugs, TDM could be useful in individual patients [60]. Examples include patients also treated with antiretroviral drugs or patients treated with rifamycines or other inducers or inhibitors of CYP3A4 [60]. For bedaquiline and delamanid, monitoring of plasma levels can also be useful because the absorption is dependent on food [60]. Although there are limited data available yet, also in patients with impaired renal or hepatic function TDM could be helpful for bedaquiline and delamanid. For these situations DBS could be useful, especially in the outpatient setting. DBS would lower costs and also sampling will be less painful for the patient.

Antiviral drugs

In general, the antiviral drugs are excreted renally, therefore dose adjustment is recommended in patients with impaired renal function [61-65]. The efficacy of these drugs is mostly monitored by the viral load of the patient. There are no important drug-drug interactions influencing the plasma concentration of these drugs [62, 64, 66]. TDM is not recommended for most of these drugs [64]. For (val)ganciclovir TDM is described to prevent subtherapeutic plasma concentrations and toxicity in special populations when there is uncertainty about the exposure [67]. For ribavirin TDM is described in the treatment of hepatitis C because of the clear relationship between ribavirin concentration and both virological response and side effects. In patients with decreased renal function, TDM could be helpful [68]. When ribavirin is used in the treatment of pulmonary viral infections, TDM could help in individual cases to optimize ribavirin dosing. In these cases DBS can be

412 useful for (val)ganciclovir and ribavirin. DBS has also been demonstrated to be useful for monitoring
413 the viral load of the patient [69].

414

415 **Antifungal drugs**

416 The triazole antifungal drugs voriconazole, posaconazole and itraconazole are subject to CYP450
417 metabolism and because of that, the plasma concentration of these drugs is influenced by drug-drug
418 interactions [36, 70-73]. Voriconazole has a nonlinear pharmacokinetic profile and there is a wide
419 intra and interindividual variety [71]. Patients are often treated with these drugs for a long period of
420 time. TDM is recommended to assure therapeutic plasma concentrations and prevent side effects
421 [71]. For itraconazole TDM can be used to assure sufficient absorption of this drug [74]. TDM of
422 posaconazole can be useful in critically ill patients, patients with presumed malabsorption, children
423 and patients taking drugs that alter gastric pH [75].

424 TDM of amphotericin B is not recommended, this drug is not suspected for drug interactions, nor
425 are dose adjustments required in patients with renal impairment[76]. Caspofungin is a poor
426 substrate for CYP450 and therefore only strong inhibitors or inducers will influence the plasma
427 concentration of caspofungin [77]. TDM is only recommended in individual cases when there are
428 pharmacokinetic changes or drug-interactions [78].

429 For caspofungin DBS could also be useful in hospitals without a local laboratory.

430

431 **Available DBS methods for drugs used in the treatment of pulmonary infections**

After deciding for which drugs DBS could be useful, we searched for publications describing an analytical DBS method for the drugs mentioned in table 1. In table 2 an overview of the results from this search is shown. We included immunosuppressant drugs in this overview because patients taking these drugs are often susceptible to pulmonary infections [79]. For immunosuppressant drugs there are a lot of papers describing an analytical DBS method for these drugs. We found 25 methods for the analysis of 5 immunosuppressant drugs. We found 16 analysis methods for 13 drugs used to treat pulmonary infections. Most analysis methods are LC–MS/MS methods. In almost all methods, part of the blood spot is punched from the paper and the drug is extracted by simple liquid extraction.

Not all papers investigated the haematocrit effect for their DBS method, 13 papers did not investigate the haematocrit effect, 17 papers did investigate it. Out of these, 6 did not observe a significant effect and 11 did observe a significant effect.

Stability data vary a lot between the publications, especially the tested period of time and the temperature conditions. Not all publications investigated the stability at ambient temperature. For some drugs, stability of the DBS sample is an issue, for example ertapenem, (val)ganciclovir and metronidazole.

Clinical validation is not performed in all studies, 16 papers did describe a clinical validation of their DBS method, 6 papers did not describe a clinical validation, 2 papers only validated their method with spiked blood samples, 7 papers used venous dried blood spots (VDBS) for validation the of their method. A large variability was observed in the number of patients used for the clinical validation.

Feasibility of developing a DBS method for drugs used in pulmonary infections

For the drugs that we decided DBS could be useful based on the results presented in table 1 but we could not find a published DBS method as shown in table 2, we searched for published analysis methods for these drugs. In table 3 these results are presented. We also present the concentration that should be required to measure based on the expected minimal plasma concentration. For most of the drugs described, it would be feasible to develop a method for DBS analysis based on the available LC-MS/MS method for that drug. The sensitivity of a LC-MS/MS method is normally sufficient for measuring the expected minimal concentration for these drugs. When there is no LC-MS/MS method available, it would be less easy to develop a DBS method. For methods with a more extensive extraction method it could be more difficult to use this analytical method for a DBS analysis. Stability of the samples is only investigated for a couple of hours in most publications. When developing a DBS method, the stability of the compound on paper should be taken into account because of transportation time of the sample at ambient temperatures.

When prioritizing development of DBS methods, it is preferred to start with developing a method for drugs in which TDM is highly recommended. Therefore, we recommend starting with DBS methods for aminoglycosides and glycopeptides. Also for drugs used in treatment of TB, a DBS analysis technique would be very advantageous because of the long term treatment and treatment in hospitals without a local laboratory or outpatient use. DBS measurement of itraconazole can also be helpful in treatment of patients who need long term itraconazole treatment and also use immunosuppressant drugs, because these patients may already be familiar with DBS sampling. DBS sampling for beta-lactam antibiotics, fluoroquinolones and caspofungin is of less priority, but may also be important for laboratories that receive a lot of samples from other hospitals.

For some of the drugs there is no LC-MS/MS method published yet. For the drugs used in the treatment of TB (clofazimine, bedaquiline and delamanid) it might be worthwhile to develop a LC-MS/MS method to be able to perform DBS in the future.

477 **Table 3: Feasibility of developing a DBS method for drugs used in pulmonary infections**

Drug	Concentration range ng/mL	LC-MS/MS method available?	Publication	Matrix	Method of extraction	LLOQ ng/mL	Stability in plasma	DBS easily possible?
Aminoglycosides								
amikacin	750[#]	yes	Bijleveld et al. [80]	plasma	PP	300	96h at AT	yes
kanamycin	<2000 [81]	yes	Dijkstra et al. [82]	serum	PP	100	24h at AT	yes
streptomycin	<1000 [83]	yes	Zhou et al. [84]	plasma	PP	10.0	8h at AT	yes
tobramycin	540 [85]	yes	Attema-de Jonge et al. [86]	plasma	PP	50	24h at AT	yes
Beta-lactam antibiotics								
Carbapenems								
doripenem	1000* [87]	yes	Ohmori et al. [88]	serum	SPE	500	No data	yes
imipenem	<1000[#]	yes	Sakke et al. [89]	plasma	PP	100	No data	yes
meropenem	200* [90]	yes	Sime et al. [91]	plasma	PP	100	4h at AT	yes

Cephalosporins								
cefazolin	2000 [92]	yes	Sime et al. [91]	plasma	PP	100	4h at AT	yes
cefotaxim	400* [93]	yes	Szultka et al. [94]	whole blood	SPME	0.465	No data	yes
ceftazidim	1500 [95]	yes	Sime et al. [91]	plasma	PP	100	4h at AT	yes
ceftriaxone	10,000* [96]	no	-	-	-	-	-	no
cefuroxim	300 [97]	yes	Partani et al. [98]	plasma	SPE	81	7h at AT	yes
Monobactams								
aztreonam	100 [99]	no	-	-	-	-	-	no
Penicillins								
amoxicillin	100* [100]	yes	Szultka et al. [94]	whole blood	SPME	0.391	No data	yes
benzylpenicillin	1000* [101]	yes	Sime et al. [91]	plasma	PP	100	4h at AT	yes
flucloxacillin	800* [102]	yes	Sime et al. [91]	plasma	PP	250	4h at AT	yes

Fluoroquinolones								
ciprofloxacin	100* [103]	yes	Szultka et al. [94]	whole blood	SPME	0.436	No data	yes
levofloxacin	1210 [104]	yes	Jourdil et al. [105]	plasma	PP	120	24h at AT	yes
ofloxacin	1000* [106]	yes	Meredith et al. [107]	plasma	PP	78	4h at AT	yes
Glycopeptides								
teicoplanin	8330 [108]	yes	Tsai et al. [109]	plasma	PP	140	24h at AT	yes
vancomycin	8000#	yes	Tsai et al. [109]	plasma	PP	500	24h at AT	yes
Oxazolidinones								
cycloserin	2000* [110]	yes	Polagani et al. [111]	plasma	PP	50.9	9h at AT	yes
Other								
bedaquiline	100* [112]	no	-	-	-	-	-	no
clofazimin	200-600#	no	-	-	-	-	-	no
ethambutol	200* [113]	yes	Zhou et al. [84]	plasma	PP	0.5	8h at AT	yes

delamanid	304 [114]	no	-	-	-	-	-	no
isoniazid	148 [115]	yes	Zhou et al. [84]	plasma	PP	4.0	8h at AT	yes
pyrazinamide	788 [115]	yes	Zhou et al. [84]	plasma	PP	4.0	8h at AT	yes
sulfamethoxazole	37,800 [116]	yes	Bedor et al. [117]	plasma	SPE	500	6h at AT	Yes
trimethoprim	810 [116]	yes	Bedor et al. [117]	plasma	SPE	50	6h at AT	yes
Antifungal drugs								
caspofungin	1770 [118]	yes	van Wanrooy et al. [78]	plasma	PP	100	72h at AT	yes
itraconazole	523#	yes	Alffenaar et al. [119]	serum	PP	100	24h at AT	yes

478 SPME: solid phase micro extraction, PP= protein precipitation, SPE: solid phase extraction, AT: ambient temperature, LLOQ: Lower Limit Of Quantification, *estimation, no exact

479 data available in publication. The method of detection in all publications was UPLC-MS/MS or LC-MS/MS. # Based on the Summary of Product Characteristics.

Discussion

DBS can be an important tool in optimizing the treatment of pulmonary infections, however there is still a lot of work to be done in developing DBS methods for the drugs used in the treatment of these infections. For several antimicrobial drugs used in the treatment of pulmonary infections, TDM can be useful. For betalactam antibiotics, TDM is recommended only in critically ill patient. Therefore DBS sampling is of limited value and would only be useful in hospitals without a local laboratory. For tetracyclines and lincosamides there is no general need for TDM, therefore there will be no value for a DBS method. Patient treated with aminoglycosides and glycopeptides could benefit from DBS sampling when they are treated at home. For drugs used in the treatment of TB (for example: rifamycines, clarithromycin, isoniazide, ethambutol) TDM is often important and DBS sampling could be really convenient for patients [18]. For smaller hospitals, DBS sampling for these drugs would lower transportation costs of samples. For antifungal drugs (posaconazole, voriconazole, itraconazole) TDM is important and DBS can be useful for these drugs [120]. Transplantation patients that use one of these drugs at home might also be familiar with DBS sampling (for immunosuppressant drugs) and may be capable to sample themselves or otherwise sample with the help of a homecare nurse.

We found several published DBS methods, especially for immunosuppressive drugs. For these drugs, DBS is helpful when performing TDM in transplantation patients. Furthermore, we found published DBS methods for antifungal drugs and some antibiotics. In this review we have excluded DPS, because DPS required centrifugation of the sample. Especially in outpatient setting, this would be less advantageous than DBS sampling. However, nowadays there are for example Noviplex™ Cards available that can generate plasma spots out of whole blood in a very short amount of time.

There are a lot of drugs used for treating pulmonary infections for which DBS would be useful but there are no published DBS methods yet. Based on the available LC-MS/MS analysis methods already published for these drugs, the future development of DBS analysis methods is considered feasible. Depending on the type of laboratory, it can be decided for which drugs the development of a DBS analysis method will be worthwhile. When a laboratory processes a lot of external samples from other hospitals, it can be useful to develop a method for aminoglycosides and glycopeptides. Also when there are many patients treated at home with these drugs, developing a DBS method for aminoglycosides and glycopeptides could be a strategic choice. When a laboratory receives a lot of samples for TB patients, it can be convenient to develop a single method for drugs used in the treatment of TB like the recently published analysis method by Kim et al. for 20 anti-tuberculosis drugs in human plasma [121]. For hospitals with many transplantation patients, developing a DBS method for antifungal drugs could be important.

In the development of a new DBS method, it is important to execute a good analytical and clinical validation. Aspects that are important in validating the method are for example haematocrit effect and stability of the sample [21, 122]. We noticed that for some methods, the stability of the sample was not tested at ambient temperature, nor at higher temperature or that it was tested for a short period of time. We recommend testing the stability of the drug in the DBS sample for at least 7 days at ambient temperature and at higher temperatures, because of possible transportation time of the sample to the laboratory. When stability of the DBS sample is insufficient at ambient temperature or at higher temperature, the DBS method is less advantageous to use because stability issues during transportation of the sample. Furthermore, we

found that the haematocrit effect was not investigated in some publications. It is important to investigate the effect of the haematocrit and correct the effect if necessary to be able to generate reliable results [21].

Also a clinical validation of the DBS method is vital. For the clinical validation we recommend using the analysis results of patient finger prick samples and compare those with the analysis results of regular venous blood samples from these patients. We found that the clinical validation of DBS methods needs more attention; this was also described recently by Wilhelm et al. [123].

In conclusion, DBS can be promising in optimizing the treatment of patients with pulmonary infections. Especially for aminoglycosides, glycopeptides, anti-tubercolosis drugs and antifungal drugs, DBS could be of added value. There is a lot of work to be done in developing new DBS methods for these drugs. It is important to perform a good analytical and clinical validation when developing a new DBS method.

Future Perspective

In the future years, DBS will become a more important and more common method for performing TDM. Because of more centralization of laboratories and more outpatient treatment, DBS is more efficient than regular blood sampling. Multi-analyte DBS analysis methods, which contain tens of drugs, could be developed in the future. This would allow the analysis of DBS for multiple analytes from one DBS extraction and maybe even in one analytical run. The limitations for such an analysis method would be based more on the molecular properties of the analytes than on the group of drugs used for one disease. This could be advantageous for the efficiency of the laboratory and for patients which are

treated for multiple diseases. Also the transportation costs and sampling costs for TDM are lower when using DBS. In the future, it might even be possible to send a sample by drone, speeding up the delivery process and therefore generating results quicker and make early adjustment of treatment possible. Because of the lower costs using DBS, TDM could be performed more often. DBS can also be used more for sampling in clinical trials, minimizing the burden for the subjects participating in these trials, while generating more data. DBS methods will be developed for more and more drugs; official guidelines for developing and validating a DBS method would create more uniformity in the field. Implementation of automated systems for sample preparation will further simplify the analysis of a DBS sample and provide an opportunity to upscale the use of DBS, both in patient care and in clinical trials. More DBS data means more knowledge about the pharmacokinetics of drugs in large populations and optimization of therapy for pulmonary infections.

Executive Summary

Introduction

- Respiratory tract infections are among the most common infections in men.
- Therapeutic drug monitoring is important for the optimization of therapy in pulmonary infections.
- Dried blood spot sampling is increasingly applied in optimization of dosing in patients with infectious diseases.

Methods

- An overview of the importance of TDM of drugs used to treat pulmonary infections is provided.

- The DBS methods for drugs used in pulmonary infections that are already known from literature are described.
- The feasibility and priority of development of DBS methods that are currently not available are shown.

Results

- TDM is important for different groups of drugs used in the treatment of pulmonary infections.
- We found 15 DBS analysis methods for 12 drugs used to treat pulmonary infections.
- For most drugs used in pulmonary infections it may be feasible to develop a DBS method.

Discussion

- Depending on the type of laboratory, it can be decided for which drugs developing a DBS method can be useful.
- Official guidelines for developing and validating a DBS method would create more uniformity in the field.
- The clinical validation of DBS methods needs more attention.

[14] *: Interesting paper that describes the importance of TDM of beta-lactam antibiotics in critically ill patients.

[18]: * interesting paper describing the use of DBS for TDM in tuberculosis.

[21] *: interesting paper describing the technical aspects of DBS and the importance of validation for DBS.

[22]: * interesting paper describing the use of potassium as a marker To predict the Hct of a given DBS.

[36]: * interesting paper about important drug-drug interactions conserning inhibition of CYP3A4 and the role of TDM.

[121]: * Interesting paper describing the LC-MS/MS analysis of 20 anti-tuberculosis drugs in plasma.

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Supplementary Table 1: An overview of drugs used in pulmonary infections in relation to therapeutic drug monitoring and the application of DBS.

Drugs	Route of administration[#]	Dose adjustments*	PK/PD	Sampling time for TDM	Pharmacokinetic interactions[$]	Duration of treatment	TDM relevant - Commonly accepted - Only in special populations - Individual cases	DBS useful
Beta-lactam antibiotics			Time above MIC [1]		No important mechanisms [5]	LT and ST	Only in special populations [3, 4]	Y
Penicillins							Only in special populations [2]	Y
amoxicillin	oral/IV	Y(R), N(H)[§]				LT and ST		Y
benzylpenicillin	IV	Y(R) [6], N(H)[Ψ]				LT and ST		Y
pheneticillin	oral	No data				ST		N
flucloxacillin	oral/IV	N(R) [7], N(H)[Ψ]				LT and ST		Y
piperacillin	IV	Y(R), N(H)[§]				LT and ST	Only in special populations [8]	Y

Cephalosporins			Time above MIC [1]	Trough [2]	No important mechanism [5]	LT and ST	Only in special populations [2]	Y
cefazolin	IV	Y(R), N(H)[§]						
cefotaxim	IV	Y(R) [6], N(H)[ψ]						
ceftazidim	IV	Y(R), N(H)[§]						
cefuroxim	IV	Y(R) [6], N(H)[ψ]						
ceftriaxone	IV	Y(R) (in high doses) [9] Y(H)[ψ]						
Carbapenems			Time above MIC [10, 11]		No specific interactions [10, 12]	LT	Only in special populations [13]	Y
doripenem	IV	Y(R) [12], N(H)[ψ]						
ertapenem	IV	Y(R) [14], N(H)[§]						
meropenem	IV	Y(R)[§] N(H)[13]		Trough [2]				

imipenem	IV	Y(R) [10], N(H)$^{\psi}$						
Monobactams			Time above MIC [1]	Trough [2]			Only in special populations [2]	Y
aztreonam	IV	Y(R), N(H) [15]			No specific interactions [16]	LT		
Tetracyclines			AUC/MIC [17]	No data	Iron [18]	ST	No recommendations in literature	N
doxycycline	oral/IV	N(R, H)§			CYP3A4 [19]			
minocycline	oral	N(R, H$^{\psi}$) [20]						
tetracycline	oral	Y(R) [6] , N(H)$^{\psi}$			CYP3A4, P-gp [19]			
Fluoroquinolones			AUC/MIC [11, 21, 22]		Cations [21]		In special populations [21][23][5]	Y
ciprofloxacin	oral/IV	Y(R), N(H) [22, 22, 24]		Cmax and trough [23]	P-gp [19]	ST [21]		
levofloxacin	oral/IV	Y(R)[25], N(H) [23]		Cmax [23]	P-gp [19]	ST		
moxifloxacin	oral/IV	N(R) [6],		AUC [23]	Al/Mg, Antacids, Fe [23]	LT and ST		

		N(H) [26]						
ofloxacin	oral	Y(R) [22], N(H)$^{\psi}$		No data	CYP3A4, P-gp [19]	ST		
Aminoglycosides			Cmax /MIC [11, 27]	Trough and Cmax [28]	Drugs influencing renal clearance [5]	LT	Commonly accepted [28]	Y
gentamicin	IV	Y(R) [29], N(H)$^{\psi}$						
tobramycin	IV	Y(R) [29], N(H)$^{\psi}$						
kanamycin	IV	Y(R) [29], N(H) [30]						
amikacin	IV	Y(R) [29], N(H) [30]						
streptomycin	IV	Y(R) [29], N(H) [30]						
Macrolides				No data	CYP450 inhibition [31]		Not recommended [5]	N
azithromycin	oral	N(R) [6],	AUC/MIC [32]		CYP3A4 [19]	LT and ST	Not recommended	N

		Caution(H)§					[5]	
clarithromycin	oral	Y(R) [11], Possible (H)§	AUC/MIC [11]		CYP3A4, P-gp [19]	ST	Only in special populations [33]	Y
erythromycin	oral	N(R) [6], Caution(H)§	Time above MIC [27]		CYP3A4, P-gp [19]	ST	Not recommended [5]	N
Rifamycins								
rifampicin	oral/IV	N(R), Y(H) [34]	Concentration dependent killing [35]	Cmax and 6 hours [36]	P-gp, antacids, food, ketoconazole, cotrimoxazole, CYP450 [30, 37]	LT	In special populations [36]	Y
Glycopeptides			Time above MIC [27]	Trough [28]		LT		Y
teicoplanin	IV	Y(R)[38], No(H) [39]			No important mechanisms [39]		Only in special populations [28, 39]	
vancomycin	IV	Y(R)(H) [28]			Drugs influencing the		Commonly accepted	

					renal clearance [5]		[28]	
Lincosamides								
clindamycin	oral/IV	N(R) [6]	Time above MIC [27]	No data	No important mechanisms [40]	LT and ST	No recommendations in literature	N
Oxazolidinones								
linezolid	oral/IV	N(R) [11]	Time above MIC [27]/ AUC/MIC [35]	Trough [35]	P-gp [41]	LT	In special populations [35]	Y
cycloserin	oral	Y(R) [11], N(H) [30]	Cmax/MIC [35]	Cmax and 10 hours post dose [36]	Food [36]	LT	In special populations [36]	Y
Other								
ethambutol	oral	Y(R) [11], N(H) [34]	AUC/MIC [11]	Cmax [36]	Antacids [37]	LT	In special populations [36]	Y
isoniazid	oral/IV	N(R) [11],	AUC/MIC [11]	Cmax and 6	Food, antacids [34]	LT	In special populations	Y

		Y(H) [34]		hours [36]			[35]	
clofazimine	oral	N(R) [11]	No data	Cmax [36]	No important mechanisms	LT	Only in special populations [36]	Y
protionamide	oral	N(R) [11]	No data	No data	No important mechanisms	LT	No recommendations in literature	N
pyrazinamide	oral	Y(R) [11], Y(H) [30]	AUC/MIC [11]	Cmax and 6hr sample [36]	No important mechanisms	LT	Only in special populations [36]	Y
thioacetazon	oral	No data	No data	No data	No important mechanisms	LT	No recommendations in literature	N
metronidazole	oral/IV	N(R), Y(H)[§]	Concentration dependent killing [42]	No data	No important mechanisms [40]	ST	No recommendations in literature	N
trimethoprim-sulfamethoxazole	oral/IV	Y(R), N(H) [43, 44]	Time above MIC [44]	No data	No important mechanisms [43]	LT and ST	Only in special populations [44]	Y
bedaquiline	oral	Y(H) [Ψ], possible(R)[§]	AUC/MIC [45]	No data	CYP3A4 [45], food [46]	LT	Individual cases [46]	Y

delamanid	oral	No data[§]	Concentration dependent [47]	No data	CYP3A4, food [48][§]	LT	Individual cases	Y
Antiviral drugs								
(val)acyclovir	oral/IV	Y(R) [49]		No data	No important mechanisms [50]	LT and ST [51]	No recommendations in literature	N
(val)ganciclovir	oral/IV	Y(R) [52], N(H) [Ψ]	No data	Trough [53]	Drugs influencing the renal clearance, no interactions involving metabolism [54]	LT and ST [51]	Only in special populations [53]	Y
cidofovir	IV	Y(R) [55], N(H) [Ψ]		No data	No important mechanisms [54]	ST	No recommendations in literature	N
foscarnet	IV	Y(R) [54], N(H) [Ψ]			No important mechanisms [54]	LT	No recommendations in literature	N
oseltamivir	oral	Y(R), N(H)[§]			No important interactions [56]	ST [56]	Not recommended [56]	N
ribavirin	oral/IV	Y(R), N(H)[§]		AUC [57]	No important	ST	Only in special	Y

					mechanisms[§]		populations [57]	
zanamivir	IV	Y(R) [58], N(H) [Ψ]		no data	No important interactions [59]	ST	No recommendations in literature	N
Antifungal drugs								
voriconazole	oral/IV	N(R), Y(H) [60]	AUC/MIC [61]	Trough level [61]	CYP2C9, CYP2C19, and CYP3A4 [62]	LT [63]	Commonly accepted [62]	Y
itraconazole	oral/IV	N(R), possible (H)[§]	AUC/MIC [61]	Random [64]	CYP3A4, drug which affects gastric pH, P-gp [19, 61]	LT [63]	Only in special populations [65]	Y
posaconazole	oral	N(R, H) [60]	AUC/MIC [61]	Random [64]	Interaction with food, drugs which affect gastric pH, agents that increase gastrointestinal motility, CYP [61, 66, 67]	LT [63]	Commonly accepted [61, 68]	Y
amphotericin B	IV	N(R) [69]	Concentration dependent killing [69]	No data	No important pharmacokinetic	LT	Not recommended [65]	N

					mechanisms [69]			
caspofungin	IV	N(R), Y(H) [60]	AUC/MIC or Cmax/MIC [70]	Trough/ Cmax	CYP [70]	LT and ST [63]	Only in individual cases [71]	Y

[#] Route of administration is based on the formulation that is marketed in the Netherlands.

*Dose adjustments suggested in renal (GFR<50 ml/min) or hepatic impairment.

$ Pharmacokinetic mechanisms influencing the components' blood levels.[Ψ] Based on the metabolism of the drug.

[§] Based on the Summary of Product Characteristics

Abbreviations: IV: Intravenous, H= hepatic impairment, R= renal impairment, Y=yes, N=no, AUC (Area under the time – concentration curve), MIC: minimal inhibitory concentration, Cmax: peak concentration, CYP: Cytochromes P450, P-gp: P-glycoprotein, LT= long term, ST= short term (<2 weeks).

Parameters that apply to multiple drugs in a group are shown in the row of this group of drugs.

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794 **Supplementary Table 2: Available DBS methods for drugs used in the treatment of pulmonary infections.**

Drugs	Publication	Detection technique	Method of extraction	Used DBS card	Partial spot vs whole spot	Haematocrit (HT) effect observed and corrected	Stability of the sample	Linear range (ng/mL)	Comparison plasma or blood sample vs DBS?	Number of patients for clinical validation
Antibiotics/ antiviral drugs/antifungal drugs										
Clarithromycin [72]	Vu et al.	LC–MS/MS	LE	31 ET CHR	8 (P)	No significant HT effect observed	60 days at AT, 30 days at 37 °C, 15 days at 50 °C.	150 – 10,000	Y	N=4, S= 12
Ertapenem [73]	la Marca et al.	UPLC–MS/MS	LE	903	3,2 (P)	Yes, corrected	Only stable at -20°C	500 – 100,000	Y (spiked samples)	N.A.
Ganciclovir and valganciclovir [74]	Heinig et al.	LC–MS/MS	LE	FTA-DMPK-B	3 (P)	N.I.	limited (VGCV) no data (GCV)	16 – 40 (GCV) 4 – 10 (VGCV)	Y (VDBS)	N.A.

Gentamicin [75]	Fujlmoto et al.	FPIA	ultra filtration	filter paper type I	W	Yes, corrected	8 days at AT	1000 – 20,000	Y (spiked samples)	N.A.
Linezolid [76]	la Marca et al.	LC–MS/MS	LE	903	32 (W)	Yes, corrected	1 month at AT and 37°C	1000 – 100,000	Y	N=9, S=15
Linezolid [77]	Vu et al.	LC–MS/MS	LE	31 ET CHR	8 (P)	No significant HT effect observed	2 months at 37°C and 1 week at 50°C	50 – 40,000	Y	N= 8
Metronidazole [78]	Cohen-Wolkowiez et al.	LC–MS/MS	LE	FTA DMPK-C	3 (P)	N.I.	No data	50 – 50,000	Y	N=23, S=50
Metronidazole [79, 80]	Suyagh et al.	HPLC-UV	LE	Guthrie cards	6 (P)	N.I.	28 days at -20°C	2.5–50 mg/mL	No data	N=32, S=203
Moxifloxacin [81]	Vu et al.	LC–MS/MS	LE	31 ET CHR	8 (P)	Yes, corrected	4 weeks at AT	50 – 6000	Y (VDBS)	N= 6, S=36
Oseltamivir [82]	Hooff et al.	UPLC–	LE	Schleicher & Schuell	5 (P)	N.I.	7 days at AT, 24 hours at	5 – 1500	Y	N=3

		MS/MS		2992			40 °C			
Piperacillin and tazobactam [83]	Cohen-Wolkowiez et al.	LC–MS/MS	LE	FTA DMPK-C	6 (P)	N.I.	No data	150 – 150,000	Y	N=32, S=37
Posaconazole [84]	Reddy et al.	LC–MS/MS	LE	Ahlstrom Alh-226, FTA DMPK-C	3 and 6 (P)	No significant HT effect observed	13 days at AT	5 – 5000	N.I.	N.A.
Posaconazole [85]	van der Elst et al.	LC–MS/MS	LE	FTA DMPK-C	8 (P)	Yes, no correction	12 days at AT, 37°C, 50°C	100 – 10,000	Y	S=8
Ribavirin [86]	Jimmerson et al.	LC-MS/MS	LE	903	3 (P)	No significant HT effect observed	140 days at AT	50-10.000	Y (VDBS)	S=28
Rifampicin [72]	Vu et al.	LC–MS/MS	LE	31 ET CHR	8 (P)	Yes, corrected	2 months at AT, 10 days at 37 °C, 50 °C	150 – 30,000	Y	N=12
Voriconazole [85]	van der Elst et al.	LC–MS/MS	LE	FTA DMPK-C	8 (P)	Yes, no correction	12 days at AT, 37°C, 50°C	100 to 10,000	Y	S=11

Immunosuppressant drugs										
Cyclosporin [87, 88]	Wilhelm et al.	LC–MS/MS	LE	903	8 (P)	No significant HT effect observed	17 days at AT	25 –1440	Y	N=36, S=38
Cyclosporin [89]	den Burger et al.	LC–MS/MS	LE	903	8 (P)	Yes, corrected	5 months at 4°C	23.6 – 787	N.I.	N.A.
Cyclosporin [90]	Hinchliffe et al.	UPLC–MS/MS	LE	903	6 (P)	N.I.	14 days at AT	8.5 – 1500	Y (VDBS)	S= 153
Cyclosporin [91]	Koster et al.	LC–MS/MS	LE	31 ET CHR	8 (P)	Yes, corrected	7 days at 22°C	20.0 – 2000	Y (VDBS)	N=57
Cyclosporin [92]	Sadilkova et al.	LC–MS/MS	LE	903	8 (P)	No significant HT effect observed	30 days at AT	30 – 1000	Y (VDBS)	S= 79
Cyclosporin [93]	Leichtle et al.	LC–MS/MS	LE	903	4 (P)	N.I.	12h at AT	No data	Y	N=55
Everolimus [89]	den Burger et al.	LC–MS/MS	LE	903	8 (P)	Yes, corrected	5 months at 4°C	1.26 – 33.7	N.I.	N.A.
Everolimus [91]	Koster et al.	LC–MS/MS	LE	31 ET CHR	8 (P)	Yes, corrected	7 days at AT	1.00 – 50.0	Y (VDBS)	N=55

Everolimus [94]	van der Heijden et al.	LC–MS/MS	LE	903	7,5 (P)	N.I.	34 days at 32°C, 3 days at 60°C	2 – 30	Y	N= 1
Mycophenolic acid [95]	Arpini et al.	HPLC	LE	903	6 (P)	Yes, corrected	20 days at AT	250 – 40,000	Y	N=19, S=77
Mycophenolic acid [96]	Wilhelm et al.	HPLC	LE	903	8 (P)	Yes, no correction	26 days at 4°C	740 – 23,400	N.I.	N.A.
Mycophenolic acid [95]	Heinig et al.	LC–MS/MS	SPE	FTA-DMPK-B, Ahlstrom Alh-226	3 (P)	N.I.	24h at AT	100-40,000	N.I.	N.A.
Sirolimus [89]	den Burger et al.	LC–MS/MS	LE	903	8 (P)	Yes, corrected	5 months at 4°C	1.34 – 35.8	N.I.	N.A.
Sirolimus [91]	Koster et al.	LC–MS/MS	LE	31 ET CHR	8 (P)	Yes, corrected	7 days at AT	1.00 – 50.0	Y (VDBS)	N=36
Sirolimus [97]	Rao et al.	LC–MS/MS	LE	FTA	10 (P)	N.I.	90 days at 4°C	1 – 100	N.I.	N.A.
Sirolimus [92]	Sadilkova et	LC–MS/MS	LE	903	8 (P)	No significant HT	30 days at AT	1.2 – 40	Y (VDBS)	N=68

	al.					effect observed				
Tacrolimus [98]	Cheung et al.	LC–MS/MS	No data	Grade CF 12	7,5 (P)	N.I.	No data	No data	Y	N= 36, S=108
Tacrolimus [89]	den Burger et al.	LC–MS/MS	LE	903	8 (P)	Yes, corrected	5 months at 4°C	1.14 – 30.3	N.I.	N.A.
Tacrolimus [90]	Hinchliffe et al.	UPLC–MS/MS	LE	903	6 (P)	N.I.	14 days at AT	2.3 – 50	Y (VDBS)	S=158
Tacrolimus [99]	Hoogtanders et al.	LC–MS/MS	LE	Grade CF 12	7,5 (P)	N.I.	9 days at AT, 7 days at 37°C, 1 day at 70°C	1-30	Y	N=24
Tacrolimus [100]	Hoogtanders et al.	LC–MS/MS	No data	Grade CF 12	7,5 (P)	N.I.	No data (described in other article) [99]	No data (described in other article) [99]	Y	N=26
Tacrolimus [101]	Koop et al.	LC–MS/MS	SPE	FTA DMPK-A	6 (P)	N.I.	1 month at AT	1 – 50	Y	N=18

Tacrolimus [91]	Koster et al.	LC–MS/MS	LE	31 ET CHR	8 (P)	Yes, corrected	7 days at AT	1.00 – 50.0	Y (VDBS)	N=50
Tacrolimus [102]	Li et al.	LC–MS/MS	LLE	903	6 (P)	No significant HT effect observed	10 days at AT, 24 hours at 50°C	1 – 80	Y (VDBS)	N=50
Tacrolimus [92]	Sadilkova et al.	LC–MS/MS	LE	903	8 (P)	No significant HT effect observed.	30 days at AT	1.2 – 40	Y (VDBS)	N=115

795 LC–MS/MS = liquid chromatography tandem mass spectrometry, UPLC-MS/MS: Ultra performance liquid chromatography tandem mass spectrometer (UPLC-MS/MS), HPLC-UV=
796 High-performance liquid chromatography analysis with UV detection, P= partial spot, W= whole spot, LE= liquid extraction i.e. protein precipitation, LLE= liquid liquid extraction,
797 SPE: solid phase extraction, AT: ambient temperature, Y=Yes, N= number of patients, S= number of samples, VDBS= venous dried blood spot, N.I.=not investigated, N.A. Not
798 applicable, 903= Whatman 903, 31 ET CHR= Whatman 31 ET CHR, FTA DMPK= Whatman FTA DMPK, Grade CF 12= Whatman® qualitative filter paper Grade CF 12, filter paper
799 type I= filter paper type I (Toyo-Roshi), FTA= FTA Whatman, FPIA= fluorescence polarization immunoassay, GCV: ganciclovir, VGCV: valganciclovir. For the linear range of the
800 method the number of significant figures was described as stated in the publication.

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