UNIVERSITY OF GENOA

Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics and Maternal and Child Sciences

PhD in Pediatric Sciences

Curriculum: Pediatric Specialties

"THE ROLE OF ANTIBIOTIC DOSING SYSTEM IN PEDIATRICS INFECTIOUS DISEASES: IT'S A LONG WAY TO THE TOP IF YOU WANNA ACHIEVE PK/PD"

Relator
Chiar.mo Prof. Pasquale Striano

Supervisor
Dr. Elio Castagnola

Candidate
Dr. Marcello Mariani

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Summary

1. Introduction

Unlike other medical specialties where chemotherapies are commonly prescribed, in infectious diseases therapy there is the possibility of directly isolating (when possible, especially for fungal or bacterial etiologies) the causative agent and testing its drugs sensitivity. The antibiogram (or antimycogram) in fact, establish a minimum inhibitory concentration (MIC) for a given drug on a given pathogen, translating into different levels of sensitivity for different molecules to choose from for a treatment. In addition, the effectiveness of an antibiotic therapy depends not only on its activity against a pathogen, but also on the possibility of maintaining adequate plasmatic levels (or at the site of infection) without undesirable effects or toxicity [1], [2]. In Pediatrics, antibiotics are among the most frequently prescribed drugs, both in outpatient setting [3] and in hospital. In Europe, more than 35% of hospitalized children were on antibiotics [4] and, according to other studies, about 50% of patients hospitalized for other problems than infectious symptoms received antibiotic therapy during hospitalization [5].

In children, treatment regimens are usually based on dosages related solely to demographic factors such as age or weight and may therefore be potentially insufficient in patients with conditions that alter pharmacokinetics [6]. Particularly, in critically-ill patient, in subjects undergoing extrarenal replacement therapy (RRT) and/or extracorporeal oxygenation (ECMO) [7]. In fact, pediatric patients admitted to intensive care units (ICU) showed antibiotic plasmatic concentration below therapeutic levels in about 95% of cases [8]. This failure to achieve pharmacokinetic (PK) target is often caused by pathological changes in volume of distribution (Vd), protein binding, and molecules clearance. It is known that pediatric patients, in response to inflammatory stimuli, respond with an increase in renal clearance (augmented renal clearance, ARC) with a consequent impact on drug elimination [9], [10]. Over the last few years, the detection also of pathogens with reduced/absent

sensitivity to antimicrobial therapies (some even never used in pediatrics) has become increasingly relevant even in pediatric field [11], [12], partly due to incorrect use of antibiotic therapies themselves [13].

In light of these critical issues, it is therefore necessary to optimize and personalize the dosage and administration schedule of antibiotic therapies, especially in selected populations.

The most important characteristics to consider for each molecule are pharmacokinetic (PK) and pharmacodynamic (PD). MIC is an important element to describe the antibiotic activity on the pathogen, but it cannot predict the success of therapeutic regimen as it is obtained in vitro and not related to systemic changes present in vivo [7]. The most frequently used PK/PD parameters to evaluate therapy efficacy in relation to a pathogen MIC are: the ratio of maximum serum concentration (C_{max}) to MIC (C_{max}/MIC) for concentration-dependent drugs, the time above MIC (t > MIC) for time-dependent drugs with little post-antibiotic effect, the ratio of area under the concentration-time curve (AUC) to MIC (AUC/MIC) for time-dependent drugs and with prolonged post-antibiotic effect [7]. The calculation of all these PK/PD parameters cannot obviously be separated from blood concentration dosing of the anti-infective drugs: object of our study was to therefore describe the role of "antibiotic dosage system" in selected target populations in order to evaluate PK/PD and provide indications about administration schedules, dosage and possible efficacy.

2. Materials and methods

Within the present study, different cohorts of pediatric patients admitted to the IRCCS Istituto Giannina Gaslini, in Genoa, Italy, were enrolled during antibiotic therapy with the molecules and according to methods listed below:

2.1. Piperacillin/Tazobactam as Continuous Infusion in Febrile Neutropenic Patient

- Admission to Pediatrics – Infectious Diseases Unit from 01/10/2022 to 31/12/2023 with diagnosis of "febrile neutropenia" according to the most recent European Conference of Infections in Leukaemia (ECIL) guidelines [14] (patients with oncological or hematological malignancy).
- Standard of care: piperacillin/tazobactam 100mg/kg (referred to piperacillin, maximum dose 4000 mg) loading dose over 1 hour, followed by amikacin 20mg/kg over 30' and then initiation of piperacillin/tazobactam 100mg/kg (referred to piperacillin, maximum dose 4000 mg) in 6 hours of infusion 4 times a day.
- Dosage: post-loading dose, 12-hour and 24-hour.

2.2. Vancomycin Continuous Infusion in Neonatal and Pediatric ICU Patient

- Hospitalization at Neonatal and Pediatric Intensive Care Unit from 01/10/2020 to 31/12/2023 without distinction of diagnosis and start of vancomycin therapy.
- Standard of care: vancomycin 10mg/kg (maximum 500 mg) loading dose in 1 hour followed by 40mg/kg/day (maximum 2000mg) as continuous infusion (IC) in 24 hours.

- Dosage: vancomycin plasmatic levels after at least 12 hours of IC initiation

2.3. Meropenem in Neonatal and Pediatric Intensive Care

- Hospitalization at Neonatal and Pediatric Intensive Care Unit from 01/01/2020 without distinction of diagnosis and start of therapy with meropenem.
- Standard of care: meropenem 60mg/kg in 3 doses daily over 3 hours infusion. Maximum dose 1000mg.
- Dosage: before V dose.

2.4. Teicoplanin with loading dose

- Patient admitted in the whole hospital from March 2018 to September 2022 and undergoing therapy with teicoplanin.
- Standard of care: three doses of 10 mg/kg at 12-hour intervals (load), followed by a dose of 10 mg/kg/day intravenously once daily (maintenance).
- Dosage: all dosages are C_{min}, at least before V dose.

2.5. Multi-dose dalbavancin in peculiar clinical settings

- Patients followed by Pediatrics Infectious Diseases Unit internal consultation service for whom dalbavancin therapy has been indicated and started.
- Standard of care: dalbavancin 22.5mg/kg/dose in patients aged 0 to 6 years, 18.5mg/kg in patients aged 6 to 17 years. Maximum dose 1500mg.
- Dosages: before following dose and on fixed intervals.

2.6. Statistical analysis

Descriptive statistics were produced for demographic, clinical and laboratory characteristics of patients. Mean and standard deviation (SD) are presented for normally distributed continuous variables, median and interquartile ranges (IQR) for non-normally distributed variables. Numbers and percentages were used for categorical variables.

To compare groups, for continuous variables, parametric (t-test) or non-parametric (Mann-Whitney or Kruskal Wallis when appropriate) tests were performed according to data distribution. For categorical variables, Pearson's $\chi 2$-test (Fisher exact test when appropriate) was performed. The association between antibiotics plasmatic levels and different potential explanatory variables was assessed using multivariable models. In multivariable models, only variables significant at univariable analysis were considered relevant. Data were analyzed by Jamovi statistical software (The Jamovi project. Version 2.4. Retrieved from https://www.jamovi.org).

3. Results

3.1. Piperacillin/tazobactam in continuous infusion

Within this cohort, 14 patients were enrolled, 3 females (21.4%). The median age was 6 years (IQR 5.75). 5/14 patients (35.7%) had leukemia as underlying condition while the others had a solid tumor. Clinical and laboratory characteristics are summarized in Table 1. The median post-loading dose level was 73.3 mg/L (IQR 44.3), at +12 hours 20.2 mg/L (IQR 22.8) and at +24 hours 27.4 mg/L (IQR 24.9). No adverse events occurred during continuous infusion.

At 24 hours, 11/14 (78.6%) patients had a piperacillin levels > 8 mg/L (considered as breakpoint for *Enterobacterales*) of which 9 had levels > 16 mg/L (breakpoint for *Pseudomonas*). For 2 remaining patients there is no data, while in the latest piperacillin plasmatic concentration was just over 4. In this latter case, however, *Escherichia coli* with MIC for piperacillin/tazobactam <=2 was isolated, making t > MIC still 100%.

Table 1: clinical and laboratory characteristics of the cohort of febrile neutropenic patients receiving piperacillin/tazobactam therapy in CI.

Patients (n)	14
Females (n, %)	3, 21.4%
Age (median, IQR)	6, 5.75
Diagnosis	
Leukemia (n, %)	5, 35.7%
Lymphoma or another solid tumor	9, 64.3%
Laboratory data	
Albuminemia (median, IQR)	3774 mg/dl, 621
Creatinine (median, IQR)	0.31 mg/dl, 0.20
eGFR (median, IQR)	134 ml/min/1.73m2, 27.2
Post load piperacillin (median, IQR)	73.3 mg/L, 44.3
Piperacillin at 12 hours (median, IQR)	20.2 mg/L, 22.8
24-hour piperacillin (median, IQR)	27.4 mg/L, 24.9

3.2. Vancomycin in ICU patients

Within this cohort, 79 patients were enrolled, 38 females (48.1%). Each patient corresponds to only a single episode as only the first dose of vancomycin was considered. The median age was 18 months (IQR 105). Clinical and laboratory characteristics are summarized in Table 2. The first vancomycin plasmatic level after therapy start (t1) was performed after a median of 14 hours (IQR 10). Median vancomycin at t1 was 12.4 mg/L (IQR 6.55). In 21/79 (26.6%) cases vancomycin at t1 was > 16.7 mg/L (equivalent to an AUC of 400 in case of CI). Clinical and laboratory comparison between patients above and below this value is shown in Table 2.

Only glomerular filtration rate estimated by modified Schwartz formula [15] (eGFR) has shown to be a significant factor at multivariate analysis (p=0.04). With a mean eGFR of 92, the probability of achieving vancomycin plasmatic levels > 16 mg/L at t1 is 33.5% (estimated mean 14 mg/L; 95% CI 12.5-16, p=0.018); with eGFR values of 141 ml/min/1.73m^2 the probability drops to 8% (estimated mean 12 mg/L; 95% CI 9-14, p=0.018), figures 1 and 2.

Table 2: clinical and laboratory characteristics of patients receiving vancomycin therapy.

	Total	**Vancomycin ≥16.7 at t1 (n=21)**	**Vancomycin <16.7 at t1 (n=58)**	**p (univariate)**	**p (multivariate)**
Sex					
Females: n (%)	38 (48.1)	12 (57.1)	26 (44.8)	0.446	
Age in months: median (IQR)	18 (105)	2 (115)	21.5 (87.5)	0.180	
Diagnosis: n (%)				0.259	
Cardiopathy	38 (48.1)	8 (38.1)	30 (51.7)		
Trauma	5 (6.3)	0	5 (8.6)		
Congenital malformation	15 (19)	4 (19)	11 (19)		
Neoplasia	5 (6.3)	2 (9.5)	3 (5.2)		
Other pathology	16 (20.3)	7 (33.3)	9 (15.5)		
Albumin supplementation: n (%)	42 (54.5)	16 (76.2)	26 (46.4)	**0.023**	0.7
Diuretic therapy: n (%)	65 (84.4)	16 (76.2)	49 (87.5)	0.291	
Biochemical Parameters: Median (IQR)					
Heart rate (bpm) at t0	127 (30)	127 (12)	126.5 (31.5)	0.991	
Mean arterial pressure (mmHg) at t0	64 (25)	64.7 (34)	64 (20)	0.855	
Body temperature (C°) at t0	37 (1.8)	36.4 (1.4)	37.7 (1.5)	**0.001**	0.47
Oxygen saturation % at t0	98 (3)	97 (5)	99 (3)	0.109	
Liquids balance at t0	+16 (122)	-27 (139)	+29 (122)	**0.004**	0.18
eGFR at t0	91 (63)	55.7 (18)	107 (39)	**0.003**	**0.04**
BUN (mg/dl) at t0	32 (27)	43 (34)	27 (21)	0.099	
C-reactive protein (mg/dl) at t0	3.88 (10.5)	3.4 (9)	3.9 (10)	0.936	
Albumin (mg/dl) at t0	3229 (807)	3182 (862)	3356 (746)	0.645	
Total protein (g/dl) at t0	5.2 (0.98)	4.8 (1.5)	5.25 (0.5)	0.367	

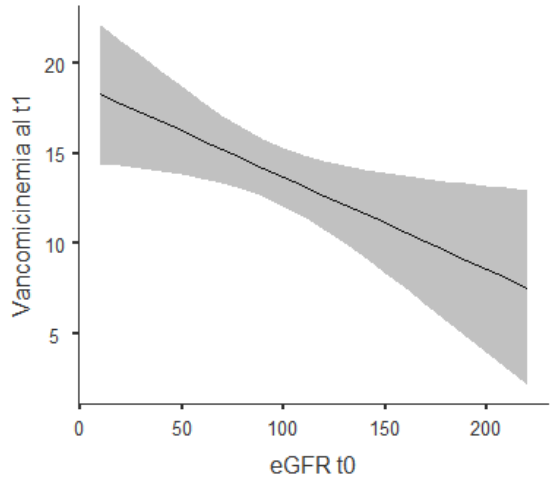

Figure 1: vancomycin at t1 related to eGFR at t0 (95% CI)

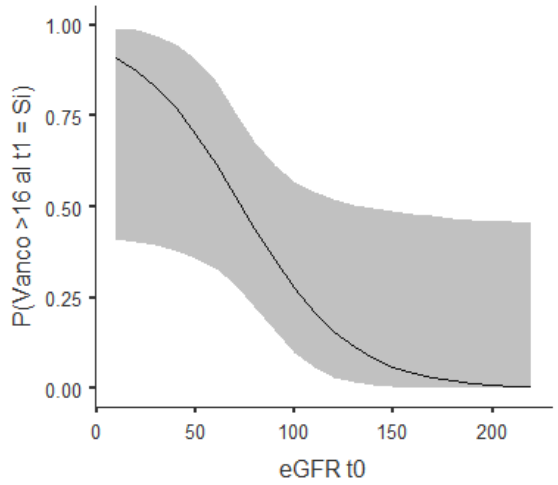

Figure 2: probability of achieving plasmatic vancomycin >16 mg/L in relation to eGFR at t0 (95% CI)

3.3. Meropenem in ICU

Within this cohort, 17 patients were enrolled, 12 females (70.6%) with a total of 23 episodes. The median age was 6 months (IQR 114). Median meropenem C_{min} was 1.6 mg/L (IQR 7.45). In 6/23 (26.1%) of the episodes, meropenem C_{min} was >8 mg/L (breakpoint MIC for *Enterobacterales* and *Pseudomonas* spp.). Episodes comparison is shown in Table 3.

Only creatinine has shown to be a factor related to meropenem prolonged infusion C_{min} in our cohort (Spearman's Rho 0.454, p=0.030). Figure 3 shows linear relationship between meropenem levels and creatinine (p=0.05).

Table 3: clinical and laboratory characteristics of patients receiving meropenem therapy.

	Total	**Meropenem C_{min} > 8 mg/L (n=6)**	**Meropenem C_{min} < 8 mg/L (n=17)**	**p**
Sex				
Females: n (%)	15 (65.2)	2 (33.3)	13 (76.5)	0.131
Age in months: median (IQR)	6 (114)	106 (201)	6 (23)	0.482
Infant: n (%)	4 (17.4)	2 (33.3)	2 (11.8)	0.27
Biochemical Parameters: Median (IQR)				
eGFR	135 (76.5)	55.7 (18)	107 (39)	0.473
Creatinine (mg/dl)	0.34 (0.32)	0.51 (0.09)	0.22 (0.24)	**0.014**
Albumin (mg/dl)	3496 (814)	3000 (1791)	3496 (507)	0.56

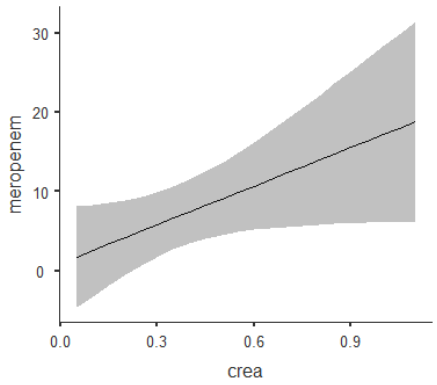

Figure 3: linear relationship between meropenem plasmatic levels and creatinine (95% CI)

3.4. Teicoplanin with loading dose

Demographic characteristics are summarized in Table 1. A total of 104 teicoplanin plasma C_{trough} levels were analyzed during a total of 56 hospitalization periods of 52 patients. The median number of episodes per patient was 1 (range 1–2). MIC was available in 74 out of 104 determinations. At the same time as teicoplanin sampling, creatinine and albumin were determined in 96 (92%) and 104 (100%) out of 104 samples, respectively. Plasma C_{trough} of teicoplanin ranged from 7.0 to 309.8 mg/L. The target C_{trough} level of 10 mg/L was reached in 97.12 % of the analyses, while 20 mg/mL was reached in 89.84%. In only 3 (2.88%) analyses teicoplanin C_{trough} levels were below 10 mg/L and in 7 analyses (7.28%) between 10 and 20 mg/L. Teicoplanin toxicity is expected for concentration values above 80 mg/L. In 28 (29.12%) analyses the concentration was higher than 80 mg/L but no toxicity was observed. Ten analyses were performed on the third day of therapy, and only 1 was below the AUC24/MIC 900 target value as suggested by some authors [16]. In 44 (78%) episodes, teicoplanin was administered as targeted therapy, while in 12 as empirical treatment. No significant difference was observed in teicoplanin levels of subjects who had received empirical therapy compared with those who had received targeted therapy (P=0.8369). For cases where teicoplanin was administered as targeted therapy, MIC ranged from ≤0.25 mg/L to 4 mg/L with C_{trough} higher than MIC in all 74 determinations (100%). No statistical correlation could be found between teicoplanin C_{trough} levels and eGFR (p=0.6565) or albumin (P=0.0977). Patients were then classified into 6 age groups: 0-1 years (Group 1), 1-2 years (Group 2), 2-6 years (Group 3), 6-12 years (Group 4), 12-18 years (Group 5), over 18 years (Group 6). Teicoplanin levels in different age groups are shown in Figure 4. No significant differences in teicoplanin concentrations were observed in different age groups except for comparisons between Group 1 and Group 3 (P=0.0005), Group 4 (P=0.0017), and Group 6 (P=0.0187). No significant difference was found in terms of teicoplanin concentrations between males and females.

Table 4: demographic characteristics of patients on teicoplanin therapy

	Females (n=22)		Males (n=30)	
	Age (Years)	**Weight (kg)**	**Age (Years)**	**Weight (kg)**
Mean	6	22	6	22
SD	7	21	7	22
Median	3	14	3	14
Min-Max	0-22	2.8-58	0-26	2.4-86

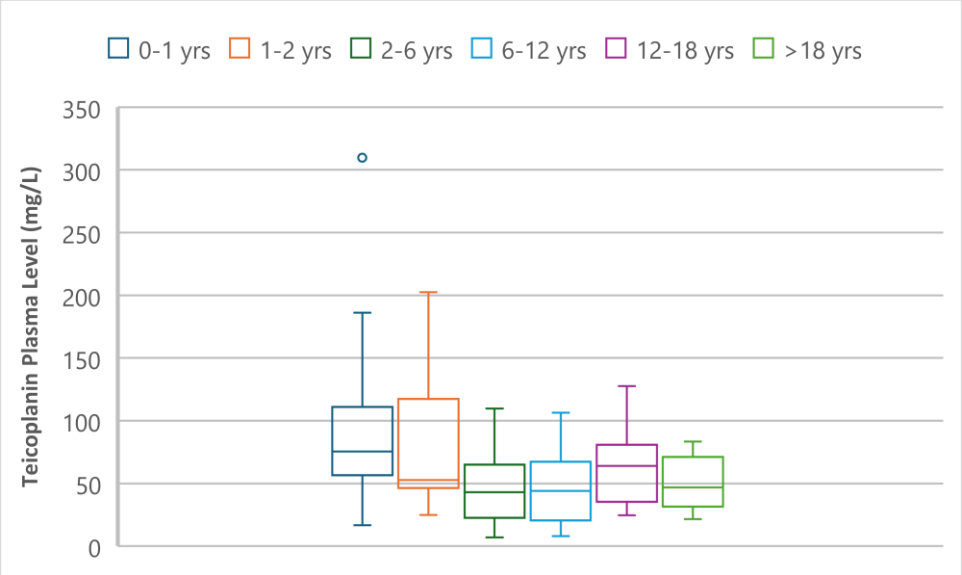

Figure 4: Teicoplanin Levels in different age groups. Yrs is years.

3.5. Multi-dose dalbavancin in particular clinical settings

We report the case of a 4-years-old male with T-cells leukemia, hospitalized for febrile neutropenia. Influenza A virus infection was diagnosed by nasal PCR swab with consequent start of oseltamivir treatment. After 5 days of antiviral, fever relapse and worsening in respiratory symptoms were observed. A thoracic CT scan showed bilateral pulmonary infiltrates. Due to methicillin-resistant *Staphylococcus aureus* (MRSA) positivity on nasal swab, ceftaroline treatment was started with prompt clinical improvement. After 10 days of antibiotic treatment, a second CT showed consolidation with cavitation in left superior lobe. Galactomannan was negative in serum and bronchoalveolar lavage and cultures were negative. Ceftaroline treatment was continued for three weeks when a third CT scan showed reduction in left lobe lesion. Due to patient good clinical conditions, to shorten hospitalization, dalbavancin was administered at 22.5mg/kg on days 0, 8 and 21. Dalbavancin was well tolerated, with plasmatic levels higher than 4 mg/L for about a month after last administration. Last follow-up CT scan showed further pulmonary improvement. Figure 5 shows dalbavancin plasmatic levels trend and Figure 4 shows radiological picture evolution.

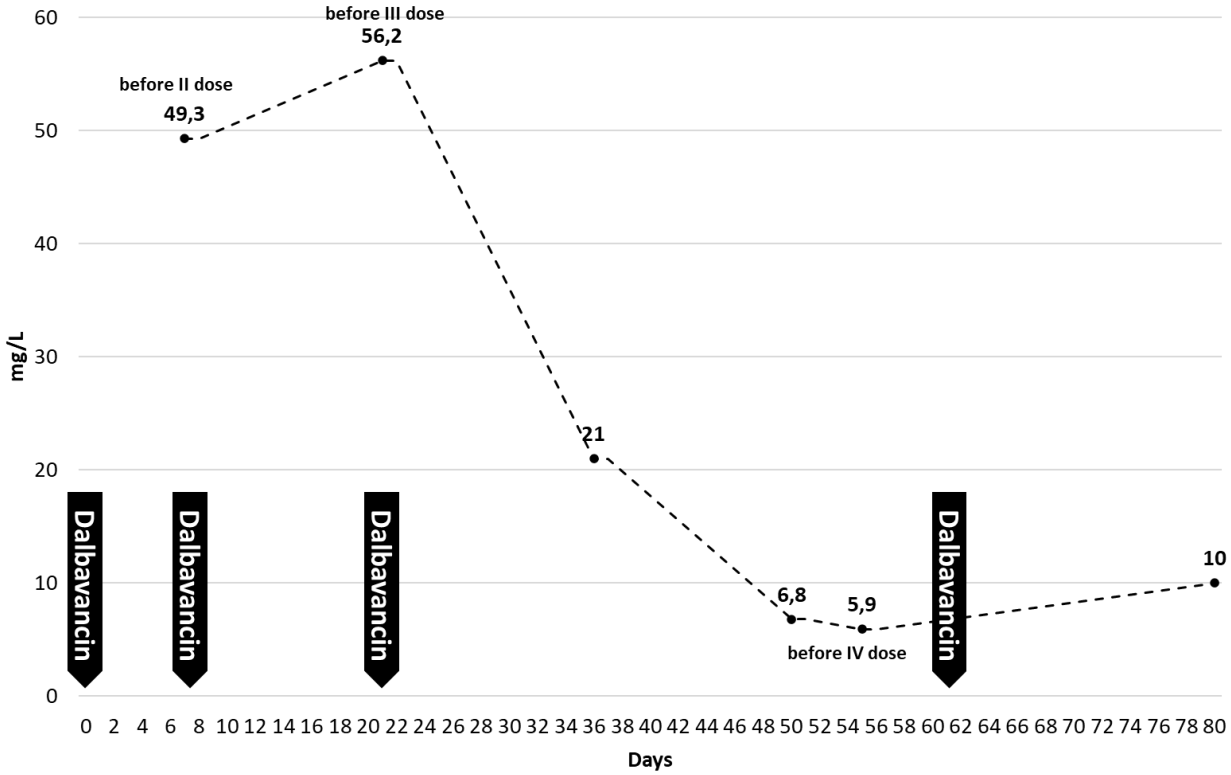

Figure 5: dalbavancin plasmatic concentration kinetic.

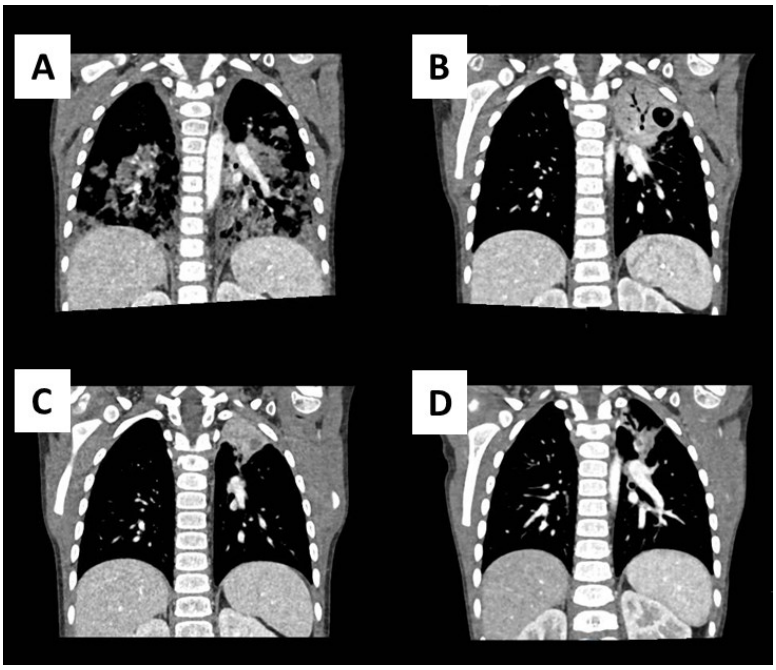

Figure 6: CT scans: A- bilateral infiltrates. B-C cavitary evolution. D- further pulmonary improving.

We report a second case of dalbavancin TDM in an unusual clinical context in a patient with invasive multidrug-resistant *Pseudomonas aeruginosa* infection and presence of multiple mediastinal lesions suggestive for *Staphylococcus aureus* abscesses (Figure 7). Given the need for combination therapy with multiple *anti-Pseudomonas* antibiotics (some molecules also in continuous infusion) and the concomitant ECMO starting due to critical clinical conditions, given the lack of Y-site compatibility between various antibacterials molecules as well as patient scarce vascular patrimony (already occupied by ECMO lines) a single dose of dalbavancin at 22.5mg/dl was administered in order to obtain anti-staphylococcal activity pending culture confirmation from exploratory laparoscopy. Frequent dalbavancin dosages were then performed after infusion. After 48 hours, dalbavancin plasmatic level went from 287.49 to 74.78 mg/L, a decrease of 74%. Since ECMO discontinuation, the decline in dalbavancin levels became more gradual, reducing by 49% in 162 hours. Data are shown in Table 5 and Figure 8.

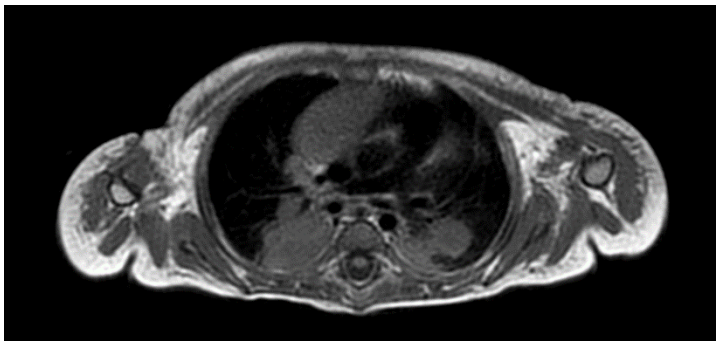

Figure 7: Pulmonary and mediastinal lesions suspected for S. aureus

Time (hours)	Dalbavancin (mg/L)
0	287
13	163
21	122
24	90
47	75
119	39
167	34
281	20

Table 5: dalbavancin plasmatic concentration over time

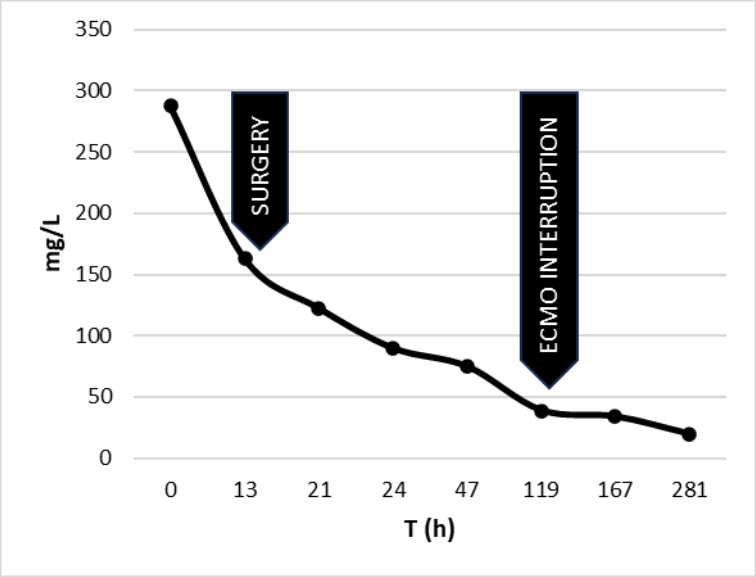

Figure 8: dalbavancin plasmatic levels during ECMO.

4. Discussion

The present study provides an overview of the role of antibacterial monitoring in a pediatric hospital setting.

Regarding the first of examined molecules, our data although limited to a small cohort of patients, demonstrate the feasibility and tolerability of continuous infusion of piperacillin/tazobactam in oncologic or hematologic patients with febrile neutropenia., with this administration schedule, in fact, several effects are achieved: some exquisitely pharmacokinetic, others more practical. Observing median eGFR, a value > 130 ml/min/1.73m^2 was found, the limit above which augmented renal clearance (ARC) is conventionally defined [16]. This finding is comparable to that of previous work from other authors which were however carried out on patients admitted to ICU [10]. In our case, instead, patients had a feverish illness but did not have clinical characteristics of severity to require ICU admission. This data highlights how common ARC could be found also in non-severely ill patients, affecting excretion of low protein binding drugs such as, for example, piperacillin [18]. Thanks to continuous infusion, piperacillin plasmatic level was > 8 mg/L in about 80% of cases (MIC breakpoint value for *Enterobacterales*) with t > MIC of 100%, optimal efficacy condition. Administration of continuous infusion, which permits removal of the empty vial and simultaneous placement of a new one (in our case, every 6 hours due to room temperature stability of formulation bought by our Institution), halves the number of times the nursing staff handles infusion set and central venous catheter (in our case, only 4 times instead of the 8 in case of pulsatile infusion). Manipulation of venous accesses is recognized as a risk factor for catheter-related infections [19], [20]. This method of drug administration could therefore have an "indirect" positive impact on healthcare-related infections.

The need to extend continuous infusion is further underlined by our data on meropenem. In our cohort in fact, despite prolonged infusion over 3 hours, only in just over 25% of cases a

meropenem C_{min} > MIC breakpoint for *Enterobacterales* (8 mg/L) was documented. We found plasmatic meropenem to be correlated with creatinine, which is consistent with the very low protein binding of this drug (around 2%) [21] and therefore significantly influenced by kidney excretion. Interestingly, the median age was higher (although not statistically significant, probably due to a small sample size) in patients with lower meropenem levels. This finding could be related to increased incidence of ARC in "older" patients, differently from what occurs in infants where eGFRs are often physiologically below 100ml/min/1.73m^2 [22].

The treatment proposal that could derive from analysis of both these case series could be that, with the exception of neonatal population (which has peculiar characteristics of renal function and protein binding of drugs for which pulsatile infusion could be acceptable - also taking into account the difficulty in finding venous accesses and often need for liquids restricting) in patients who present signs and symptoms of infection, even not necessarily severe, they may still benefit in terms of probability of target attainment (PTA) from continuous infusion of piperacillin/tazobactam and meropenem.

Vancomycin dosage data further emphasize renal function as a major player in the PK of lower protein binding drugs. In the present study we could confirm what was previously published by our group [23] i.e. that, as the eGFR increases, there is a simultaneous reduction in vancomycin plasmatic levels. A further critical issue that emerged from the analysis of our data is that, in an average sample of ICU patients under vancomycin therapy, the standard of care currently provided in vancomycin Italian data sheet (40mg/kg/day) is completely inadequate to achieve PK/PD target.

On the other hand, regarding the dosage of drugs with higher protein binding, the data on teicoplanin show C_{trough} level above 10 mg/L in 97.12% of the analyses and above 20 mg/mL in 89.84% and it was higher than MIC in all 74 determinations where MIC was available. Our results indicate that teicoplanin, with its single daily schedule of administration, is a viable

alternative to other active antibiotics against beta-lactams-resistant Gram positive especially in presence of toxicity, resistance or impossibility to achieve adequate concentrations (e.g. in case of ARC).

Antibiotic monitoring system in pediatrics can also have practical repercussions in infectious diseases treatment in particular contexts. As far as dalbavancin is concerned, in the first case described, a multi-dose administration schedule borrowed from that proposed by other authors for off-label indications was applied [24]. In this case, TDM made it possible to monitor drug kinetics over time in order to schedule the subsequent infusion to maintain levels constantly above 4 mg/L, effective on strains of *S. aureus* with MIC up to MIC_{90} [25].

In the second case description, on the other hand, we emphasize the application of TDM in a completely unexplored field such as ECMO in pediatric setting: in our experience, for example, a very rapid drop in plasma levels of dalbavancin was found, explained by a possible sequestration phenomenon by the extra corporeal circulation circuit. These are obviously preliminary data and would need future investigation.

In conclusion, from the overall analysis of our data we believe that within a III level pediatric hospital, the possibility of performing TDM for different molecules is an indispensable tool for achieving and developing precision medicine. The possibility of dosing antibiotic molecules in patients undergoing therapy can have both important scientific implications and, more importantly, be reflected in daily clinical activity.

With a solid TDM system the clinician could go beyond the choice of the best molecule for the single pathogen, but also adapt the administration schedule and the posology on individual patient in the individual hospitalization setting.

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