4.2.3 Therapeutic drug monitoring (TDM)

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1. INTRODUCTION

- Pharmacokinetic parameters [i.e. Absorption, Distribution, Metabolism and Excretion (ADME)] of certain drugs differ significantly in CF. The exact mechanisms of this difference are not fully elucidated but some of the following have been suggested:
  - Slower and variable gastro-intestinal drug absorption (e.g. ciprofloxacin).
  - Increased distribution volume expressed in L/kg body weight (e.g. hydrophilic drugs such as aminoglycosides and beta-lactams). This mechanism is considered relevant in undernourished patients → decreased adipose tissue → increased lean tissue/kg body weight.
  - Increased hepatic drug metabolism (e.g. sulfamethoxazole).
  - Increased renal clearance (e.g. trimethoprim, aminoglycosides, cephalosporins).
  - Increased drug elimination in bile and/or bronchial secretions has been hypothesized but evidence is lacking.
- Consequently, plasma concentration exposure can vary in CF patients receiving standard dosages of conventional drugs and for some drugs higher doses/kg body weight may be required to reach therapeutic levels.
- Therapeutic drug monitoring (TDM) is based on the general assumption that the pharmacodynamic effects of drugs correlate better with circulating concentrations than with administered doses.
- TDM involves the measurement of drug concentrations in patients to optimize their drug dosage regimen by ensuring adequate exposure levels (good efficacy, tolerability and safety).

2. GENERAL CONSIDERATIONS

- TDM measurement must be done at the pharmacokinetic steady state and at the "trough"/residual time point, i.e. at the end of the dose interval (otherwise, special calculations are needed to estimate accumulation and elimination precisely).
- In theory, under regular dosage (intermittent administration or continuous infusion) and stable elimination mechanisms (renal excretion, hepatic metabolism), stable steady state is reached after 3 to 5 drug elimination half-lives.
- **"Trough"/residual concentration:** it corresponds to the point of the pharmacokinetic curve that is just before the next dose (practically about 5-10 minutes before) **(Figure 1)**.
- "**Peak" concentration**: sometimes it is determined for anti-infective agents even if it doesn't correspond exactly to the maximum plasma levels expected just at the end of drug infusion. As a rule, "peak" TDM samples must be drawn at the beginning of the elimination phase, when the distribution is complete **(Figure 1).** It is thus important to perform sampling at a standardized time-point after drug administration **(Table 1)**.

3. WHEN SHOULD TDM BE CONSIDERED?

- **There are no clear recommendations in the literature, regarding measurement of "trough" or "peak" concentrations of anti-microbial drugs in CF.** Most data in TDM of anti-infective agents originate from studies performed in the critical care context and this information may not be directly translatable to other clinical situations.
- **Practically, regarding "trough" concentration measurement in CF care:**
  - **For aminoglycosides and vancomycin a trough concentration is recommended routinely** as it informs about their toxicity. This is generally performed when the steady state has been reached. Then a check is commonly performed once a week. After a dosage adaptation, a new check is proposed once the new steady state has been reached.
  - **For voriconazole "trough" levels are recommended routinely.** This agent has well defined trough upper limits, above which there is an increasing risk of encephalopathy. Moreover, voriconazole can follow nonlinear pharmacokinetics due to saturable hepatic clearance at conventional dosing leading to disproportional variation of levels.
  - **For itraconazole and posaconazole "trough" levels are advised** due to the large variation in bioavailability of these agents and to the potential drug-to-drug interactions.
  - **For the other anti-infective agents measurement of "trough" concentration can be helpful in cases of:**
    - insufficient clinical response
    - suspected drug-related toxicity or overdose
    - metabolism or excretion that are not possible to evaluate with conventional estimation means (such as the Cockcroft and Gault formula for kidney function)
    - sepsis/septic shock
    - infection with MDR organisms (such as *B. cepacia* complex) for which MICs are high and would need higher doses and/or continuous perfusion of antibiotics
- **Practically, regarding "peak" concentration measurement in CF care:**
  - It is not routinely recommended but may be requested for **aminoglycosides** to ensure adequate blood levels are reached (these agents have a concentration-dependent mechanism of action, which means that the efficacy is related to the "peak" concentration).
  - For **colistin**, the "peak" concentration alone is not recommended to assess antimicrobial efficacy. "Peak" and "trough" concentrations are needed to estimate the Area Under the Curve (AUC) which is used in the AUC/MIC ratio. This ratio is considered the parameter best associated with efficacy.
  - Maximum concentration may be informative for monitoring **rifampicin** because trough levels are generally by far below quantification limits. Moreover, rifampicin is administered oral-ly with risks of compliance or absorption defects. Target range is not defined for non- tuberculous mycobacteria, so the classical target range for tuberculosis treatment may be used.
- Blood levels are formally not recommended for inhaled drugs, because systemic concentrations are low due to limited pulmonary absorption. However, a few case reports have been published with renal or cochlear-vestibular toxicity due to inhaled tobramycin in CF patients, particularly in those suffering from renal insufficiency. Therefore, in patients presenting with potential side effects of inhaled antibiotics, through levels should be considered.

4. INTERPRETATION OF THE RESULTS

- **TDM consists of a three-step process: a) quantification of plasma drug concentration, b) interpretation of the result and c) dosage adaptation if needed.**
  - TDM is a tool to help physicians in optimal dosage determination but **should always be considered critically in the context of the specific clinical situation.**
    - The initial questions should be: is the measurement result reliable? Is this result expected in the context of the specific patient and his/her drug dosage?
    - This first step is very important because there are many possible biases: inaccurate time of administration and/or sampling (e.g. treatment not having reached the steady state or sampling not performed at trough), dose administration error or analytical errors.
  - Then the suitability – or the appropriateness – of drug plasma concentration should be evaluated, taking into consideration the targeted concentration, the expected clinical response and the suspected side effects.
  - Finally, treatment dosage can be adapted if needed.
- Anti-infective agents are mainly used in CF during pulmonary exacerbations and most antibiotics (e.g. aminoglycosides and beta-lactams) are usually administered concomitantly for their synergic effects. TDM of anti-infective agents is performed in blood even if the most clinically relevant site of drug action during a pulmonary exacerbation is the pulmonary secretions:
  - It is important to keep in mind that, in case of systemic administration, drug concentration will be largely higher in the blood compared to the pulmonary secretions (the contrary will be true for inhaled drugs).
  - Even though levels in the pulmonary secretions may still be insufficient, circulating levels should not exceed the targets set for the treatment of systemic infections. Exceeding target blood levels may expose to toxic effects such as encephalopathy.
- **Plasma concentrations of anti-infective agents commonly measured correspond to free and protein bound molecules even if only the free concentration is considered active against bacteria**. The free concentration is rarely quantified due to technical challenges but can be estimated with the formula: free concentration = total concentration x free fraction, where free fraction = 1 – bound fraction.
  - For example, considering a trough aztreonam total concentration of 24 mg/L with a protein binding at 56% (according to **Table 1**), the free aztreonam concentration is equal to 24 x (1-0.56) = 24 x 0.44 = 11 mg/L. For an optimal effect, this free concentration, rather than the total concentration, must be above the MIC90 of the bacterium targeted (time-dependent agent).

5. TREATMENT ADJUSTMENT

- **If treatment adjustment has to be considered, a cross-multiplication represents a simple way to calculate a more convenient dosage** (adjusted dose = current dose $\times \frac{\text{target concentration}}{\text{observed concentration}}$). Otherwise, if for example the frequency of administration has to be modified, complex calculations are needed and couldn't be done without specific tools, such as Bayesian adaptive feedback software. Moreover, in case of intoxication/very high or too low blood levels, it could be necessary to prolong or shorten respectively the interval

between the last and the next doses. In all these cases, advanced pharmacokinetics skills are needed and a specialized advice is suitable.

- Once a new steady state has been reached, a new check should be considered.

Figure 1: Typical plasma concentration with TDM “peak” and “trough” concentration indicated

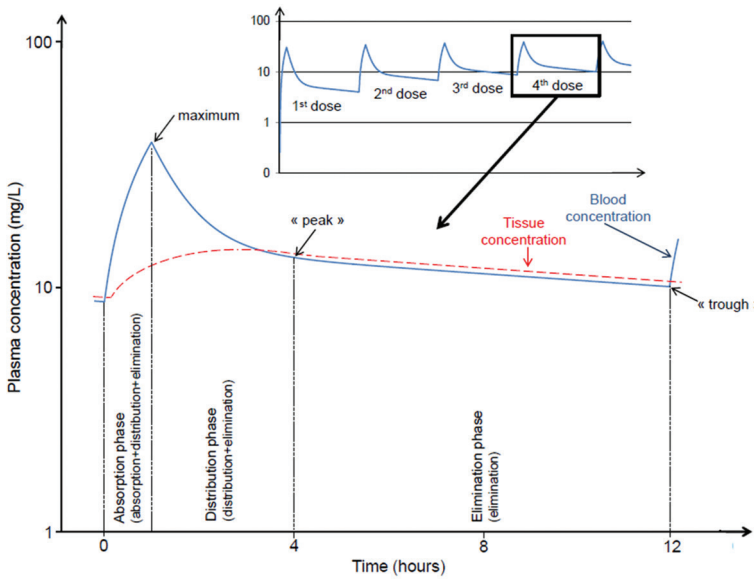

Table 1: TDM recommendations for anti-infective agents commonly used in CF

Drugs	Time to steady state*[1]	Sampling moments	Timing for peak level (after infusion ending)	Corresponding drug levels (mg/L)*[2]	Protein binding (%)	Comment
Aminoglycosides: concentration-dependent agents ("peak" level should reach about 10 times the MIC) with post-antibiotic effect. Monitoring to ensure a) adequate "peaks" and b) sufficiently low "troughs" to prevent oto- and nephrotoxicity.						
Amikacin	After 2 or 3 doses	"peak"	30 minutes	Depends on dosing*[3]	<10	**- "Trough" levels are recommended routinely.** - "Peak" levels are not routinely performed but may be used to ensure adequate blood levels of these concentration-depended agents - TDM should not be routinely used for inhaled aminoglycosides
		"trough"		Depends on dosing*[3]		
Gentamicin		"peak"		10 – 12	30	
		"trough"		< 1		
Streptomycin		"peak"		50 – 70	~25	
		"trough"		< 5		
Tobramycin		"peak"		20 – 40	<10	
		"trough"		< 1		
Glycopeptides: Generally considered as time-dependent agents. Monitoring to ensure a) blood levels above MIC even between administrations and b) sufficiently low "troughs" to prevent oto- and nephrotoxicity. In fact, AUC/MIC seems to best describe their efficacies.						
Vancomycin	After 3 doses	"trough" ("peak")	4 hours	10 – 15 15 – 20*[4]	30 – 55	**- "Trough" levels are recommended routinely** - "Peak" levels are not routinely recommended

Polymyxins: time-dependent agents						
Colistin (colistimethate)	After 3 doses	"trough" (« peak »)	4 hours	> 2 > 4*[5]	(~50)	- There is insufficient data to make strong, evidence-based recommendations for the TDM of colistin. -"Trough" levels may be helpful in suspected drug-related toxicity [large inter-patient variability of concentration, risk of nephrotoxicity and neurotoxicity, colistin is administered as an inactive prodrug (IV colistimethate sodium) and then is metabolized to the active colistin] -"Peak" levels are not routinely recommended -TDM should not be used for inhaled colistin
Rifamycins: concentration-dependent agents						
Rifampicin	After 1st dose	"Maximum"	2h after oral intake or after the end of the infusion	8 – 24	80	- "Maximum" levels may be helpful (see text) -"Trough" levels should be undetectable
Beta-lactams: time-dependent agents. Monitoring to ensure blood levels above the MIC even between each administration. Maximum pharmacodynamic effect is reached when serum levels stay about 4 times above MIC.						
Cefepime	After 3 doses	"trough"		2 – 15 8 – 15*[5]	20	"Trough" levels can be helpful in suspected drug-related toxicity [cefepime is the only beta-lactam with a well-defined toxic (encephalopathy) cut-off related to trough concentration]
Ceftazidime	After 3 doses	"trough"		> 2 > 8*[5]	20	TDM can be helpful in cases of insufficient clinical response, suspected overdose or metabolism or excretion that are not possible to evaluate by conventional estimation means. Also potentially helpful in case of MDR organisms with high MIC
Imipenem	After 3 doses	"trough"		> 2	20	
Meropenem	After 3 doses	"trough"			2	
Piperacilline – (tazobactam)	After 3 doses	"trough"		> 8 > 16*[5]	15	

Aztreonam	After 3 doses	"trough"		> 35*[5]	56	-TDM can be helpful in cases of insufficient clinical response, suspected overdose or metabolism or excretion that are not possible to evaluate by conventional estimation means -TDM should not be used for inhaled aztreonam
Antifungals: time-dependent agents						
Itraconazole	After 5 to 7 days	"trough"		> 0.5	>99	**-"Trough" levels are advised** (the hydroxy metabolite of itraconazole is also pharmacologically active, concentration-related toxicity, variable absorption) - The upper limit of therapeutic range is not established
Posaconazole	After 5 to 7 days	"trough"		>0.5 prophylaxis > 1 treatment	98	**"Trough" levels are advised** (large inter-patient variation in bioavailability, drug-to-drug interactions)
Voriconazole	After 5 to 7 days	"trough"		2 – 5*[6]	60	**-"Trough" levels are recommended routinely** because of the potential non-linear pharmacokinetics of voriconazole and the associated risk of accumulation - Voriconazole has a well-defined therapeutic interval with a well-defined toxic (encephalopathy) cut-off

Time-dependent agents: optimal effect at a concentration above MIC. Between dosing intervals, target concentrations should remain above the MIC. Examples: beta-lactams (incl. aztreonam and carbapenems), macrolides, clindamycin, tetracyclines, linezolid, azole antifungals.

Concentration-dependent agents: increasing effect with increasing concentrations (optimal effect at a concentration several times higher than the MIC; the target depends on the anti-infective agent and the infectious agent). Typically, they exert a postantibiotic effect, i.e. bactericidal activity for a period of time after the concentration has fallen below the MIC. Examples: aminoglycosides, rifampicin, quinolones, amphotericin B.

*[1] This corresponds to the theoretical steady state, without altered elimination pathway.

*[2] Drug levels indicated refer to bacteria. They have been principally determined according to the MIC90 of EUCAST database and corrected for protein binding. Fungal MICs are not considered; one should only refer to the recommended drug level in case of fungal infection.

*[3] Target blood levels for acute pulmonary exacerbation due to *P. aeruginosa*: for 30-35 mg/kg 1x/day, peak range 80-120 mg/L and trough levels <1 mg/L

Target blood levels for non-tuberculous mycobacteria infection:
-For 15mg/kg 1x/day: aim for peak levels 35-55 mg/L and trough levels ≤1.5 mg/L
-For 7.5mg/kg 2x/day: aim for peak levels 20-30 mg/L and trough levels ≤5 mg/L
-For 25mg/kg 3x/week (no literature data for TDM target): suggested peak levels 60-90 mg/L and trough levels ≤1.5 mg/L

*[4] Target blood levels in case of MRSA infection.

*[5] Target blood levels if MIC=2 mg/L

*[6] Levels <1 mg/L have been associated with therapeutic failure whereas levels >5.5 mg/L with toxicity. For fungal infections of poor prognosis, associated with less susceptible species (e.g. *Scedosporium* ssp.): target blood levels >2 mg/L, avoid exceeding 6 mg/L, consider combination with other antifungal agents in collaboration with the Infectious Disease specialist **(see also Chapter "*Fungi*").**

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