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Pharmacokinetics and PK/PD of temocillin in non-ICU urinary tract infection patients with various stages of renal insufficiency

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Background: Temocillin, a 6-α-methoxy derivative of ticarcillin, is a penicillin developed in the 1980s that has been revived in recent years, mostly as an alternative to carbapenems in the management of urinary tract infection (UTI) caused by (ESBL and AmPC) Enterobacterales. As for other forgotten antibiotics, the scientific debate about optimal drug dose regimens is still ongoing. While pharmacokinetic (PK) data is available for ICU and dialysis patients, it is scarce for those without critical illness or end-stage renal disease. In this study, we evaluated the plasma PK and PK/PD of temocillin in non-ICU UTI patients without and with mild or moderate renal insufficiency (RI).

Methods: 20 non-ICU UTI patients were divided into 3 groups based on renal function as measured by GFR (no, mild or moderate RI). All patients were treated with temocillin at the standard dose (2g q12h, intravenous infusion over 30 min) for a minimum of 4 days. After drug administration (≥ 3rd drug dose), venous blood was collected at specific time points over 12 h. Total and unbound concentrations in plasma were measured via a validated LC-MS/MS method. Non-compartmental analysis was performed in Pmetrics v1.9 and statistical analysis in Graphpad Prism v4.0.

Results: After IV temocillin administration, patients with mild and moderate RI showed significantly decreased drug clearance (Cl, fCl) and increased plasma drug exposure (AUC, fAUC) as compared to patients without RI (table 2). The fT>MIC, or the percentage of the time that free drug concentrations remained above the minimum inhibitory concentration (MIC, EUCAST ECOFF = 16 mg/l) in between dosing intervals, was 25% (3/12h), 33.3% (4/12h) and 66.6% (8/12h) for patients without, or with mild and moderate RI, respectively.

Conclusion: Based on the common PK/PD target for penicillins in non-critically ill patients (30-40% fT>MIC), the 2g q12h standard dose of temocillin seems appropriate to treat UTI in patients with mild or moderate RI. Patients with normal renal function may benefit from a higher dose, such as 2g q8h, as this would increase the fT>MIC from 25% (3/12h) to 37.5% (3/8h).

Empirical antimicrobial use in ICU and outcome before and after abandoning the concept of healthcare-associated pneumonia: a single center retrospective analysis

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Background: The concept of healthcare-associated pneumonia (HCAP) was introduced in 2005 to identify patients with pneumonia from outside the hospital at higher risk of infection with antimicrobial-resistant pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*, warranting a broader spectrum empirical antimicrobial therapy. Controversy still exists about the role of the HCAP entity, even after abandoning this concept in 2017.

Objectives: To assess empirical antimicrobial use and short-term outcomes before and after abandoning the HCAP concept in patients admitted to an adult Intensive Care Unit (ICU) using prospectively collected patient data.

Methods: Patients with pneumonia coming from outside the hospital requiring admission to the ICU of Ghent University Hospital between January 2011 and December 2020 were included. Prior to January 1st 2017 (period 1), patients were categorized either as community-acquired pneumonia (CAP) or HCAP; after this date (period 2), patients were solely categorized as CAP. Antimicrobial use during the first 48 hours after ICU admission was compared between both periods in terms of antipseudomonal and anti-MRSA coverage. Comparative statistical analysis was performed using Chi-Square, Mann-Whitney and Z-test for proportions.

Results: Of 1078 patients, 556 were admitted in period 1 and 522 in period 2, respectively.

In period 1, 231 patients (41,5%) were categorized as HCAP. Patient age and disease severity (APACHE 2- and SOFA-scores, classification according to Sepsis-3 definition) were similar in both periods. During period 1, more antipseudomonal (30,4% vs 19,8%, p<0,001) and anti-MRSA (3,9% vs 2,4%, p=0,049) antimicrobial agents were prescribed empirically as compared to period 2. The empirical use of piperacillin-tazobactam (p<0,001), antipseudomonal cephalosporins (p=0,048), ciprofloxacin (p=0,003) and glycopeptides (p=0,008) was higher in period 1 than in period 2. No significant difference in hospital survival (71,9% vs 74,1%, p=0,46) nor in median length of stay (14 vs 15 days, p=0,16) was found between both periods.

Conclusion: In our ICU, abandoning the HCAP concept was associated with a reduced use of broad-spectrum empirical antimicrobial therapy for non-nosocomial pneumonia, without a change in short-term outcomes. These findings support the notion that using the HCAP concept leads to antimicrobial escalation without improving patient outcome.

Clinical impact of PCR-based Aspergillus and azole resistance detection in invasive aspergillosis. A prospective multicenter study

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Objectives: Prompt detection of azole-resistant *Aspergillus fumigatus* will result in the timely start of active treatment and may improve survival of invasive aspergillosis(IA). The use of a multiplex polymerase chain reaction(PCR) targeting Aspergillus species and fumigatus DNA as well as the 2 most prevalent resistance mutations, could shorten the time to detect azole resistant IA.

Methods: In a prospective study in 12 Dutch and Belgian centers, we evaluated the clinical value of the multiplex AsperGenius®PCR in haematology patients with a pulmonary infiltrate undergoing bronchoalveolar lavage(BALf) sampling. The primary endpoint was antifungal treatment failure in patients with azole-resistant IA detected. Patients with a mixed azole-susceptible/resistant infection were excluded.

Results: Of 323 patients enrolled, sufficient BALf for PCR testing remained in 299. Probable fungal disease was diagnosed in 95(34%), Aspergillus cultured in 24(8%), Aspergillus DNA detected in 118 (39%) and *A. fumigatus* DNA in 88 (29%) patients. The resistance PCR was conclusive in 54/88 (61%) and RAMs were detected in 8 (15%). All 8 had probable IA but 2 had a mixed infection and were excluded. In the 6 remaining patients, treatment failure was observed

in one. Compared with the GM negative patients and despite antifungal therapy, a positive GM test was associated with a 13% higher 6-week overall mortality ($p=0.01$), table 2. Surprisingly, the 6-week mortality in the 65 patients who had a positive *Aspergillu*s PCR but a negative GM and culture was not increased compared to those with a negative PCR (PCR+ 14% versus PCR- 16% mortality, $p=0.68$).

Conclusions: In patients with an underlying haematological disease and a pulmonary infiltrate, the detection of Aspergillus DNA by PCR on BALf was not associated with an increased mortality. The exact place of the *Aspergillus* PCR in the EORTC-MSGERC invasive fungal infection criteria is therefore uncertain. In 15% of the patients in whom *A. fumigatu*s DNA was present, azole RAMs were detected by PCR. In only 1 of the 6 probable cases of IA with RAMs detected, antifungal treatment failure was observed. Basing the choice of antifungal therapy on the result of a cyp51a resistance PCR may help to reduce the impact of azole resistance on mortality.

Cefiderocol Susceptibility Testing: Disk-Diffusion compared to Broth MicroDilution

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Introduction: Cefiderocol (CFD) is a new siderophore cephalosporin with enhanced activity against multidrug-resistant gram-negative bacilli (MDRGNB). We validated and compared a disk diffusion (DD) method to a commercial broth microdilution (BMD) method for the CFD susceptibility testing on a panel of MDRGNB isolates.

Methods: 287 non-duplicate carbapenem-non-susceptible MDRGNB clinical strains collected in 2019 at the National Reference Center were tested for CFD susceptibility in parallel by DD (30-µg CFD disk (Liofilchem) on MH agar (BioRad)) and by BMD (customized Sensititre panel (ThermoFisher)). Categorical interpretation was performed based on clinical breakpoints (or PK/PD for *Acinetobacter* spp.) using EUCAST 2021 recommendations. E. coli ATCC 25922 and *P. aeruginosa*ATCC 27853 strains were used as control strains and for the evaluation of intra- and inter-assay reproducibility. Isolates showing errors between BMD and DD were retested to solve discrepancies. Categorical agreement (CA), very major error (VME) and major error (ME) were calculated for CFD DD compared to the reference BMD following discrepancy resolution.

Results: 235/287 strains (78%) were susceptible and 52 (22%) resistant to CFD by BMD. 34/287 strains showed discrepant category results and had an inhibition zone between 18 and 22 mm (area of technical uncertainty, ATU). Following retest, 15/34 cases were confirmed as categorical errors leading to an overall CA (94.8%; n=272), ME (4.5%; n=13) and VME (0.7%; n=2) between DD and BMD methods. The 2 isolates with VMEs showed inhibition zone of 22 mm and a MIC at 4 mg/mL. Perfect intra-assay (n=3) and inter-assay (n=4) reproducibility rates were achieved with 100% of the results for the ATCC strains within acceptable ranges for both DD (target zone diameter +-1 mm) and BMD (identical MIC).

Conclusion: These results met the validation requirements of a new susceptibility testing method (CA >90%, VME ≤3% according to Cumitech 31A). The higher percentage of ME could be explained by inhibition diameters between 18 to 22 mm. We conclude that DD method is a reproducible and accurate method that can be routinely used to determine CFD susceptibility among MDRGNB. We suggest retesting GNB strains showing inhibition diameters within the ATU zone by an alternative method (BMD).