

The role of the laboratory in optimizing anti-infective therapies in critically ill patients

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Scope of the lecture:

This lecture describes the growing role of the clinical laboratories in the personalized medicine concept, applied to anti-infective agents for critically ill patients. Personalized medicine is based on a multidisciplinary laboratory approach involving the TDM but also the microbiology and the molecular/genetic testing laboratory.

Learning objectives:

1. Understand that a fast onset of adequate anti-infective treatment should assure a maximum chance of success
2. Summarize the progress observed in TDM approaches (analytics, pharmacokinetics and – genetics)
3. Identify the progress ongoing in the laboratory of microbiology

Extended abstract:

Since several decades, therapeutic drug monitoring (TDM) of anti-infective drugs has been widely recommended for aminoglycosides (gentamicin, amikacin, tobramycin) and glycopeptides (vancomycin, teicoplanin). More recently, some beta-lactam, antifungal, anti-tuberculosis or anti-viral agents were demonstrated good candidates for TDM as well. During the last decade impressive progresses were observed both in analytical methods (immunoassays, HPLC-UV or LC-MSMS) and in pharmacokinetics modelisation (e.g. population pharmacokinetics with bayesian estimators), improving the efficiency of such activity. However, limiting factors still remain:

- the risk of inaccuracy in the drug dosing and patient information provided (e.g. sampling times, doses, intervals, patients characteristics and biometrics, etc...)
- the delay in responding with appropriate interpretation, particularly in specific populations of critically ill patients

The critically ill populations include hematologic patients, immunocompromised, sepsis, cystic fibrosis, oncology, intensive cares, premature babies, severe renal insufficiency, nosocomial pneumonia, etc...). These pathologies are characterized by an important mortality rate during severe infections. It is well established that a significant part of the therapeutic efficacy depends on a fast onset of the adequate treatment/dosis of anti-infective agents.

Many of these pathologies are also characterized by variable and unstable pharmacokinetics. For instance, septic patients frequently display increased volume of distribution requiring larger drug doses as compared to the standard empirical regimen recommended in the literature. In such patient populations, the laboratory plays a key role in detecting rapidly inadequate dosage regimen. Some azole antifungals display variable pharmacokinetics (drug/food interactions, saturable metabolism of drug absorption, genetic polymorphism of metabolising enzymes, etc...). The degree of drug penetration into the target site may be affected by various covariates including the free fraction of the drug.

At the same time, other important laboratory contributions were observed in the landscape of the microbiology laboratory. The emergence of MALDI TOF and molecular testing

approaches in the routine laboratory allowed faster pathogens identification and resistance (susceptibility) profiles, through microarrays, PCR multiplex or NGS. PCR 16S rRNA may appear as a promising tool to rapidly identify bacteria and fungi. Manufacturers are currently intensively working in this competitive area (GeneXpert, Biomérieux, Stat-DX, GenMark, Luminex, Qiagen, BioFire ...). Automation, miniaturization, sequencing and bio-informatics are appearing in microbiology as in other fields. This revolution should contribute to obtain a faster selection of the most efficient therapy. What needed a few days in the past may now take a few hours!

Pharmacodynamic biomarkers identified by the laboratory (MIC, AUIC) should also be followed as complementary approach to support personalized therapies. Large multicentre trials are currently ongoing attempting to integrate all of these factors in one single approach. More than ever, the laboratory (as multi-disciplinary actors: microbiology, TDM, pharmacogenetics, molecular testing) plays a pivotal role in the success of individualized anti-infective therapies, particularly important in critically ill patients.

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- 3) Taccone FS et al. Insufficient B lactams concentrations in the early phase of severe sepsis and septic shock, *Crit Care*, 2010, 14, R126
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- 6) Buchan BW, Ledebor NA. Emerging technologies for the clinical microbiology laboratory. *Clin Microbiol Rev*, 2014, 27, 783-822