**Colistin**

*Resistance threatens the advances of modern medicine.*

Each year 4 million patients acquire a healthcare-associated infection in the European Union and about 37,000 of them die as the direct consequence of the infection (European Center for Disease Prevention and Control 2012: Surveillance of healthcare-associated infections in Europe 2007). Healthcare-associated infections are infections that occur after exposure to healthcare and carry a high risk of resistance. Modern anti-cancer strategies, organ transplantsations, and intensive care treatment are based on effective anti-infective drugs. Resistance threatens the future of these medical treatment concepts.

*No other choice – Relying on old antibiotics.*

According to the European-wide resistance surveillance system EARS-Net, frequent pathogens that cause healthcare-associated infections continue to show increasing resistance rates to many or even all commonly used antibiotics. Novel antibiotics with activity against important multidrug-resistant bacteria are not on the horizon. In such situations physicians resort to old and “forgotten” antibacterial drugs as these drugs may have retained their activity over all the years of not being used. As these old antibiotics have never been characterized in a structured process for drug assessment and approval essential issues have not been addressed. Such vital questions concern the appropriate dosage to maximize the activity while minimizing toxic effects and resistance development as well as modern concepts of individualized treatment decisions in severely ill patients.

*AIDA studies old drugs to optimize current usage.*

The European Commission decided to include the characterization of old off-patent antibiotics in their funding scheme of the 7th Framework program (FP7). One of the work packages of the project AIDA (Preserving old antibiotics for the future) aims at answering the question of optimal dosing regimens and clinical effectiveness of Colistin.

*Colistin is a revived old drug to treat multidrug resistant bacteria.*

Colistin - a mixture of cationic polypeptides from the group of polymyxin antibiotics - was discovered in 1949 and first used as an intravenous formulation in the 1950s. In the early 1980’s, colistin use was largely abandoned due to reported nephrotoxicity and the availability of newer antibiotics. Colistin was never subject to regulations in a modern kind of way and systematic trials on pharmacokinetics and dose finding are just beginning to be conducted. Through all these years colistin has been used in Cystic Fibrosis as inhalative treatment adjunct and in various topical formulations. The optimal parenteral dosing of colistin in severely ill patients is largely unknown and not standardized. This uncertainty and absence of any regulation or standardisation of dose puts a high burden on physicians and unacceptable risk on patients. Additionally, inadequate usage favors resistance development and threatens colistin’s life span.

*Colistin comes in different preparations – Perfect for confusion.*

Various generic preparations of colistin are commercially available across the world with different formulations, strengths, dosage measures, labeling of the content, and even numerous unidentified impurities. Colistin is marketed as colistin sulfate for non-systemic usage and colistimethate sodium (CMS) as an inactive prodrug of colistin for parenteral and inhalation treatment. The non-standardized information is not interchangeable and prone to confusion.
Fast bacterial killing and resistance.

Colistin (identical to Polymyxin E) is a polypeptide mixture with colistin A and colistin B as the main active components. The components bind to the cell membrane of Gram-negative bacteria, disrupting the membrane permeability, and thus, rapidly killing the bacteria. Colistin’s antimicrobial activity comprises the Gram-negative bacteria Acinetobacter, Pseudomonas and most enterobacteriaceae. The early concentration-dependent killing is compromised by two phenomena: reduced activity when a high bacterial load is present and a prompt regrowth of the bacterial population despite susceptibility in in vitro testing. This effect is called heteroresistance and is expected to accelerate the development of resistance in the individual patient but also in the society. Strategies to combat resistance development against the last-resort antibiotic colistin are clearly needed.

The key: Knowing the pharmacokinetics

Not knowing a drug’s fate in the body makes it impossible to determine an optimal dosage regimen. Presently, this is still the case with colistin but deciphering the pharmacokinetics is progressing. Early studies determined the colistin concentrations with a biological assay that is not appropriate for this drug as it cannot distinguish between active and inactive drug. Colistin Base, CMS and colistin sulfate have different pharmacokinetic properties and are not interchangeable. CMS and colistin have mixed routes of renal and nonrenal elimination, a half-life that varies between different patient populations, and a volume of distribution that increases with critical illness. The complex pharmacokinetics of colistin has only recently begun to unfold based on newly developed specific analytical methods. The main challenges with determining the pharmacokinetics are:

- The parenterally administered inactive prodrug CMS is hydrolysed to a complex mixture of metabolites and colistin itself. The CMS degradation after sampling and during the workup procedure might cause an artificially high measured active colistin concentration.
- The drug is “sticky”. It binds to equipment surfaces but also cell components as well as to the acute phase protein α1-acid glycoprotein in plasma. The bound fraction of drug is not available for measurement or antibacterial activity but determining the unbound colistin concentrations is challenging.
- The fraction of CMS being hydrolyzed to colistin depends on the renal elimination of CMS and thus the kidney function. The elimination of formed colistin does not depend on the kidney function.
- Pharmacokinetics in severely ill patients is even more complex due to pathophysiological changes and a high inter- and intra-patient variability.

In the AIDA project, the generated pharmacokinetic information will be integrated in PK/PD modeling and the derived optimal dosage regimen will be validated in a prospective randomized multicenter clinical trial.

Dosing of colistin – A guess work.

Worldwide the recommended dosages in the labels vary considerably according to the supplier. Accordingly, physicians use dosage regimens that differ in the amount of the single dose as well as the dosing interval. Preliminary study results show that currently approved dosage regimens are inappropriate and may not only risk clinical failure but also fast development of resistance as the active colistin concentrations might be much lower than previously thought.

Current study results suggest a loading dose to achieve active colistin concentrations quickly and a maintenance dosing regimen that is based on the patient’s kidney function. According to predictions from a PK/PD model the dosing regimens of CMS for patients with normal weight and kidney function is: 9 Mill. IU loading dose and 4.5 Mill. IU q12h maintenance dose.
The AIDA project aims to address the gaps in our knowledge regarding dosing of colistin:

- What is the optimal concentration profile of colistin concentrations in the body in relation to the susceptibility of the pathogen and potential emergence of resistance?
- What is the optimal loading dose the optimal maintenance regimen for severely ill patients?
- What is the correlation of drug exposure (dosing) to the clinical outcome?
- How is the tested dosing regimen effecting toxicity?
- What is a practical therapeutic drug monitoring scheme?
- Is a combination with a carbapenem superior to colistin alone?

Is colistin toxic?
The frequent nephrotoxic effects of colistin published in the early literature has not been verified in current carefully monitored patients. Total cumulative colistin dose seems to be associated with kidney damage but dosing regimens, influence of disease state, metabolic disorders, and co-medication still need to be defined as predictors of toxicity. Other toxicities such as neurotoxicity are not common and will be carefully evaluated in the AIDA clinical trial.

AIDA – A breakthrough in developing old antibiotics.
The last resort antibiotic colistin is re-evaluated to surpass efficacy and toxicity drawbacks of its development 60 years ago. The project AIDA generates and leverages extensive nonclinical knowledge to define the dose (exposure) – response relationship. The determined drug exposure will be translated into an appropriate dosage regimen to optimize clinical outcomes while reducing the risk of emergence of resistance and minimizing the risk of toxicity. These model-based dosage strategies will be validated in a multicenter clinical randomized study. A sparse blood sampling strategy based on predictions of a PK/PD model will provide pharmacokinetic blood and tissue data from individual patients. The generated feedback from pharmacokinetic and clinical data will refine the PK/PD modeling to be fed into the interpretation of clinical results. The variability of the susceptibility of the pathogens, of pharmacokinetic values in a critically ill patient population, and of the chosen PK/PD target will allow for clinical dosage recommendations based on integrating clinical data and results from PK/PD simulations. As the clinical trial is designed as a comparative study the value of combining colistin with a carbapenem will be determined. The AIDA project may serve as a model for the re-evaluation of old antibiotics in the non-profit space.

Recommended reading: