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Impact of a newly established expert clinical pharmacological advice programme based on therapeutic drug monitoring results in tailoring antimicrobial therapy hospital-wide in a tertiary university hospital: Findings after the first year of implementation

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ABSTRACT

Objectives: Therapeutic drug monitoring (TDM) may be helpful in tailoring antimicrobial treatment, and expert interpretation of the results may make it more clinically useful.
Methods: This study aimed to assess retrospectively the first-year impact (July 2021 to June 2022) of a newly established expert clinical pharmacological advice (ECPA) programme based on TDM results in tailoring therapy with 18 antimicrobials hospital-wide in a tertiary university hospital. All patients having ≥1 ECPA were grouped in five cohorts [haematology, intensive care unit (ICU), paediatrics, medical wards and surgical wards]. Four indicators of performance were identified: total ECPAs; total ECPAs recommending dosing adjustments/total ECPAs both at first and at subsequent assessments; and turnaround time (TAT) of ECPAs, defined as optimal (<12 h), quasi-optimal (12–24 h), acceptable (24–48 h) or suboptimal (>48 h).
Results: A total of 8484 ECPAs were provided for tailoring treatment in 2961 patients, mostly admitted in the ICU (34.1%) and medical wards (32.0%). The proportion of ECPAs recommending dosing adjustments was >40% at first assessment (40.9% haematology; 62.9% ICU; 53.9% paediatrics; 59.1% medical wards; and 59.7% surgical wards), and decreased consistently at subsequent TDM assessments (20.7% haematol-

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ogy; 40.6% ICU; 37.4% paediatrics; 32.9% medical wards; and 29.2% surgical wards). The overall median TAT of the ECPAs was optimal (8.11 h).
Conclusion: The TDM-guided ECPA programme was successful in tailoring treatment with a wide panel of antimicrobials hospital-wide. Expert interpretation by medical clinical pharmacologists, short TATs, and strict interaction with infectious diseases consultants and clinicians were crucial in achieving this.

1. Introduction

Personalised treatment is becoming a paradigm in many therapeutic areas of modern medicine, including that of antimicrobial chemotherapy [1]. In the last few decades, progress in pharmacokinetic/pharmacodynamic (PK/PD) knowledge has allowed a better understanding of how to properly use antimicrobials [2]. Attainment of adequate antimicrobial exposure at the infection site may be impeded by pathophysiological conditions and/or interacting co-medications, which are common findings and may cause wide intra- and inter-individual pharmacokinetic variability in critically ill patients [3]. Consequently, among critically ill patients, choosing the right antimicrobial dose for properly treating severe infections is often very challenging [4].

Therapeutic drug monitoring (TDM) is a tool that, by measuring serum concentrations of antimicrobials, may be very helpful in attaining optimal PK/PD targets of efficacy in each single patient while avoiding toxicity risk [5]. Historically, TDM of antimicrobials was first introduced for vancomycin and the aminoglycosides, essentially for safety reasons [6]. However, in the last 20 years or so its use has been progressively extended for improving the effectiveness of treatment with several other antimicrobials, including linezolid, voriconazole [6,7] and β-lactams [8].

A recent position paper stated that TDM should be considered as the only safe and effective way of ensuring optimal exposure attainment with antimicrobials in critically ill patients [9]. A recent meta-analysis also showed that TDM-guided dosing of β-lactams may improve clinical and microbiological cure in critically ill patients [10].

Implementing antimicrobial TDM programmes for emerging TDM candidates may be quite challenging [11], and expert interpretation of the results should be performed to make them more clinically useful. Expert interpretation should advise the most appropriate dosage adjustment based on pathogen susceptibility, the patient's pathophysiology, the type/site of infection and/or the patient's co-medications [12].

In our tertiary university hospital, a novel Clinical Pharmacology Unit (CPU) was established in January 2021 with the aim of tailoring antimicrobial therapies by means of a TDM-guided expert clinical pharmacological advice (ECPA) programme. The programme was initially focused on tailoring therapy in critically ill patients [13] but was subsequently extended hospital-wide as it was thought that it could also be valuable for several other vulnerable patient populations.

The aim of this study was to describe the first-year impact of the TDM-guided ECPA programme in tailoring antimicrobial therapy among different patient population settings in our tertiary university hospital.

2. Methods

2.1. Study setting

The IRCCS Azienda Ospedaliero–Universitaria di Bologna (Bologna, Italy) is a tertiary university hospital with 84 clinical units and a total of 1498 beds, in which a new CPU was established in January 2021 and was provided with three medical (MD) clinical pharmacologists. The organisational procedures of the CPU are described in our previous study in the intensive care unit (ICU) setting [13].

Briefly, the TDM-guided ECPA programme was active Monday to Friday for tailoring therapy with 18 different antimicrobials, including 12 antibiotics (ampicillin, ceftazidime, cefepime, meropenem, piperacillin/tazobactam, linezolid, levofloxacin, ciprofloxacin, amikacin, gentamicin, teicoplanin and vancomycin), 4 antifungals (fluconazole, voriconazole, posaconazole and isavuconazole) and 2 antivirals (ganciclovir and acyclovir). It was made available hospital-wide for all admitted patients. Clinicians were free to select the option of requesting TDM alone or TDM plus ECPA. TDM of antimicrobials was performed by bioanalytical experts at the LUM of Bologna by means of validated fluorescence polarisation immunoassay (FPIA) and/or liquid chromatography tandem mass spectrometry (LC-MS/MS) methods. TDM results were made available via the intranet to the MD clinical pharmacologists, who promptly provided the ECPAs to the applicant clinicians. The ECPA was structured as an expert interpretation of each TDM result by considering the site of infection, patient's underlying conditions and/or eventual iatrogenic interventions (i.e. application of renal replacement therapy, drug–drug interactions due to co-treatments), as described previously [13]. Each ECPA could have confirmed current dosing or recommended dosing adjustments (i.e. increase/decrease). Dosing adjustments were based usually on expert opinion, and model-informed precision dosing based on Bayesian a posteriori pharmacokinetic estimates was used in selected cases. More details on how dosing adjustments were provided have been described in our previous study [13]. Clinicians were free to accept or reject dosing adaptation suggested by the ECPA. TDM re-assessment was performed every 48–72 h on a case by case basis. The clinical and laboratory data needed for providing the ECPA and the desired PK/PD targets of antimicrobials are summarised in Table 1.

Figure 1 depicts the sequential phases of the ECPA production. All TDM samples delivered to the LUM by 11:30h were processed immediately, and TDM-guided ECPAs were provided by the mid-afternoon on the same day. Otherwise, they were processed the following day. Each ECPA usually took 10–30 min depending on case-mix complexity.

2.2. Study population and indicators of performance

All hospital admitted patients who had at least one TDM-guided ECPA for tailoring therapy with antimicrobials between July 2021 and June 2022 were retrospectively included. Patients were grouped into five cohorts according to the type of admission ward, namely haematology, ICU, paediatrics, medical wards and surgical wards.

Four indicators of performance were identified. First, the total number of delivered ECPAs (both absolute and normalised to 100 beds) was assumed as an indicator of the overall clinical impact of the ECPA programme in each of the five hospital settings. Sec-

Table 1
Clinical and laboratory data examined for providing therapeutic drug monitoring (TDM)-guided expert clinical pharmacological advice for antimicrobial dose optimisation, and therapeutic ranges for empirical and MIC-driven therapy [9]

Antimicrobial class/agent	Clinical and laboratory data				PK/PD target	
	eGFR or mCL_{Cr}	ALT, AST, GGT	Serum albumin	Co-medications	Empirical therapy	Targeted therapy
β-Lactams						
Piperacillin/tazobactam [a]	✓				C_{ss}/CB 4–8 [b]	C_{ss}/MIC 4–8 [b]
Meropenem [a]	✓				C_{ss}/CB 4–8 [b]	C_{ss}/MIC 4–8 [b]
Ceftazidime [a]	✓				C_{ss}/CB 4–8 [b]	C_{ss}/MIC 4–8 [b]
Cefepime [a]	✓				C_{ss}/CB 4–8 [b]	C_{ss}/MIC 4–8 [b]
Ampicillin [a]	✓				C_{ss}/CB 4–8 [b]	C_{ss}/MIC 4–8 [b]
Glycopeptides						
Vancomycin [a]	✓				C_{ss} 20–25 mg/L	AUC/MIC 400–600
Teicoplanin	✓		✓		C_{min} 20–30 mg/L	AUC/MIC 500–900
Oxazolidinones						
Linezolid	✓			✓	C_{min} 2–8 mg/L	C_{min} 2–8 mg/L
Azole antifungals						
Voriconazole		✓		✓	C_{min} 1–3 mg/L	C_{min} 1–3 mg/L
Posaconazole		✓		✓	C_{min} 1–3 mg/L	C_{min} 1–3 mg/L
Fluconazole	✓			✓	C_{min} 10–20 mg/L	AUC/MIC $\geq$ 55–100
Isavuconazole		✓	✓	✓	C_{min} 1–5.13 mg/L	C_{min} 1–5.13 mg/L
Fluoroquinolones						
Levofloxacin	✓			✓	C_{min} 1–3 mg/L; C_{max} 7–10 mg/L	C_{min} 1–3 mg/L; C_{max}/MIC 10
Ciprofloxacin	✓	✓		✓	C_{min} 0.5–2 mg/L; C_{max} 4-7 mg/L	C_{min} 0.5–2 mg/L; C_{max}/MIC 10
Aminoglycosides						
Gentamicin	✓				AUC/CB $\geq$ 110	AUC/MIC $\geq$ 110
Amikacin	✓				AUC/CB $\geq$ 110	AUC/MIC $\geq$ 110
Antivirals						
Ganciclovir	✓				C_{min} 0.3–1.6 mg/L	C_{min} 0.3–1.6 mg/L
Acyclovir	✓				C_{min} 0.6–1.8 mg/L	C_{min} 0. 6–1.8 mg/L

ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the concentration–time curve; CB, EUCAST MIC clinical breakpoint; C_{max}, peak concentration; C_{min}, trough concentration; C_{ss}, steady-state concentration; eGFR, estimated glomerular filtration rate; EUCAST, European Committee on Antimicrobial Susceptibility Testing; GGT, gamma-glutamyl transferase; mCL_{Cr}, measured creatinine clearance; MIC, minimum inhibitory concentration; PK/PD, pharmacokinetic/pharmacodynamic; PLT, platelet; WBC, white blood cell.

[a] Administered by continuous infusion according to clinical practice.

[b] C_{ss}/MIC = 6–8 in case of pneumonia.

ond, the ratio at first TDM assessment between the total number of ECPAs recommending dosing adjustments and the total number of delivered ECPAs was assumed as an indicator of performance of the usefulness of the programme in allowing early optimisation of antimicrobial exposure. Third, the ratio at subsequent TDM assessments between the total number of ECPAs recommending dosing adjustments and the total number of delivered ECPAs was assumed as indicator of performance of the ECPA programme in allowing optimisation of antimicrobial exposure during the overall treatment period. Fourth, the turnaround time (TAT) of the ECPAs (defined as the timeframe elapsed between the delivery of the TDM blood sample to the LUM and publication on the intranet system of the TDM-guided ECPA) was assumed as an indicator of performance of timely usefulness of the ECPA programme in allowing prompt dosing adaptation. The TAT was defined as optimal when <12 h, quasi-optimal when 12–24 h, acceptable when 24–48 h and suboptimal when >48 h.

Numerical data are presented as the median and interquartile range (IQR) or range, whereas categorical data are presented as count and percentage.

3. Results

A total of 8484 TDM-guided ECPAs were provided for tailoring antimicrobial treatment in 2961 patients. All of the TDM performed in the study period was requested by clinicians in the combined form of TDM plus ECPA. Patients' demographic and clinical characteristics are summarised in Table 2. Overall, patients admitted to the ICU and to the medical wards accounted for almost two-thirds of the total (1958/2961; 66.1%). Male sex was prevalent and the median body mass index (BMI) was normal. The median (IQR) estimated glomerular filtration rate (eGFR) among groups ranged between 51 (21.8–90.0) mL/min/1.73m^2 and 120 (64.8–176.5) mL/min/1.73m^2.

The main reasons for antimicrobial treatment differed among groups. In haematology, febrile neutropenia (FN) and invasive fungal infections (IFIs) accounted for most of the indications (322/359; 89.7%). In the ICU, bloodstream infections (BSIs) and pneumonia accounted for more than one-half of cases (573/1010; 56.7%). FN, BSIs and IFIs represented more than one-half of indications in paediatrics (123/232; 53.0%). Sepsis, BSIs and intra-abdominal infections (IAIs) accounted for approximatively two-thirds of indications in the medical wards (538/948; 56.8%). Finally, IAIs and BSIs were the two main reasons for antimicrobial use in the surgical wards (233/412; 56.6%). Antimicrobial therapy was empirical in most cases. The highest microbiological identification rate was in the ICU (37.7%) and the lowest in haematology (7.2%). Most of the clinical isolates were Gram-negative bacteria.

The distribution of the total delivered TDM-guided ECPAs for each antimicrobial treatment is depicted in Figure 2. Piperacillin/tazobactam, meropenem, teicoplanin, voriconazole, posaconazole and linezolid had more than 500 ECPAs each, and overall 13/18 antimicrobials had >100 ECPAs.

The total number of ECPAs grouped by hospital setting is depicted in Figure 3. The highest was in the ICU (2871/8484; 33.8%), followed by the medical wards (2490/8484; 29.4%), surgical wards (1265/8484; 14.9%), haematology (1054/8484; 12.4%) and paediatrics (804/8484; 9.5%). After normalising data per 100 beds/year, the highest was in haematology (3194/100 beds/year; 50.3%), followed by the ICU (1840/100 beds/year; 29.0%), paediatrics (705/100 beds/year; 11.1%), medical wards (352/100 beds/year; 5.5%) and surgical wards (259/100 beds/year; 4.1%).

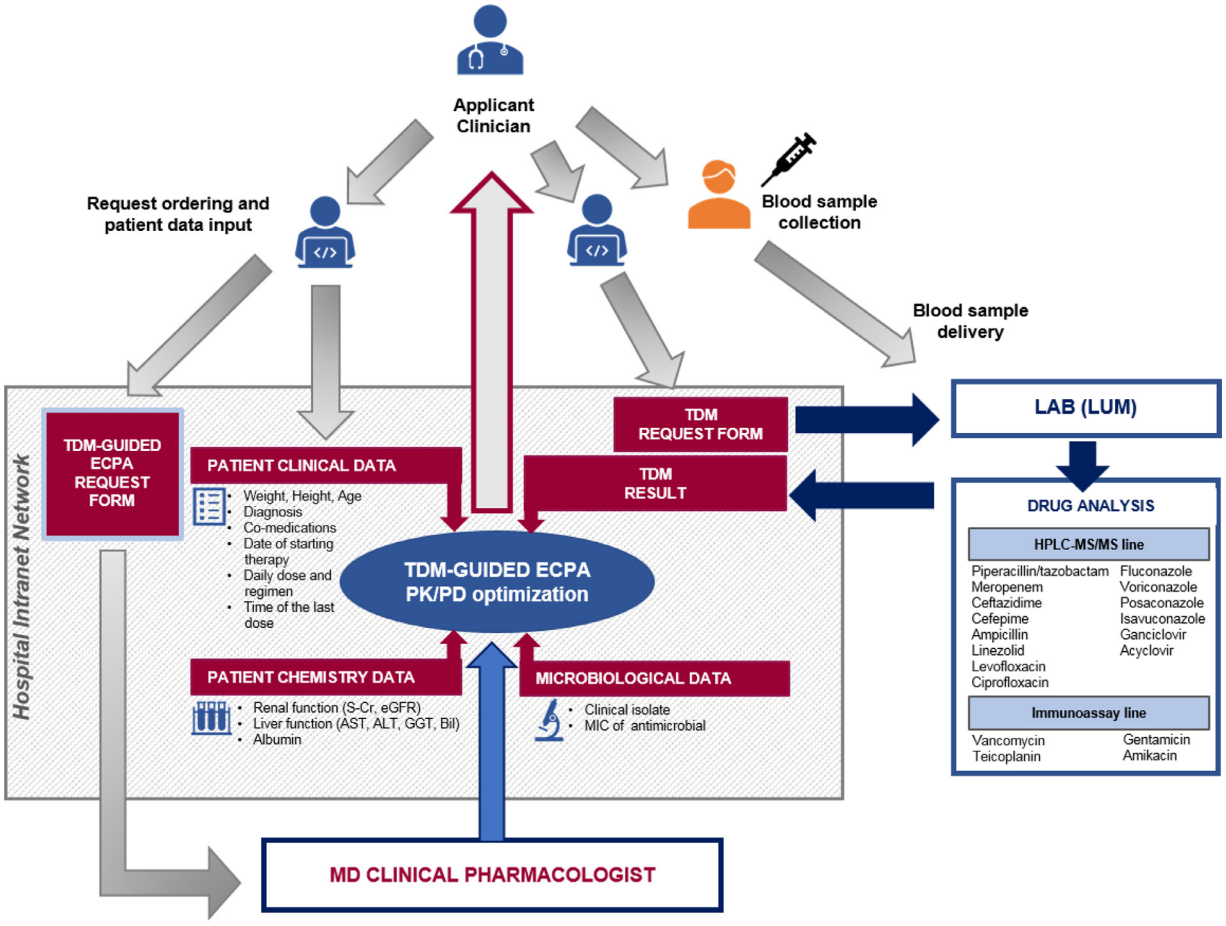

Figure 1. Different phases of production of the TDM-guided ECPA. ALT, alanine aminotransferase; AST, aspartate aminotransferase; Bil, bilirubin; ECPA, expert clinical pharmacological advice; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transferase; MIC, minimum inhibitory concentration; PK/PD, pharmacokinetic/pharmacodynamic; S-Cr, serum creatinine; TDM, therapeutic drug monitoring.

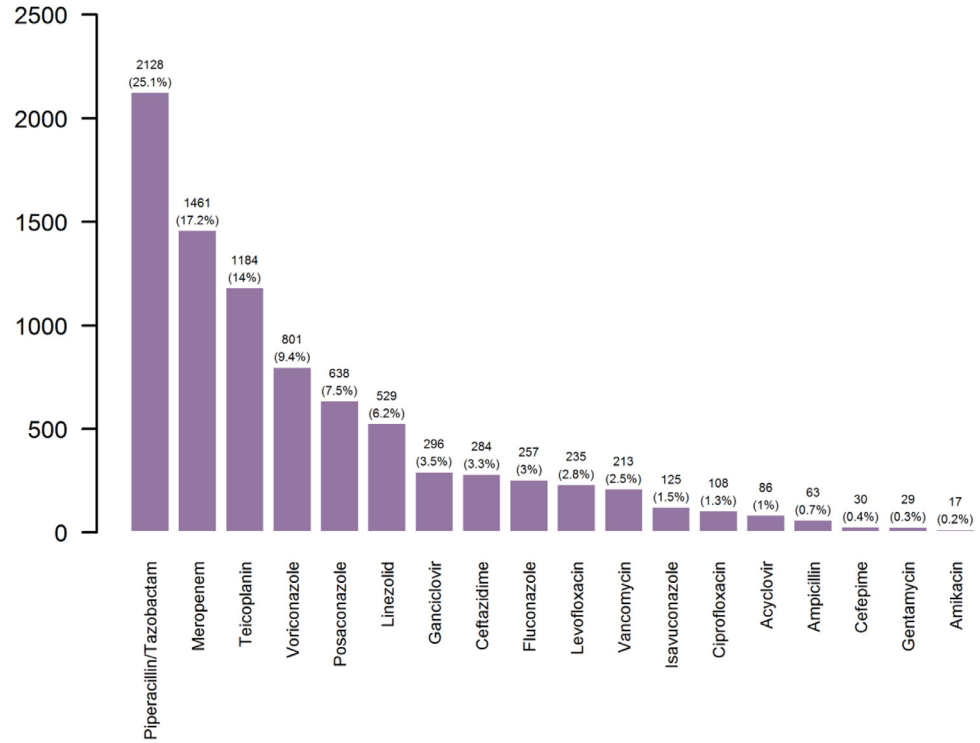

Figure 2. Histogram of the distribution of TDM-guided ECPA (n = 8484) groups by antimicrobials provided during the study period (July 2021 to June 2022). ECPA, expert clinical pharmacological advice; TDM, therapeutic drug monitoring.

Table 2
Demographic and clinical characteristics of the population according to different clinical settings

Variable	Clinical setting					*P*-value
	Haematology	ICU	Paediatrics	Medicine	Surgery	
Total number of patients	359	1010	232	948	412	<0.001
Age (years)	56 (46–67)	64 (54–73)	7 (2–13)	69 (57–79)	65 (50–75)	<0.001
Male sex	208 (57.9)	686 (67.9)	160 (68.9)	612 (64.6)	267 (64.8)	0.010
Body weight (kg)	70 (64–81)	75 (65–85)	21 (12.3–50)	70 (60–80)	70 (60–80)	<0.001
BMI (kg/m^2)	24.5 (21.8–27.8)	25.5 (22.5–28.7)	17.0 (13.9–20.8)	24.4 (21.7–27.7)	24.8 (21.5–27.8)	<0.001
SCr (mg/dL)	0.72 (0.6–1.0)	1.16 (0.65–2.0)	0.31 (0.21–0.54)	1.28 (0.79–2.66)	0.90 (0.61–1.75)	<0.001
eGFR (mL/min/1.73m^2)	103 (80.0–117.8)	60 (30.0–99.0)	120 (64.8–176.5)	51 (21.8–90.0)	81 (37.5–104.8)	<0.001
Reason for antimicrobial treatment						
Invasive fungal infection	173 (48.2)	6 (0.6)	35 (15.1)	31 (3.3)	3 (0.7)	<0.001
Febrile neutropenia	149 (41.5)	3 (0.3)	52 (22.4)	26 (2.7)	1 (0.2)	<0.001
Bloodstream infection	25 (6.9)	307 (30.4)	36 (15.5)	121 (12.7)	91 (22.1)	<0.001
CMV/HSV infection	7 (1.9)	2 (0.2)	14 (6.0)	12 (1.3)	6 (1.5)	<0.001
Intra-abdominal infection	2 (0.6)	157 (15.5)	31 (13.4)	87 (9.2)	142 (34.5)	<0.001
Pneumonia	1 (0.3)	266 (26.4)	30 (12.9)	124 (13.1)	12 (2.9)	<0.001
Skin and soft-tissue infection	1 (0.3)	19 (1.9)	3 (1.3)	42 (4.4)	39 (9.5)	<0.001
Urinary tract infection	1 (0.3)	30 (2.9)	3 (1.3)	58 (6.1)	9 (2.2)	<0.001
Sepsis/septic shock	0 (0.0)	199 (19.7)	17 (7.3)	330 (34.8)	53 (12.8)	<0.001
Bone and joint infection	0 (0.0)	14 (1.4)	3 (1.3)	93 (9.8)	52 (12.6)	<0.001
Endocarditis	0 (0.0)	5 (0.5)	0 (0.0)	13 (1.4)	2 (0.5)	0.035
CNS infection	0 (0.0)	2 (0.2)	8 (3.5)	11 (1.2)	2 (0.5)	<0.001
Patients with microbiological clinical isolates	26 (7.2)	381 (37.7)	34 (14.7)	277 (29.2)	89 (21.6)	<0.001
Gram-positive bacteria	3/26 (11.6)	16/381 (4.2)	6/34 (17.6)	80/277 (28.9)	14/89 (15.7)	<0.001
Gram-negative bacteria	22/26 (84.6)	356/381 (93.4)	27/34 (79.4)	194/277 (70.0)	75/89 (84.3)	<0.001
Fungi	1/26 (3.8)	9/381 (2.4)	1/34 (2.9)	3/277 (1.1)	0/89 (0.0)	0.351
Total number of ECPAs[a]	1054 (12.4)	2871 (33.8)	804 (9.5)	2490 (29.4)	1265 (14.9)	<0.001
Number of ECPAs per patient	2 (1–3)	2 (1–4)	2 (1–3)	2 (1–3)	2 (1–3)	0.002
Distribution of concentrations at first ECPA						
Within desired range	212 (59.2)	375 (37.2)	107 (46.1)	389 (41.0)	166 (40.3)	<0.001
Underexposure	86 (23.9)	110 (10.9)	90 (38.8)	133 (14.0)	69 (16.8)	<0.001
Overexposure	61 (16.9)	525 (51.9)	35 (15.1)	426 (44.9)	177 (42.9)	<0.001

NOTE: Data are presented as the median (interquartile range) for continuous variables and as *n* (%) for dichotomous variables.
BMI, body mass index; CMV, cytomegalovirus; CNS, central nervous system; HSV, herpes simplex virus; ECPA, expert clinical pharmacological advice; eGFR, estimated glomerular filtration rate; SCr, serum creatinine.
[a] Percentage given out of total number of ECPAs.

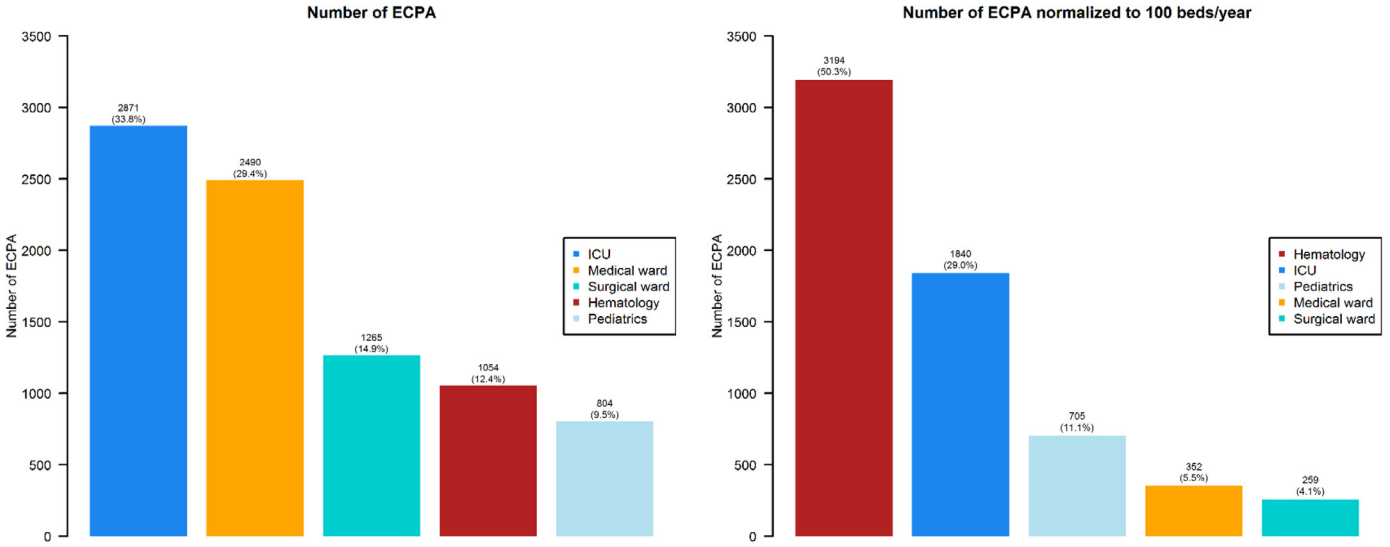

Figure 3. Distribution of (A) total number of TDM-guided ECPAs and (B) normalised to 100 beds/year, grouped by admission ward (haematology, intensive care unit, paediatrics, medical wards and surgical wards). ECPA, expert clinical pharmacological advice; TDM, therapeutic drug monitoring.

The distribution over time of the monthly delivered ECPAs in the five different settings is depicted in Figure 4. By comparing the first quarter (July–October 2021) with the last quarter (March–June 2022) of the study period, the proportion of delivered ECPAs remained stable in the ICU (10.80% vs. 10.56%; $P = 0.589$) and in the medical wards (9.64% vs. 10.07%; $P = 0.294$) but increased significantly in haematology (2.69% vs. 5.81%; $P < 0.001$), paediatrics (2.72% vs. 3.8%; $P < 0.001$) and surgical wards (4.05% vs. 5.85%; $P < 0.001$).

Figure 5 shows the radar plots of the proportions of dosing confirmations versus dosing increases and decreases, grouped by admission ward, that were provided at the first (left panel) and subsequent (right panel) TDM assessments for those antimicrobials having a total number of delivered ECPAs ≥10. Overall,

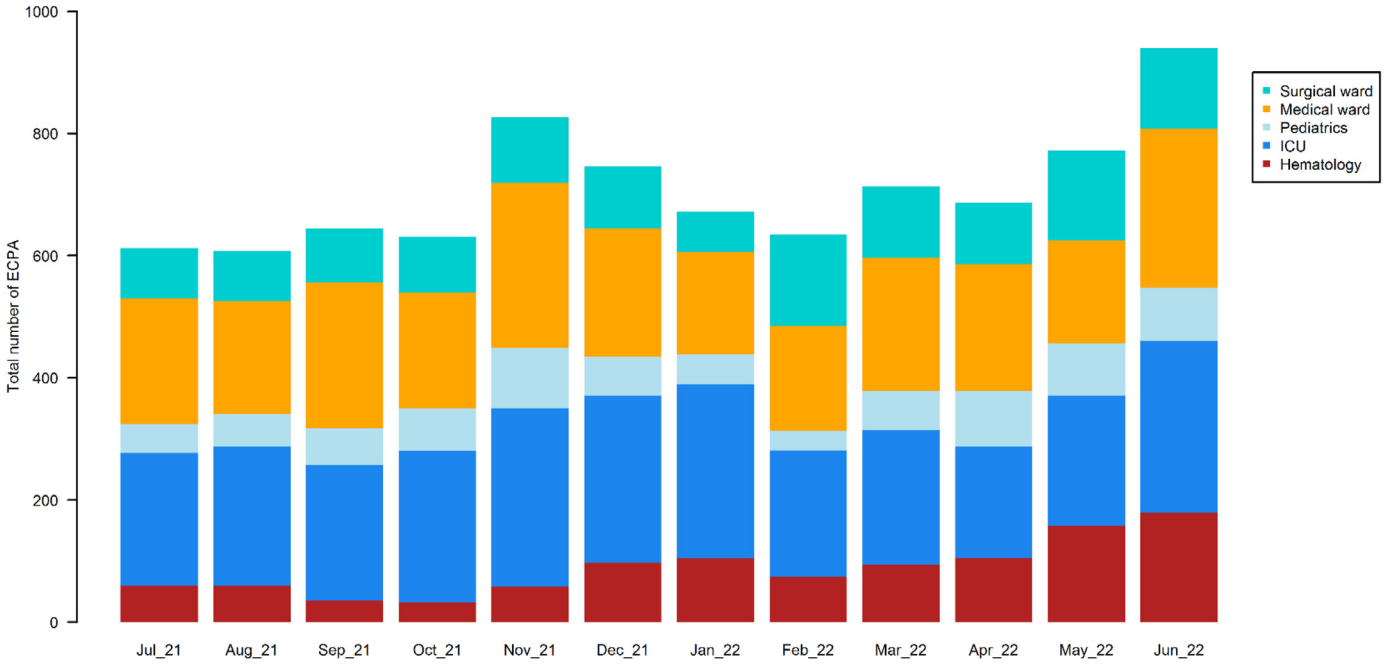

Figure 4. Monthly distribution of the total number of TDM-guided ECPAs in the study period (July 2021 to June 2022) grouped by admission ward (haematology, intensive care unit, paediatrics, medical wards and surgical wards). ECPA, expert clinical pharmacological advice; TDM, therapeutic drug monitoring.

ECPA recommendations were always accepted by clinicians and were delivered mainly for optimising treatment with posaconazole and meropenem in haematology [527/1054 (50.0%) and 172/1054 (16.3%), respectively], with piperacillin/tazobactam and meropenem in the ICU [984/2871 (34.3%) and 846/2871 (29.5%), respectively], with voriconazole and piperacillin/tazobactam in paediatrics [193/804 (24.0%) and 131/804 (16.3%), respectively], with piperacillin/tazobactam and teicoplanin in the medical wards [608/2490 (24.4%) and 549/2490 (22.0%), respectively] and with teicoplanin and piperacillin/tazobactam in the surgical wards [451/1265 (35.7%) and 267/1265 (21.1%), respectively]. At first TDM assessment, the overall proportion of ECPAs recommending dosing adjustments was >40% in all of the different settings [40.9% (147/359) in haematology, 62.9% (635/1010) in ICU, 53.9% (125/232) in paediatrics, 59.1% (560/948) in the medical wards and 59.7% (246/412) in the surgical wards]. The prevalent recommendation of dosing adjustment was increase in haematology and paediatrics and decrease in the other three settings. At subsequent TDM assessments, the proportion consistently decreased in all of the different settings [20.7% (144/695) in haematology, 40.6% (756/1861) in ICU, 37.4% (214/572) in paediatrics, 32.9% (508/1542) in the medical wards and 29.2% (249/853) in the surgical wards].

When looking at the most frequently delivered types of ECPAs, the magnitudes of the proportion decrease in recommending dosing adjustments at subsequent TDM assessments differed in the various hospital settings.

In haematology, it was very relevant for meropenem (50.7% vs. 24.3%), piperacillin/tazobactam (45.2% vs. 29.4%) and voriconazole (78.9 vs. 44.7%) and was almost zero for posaconazole (15.2% vs. 15.0%). In the ICU, it was very relevant for meropenem (62.0% vs. 36.5%) and was quite relevant for piperacillin/tazobactam (61.3% vs. 47.7%), voriconazole (51.2% vs. 34.7%) and linezolid (54.1% vs. 34.7%). In paediatrics, it was very relevant for piperacillin/tazobactam (59.1% vs. 38.4%) and was quite relevant for voriconazole (56.3% vs. 46.3%) and vancomycin (75.8% vs. 61.4%). In the medical wards, it was very relevant for piperacillin/tazobactam (65.7% vs. 36.4%), teicoplanin (63.5% vs. 20.6%) and meropenem (57.3% vs. 33.7%) and was almost zero for linezolid (41.5% vs. 40.8%). In the surgical wards, it was very relevant for teicoplanin (54.8% vs. 28.4%), piperacillin/tazobactam (68.0% vs. 31.3%) and ganciclovir (75.0% vs. 24.1%) and was quite relevant for meropenem (52.2% vs. 34.4%).

The overall median TAT of the TDM-guided ECPAs was 8.11 h (range, 1.51–160.72) and the median TAT of each single antimicrobial was always <12 h.

4. Discussion

To the best of our knowledge, this is the first study assessing the impact of a newly established TDM-guided ECPA programme including several emerging TDM candidates in tailoring antimicrobial therapies hospital-wide in a tertiary university hospital.

The first-year findings showed that this programme was much welcomed by the clinicians in all of the hospital settings and that overall it had a great impact in improving tailoring of antimicrobial therapy. In Italy, the MD clinical pharmacologist is a specialist that couples pharmacokinetic and pharmacodynamic knowledge on drugs with a medical background and may provide valuable advice and recommendations on optimal drug use to clinicians. In this regard, expert and comprehensive clinical interpretation of the TDM results by the MD clinical pharmacologist was fundamental in increasing the awareness of clinicians of the importance that intranet-delivered ECPAs may have had in making real-time dosing adaptation feasible, thus enabling timely optimisation of antimicrobial exposure in each single patient.

Overall, the total number of delivered ECPAs was very high and most of the applications came from the ICU. Indeed, this was an expected finding based on our previous experience [13] and was in agreement with the recommendations of optimising antimicrobial dosing in critically ill patients based on PK/PD principles and on adaptive TDM strategy [14].

Interestingly, after normalising data to 100 beds/year, haematology had the highest ECPA application rate followed by the ICU. Indeed, these two settings may benefit the most from a personalised programme of dosing adaptation of antimicrobials. Patients admitted in these settings may receive several co-medications and

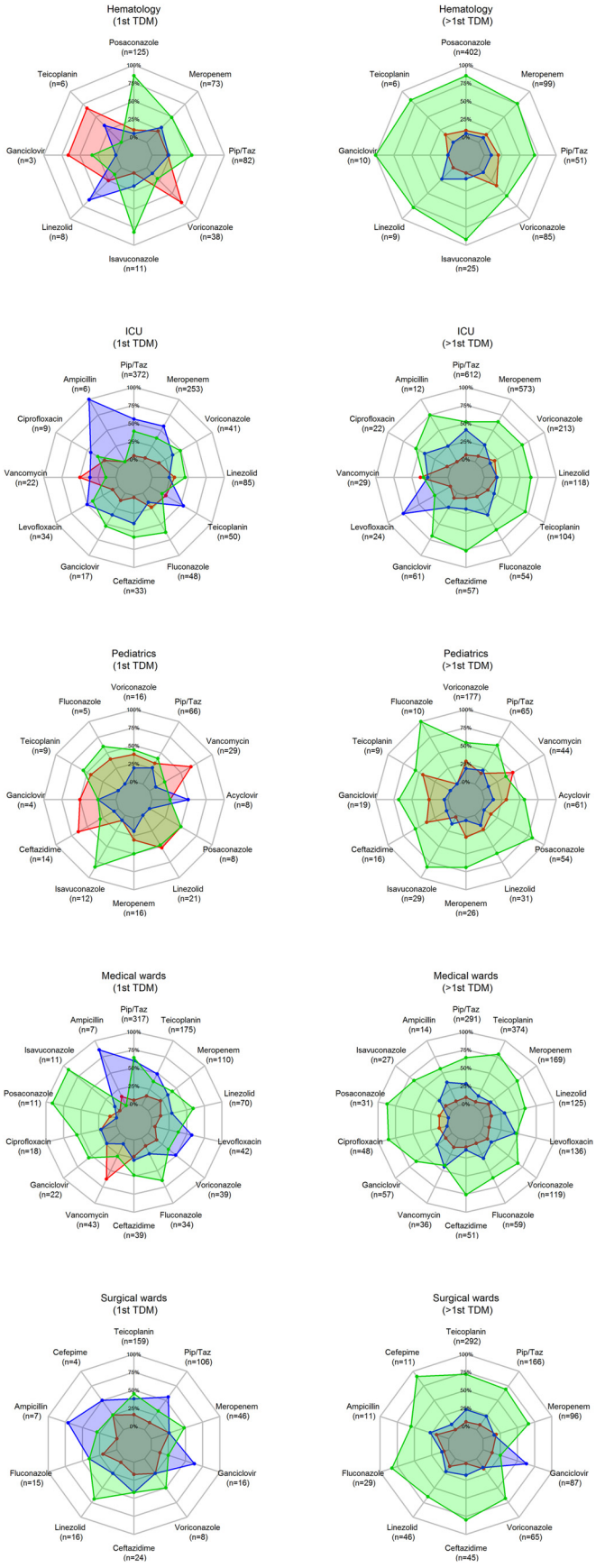

Figure 5. Radar plot of the proportion of dosing recommendations (green = dose confirmed; red = dose increased; blue = dose decreased) at first (left panel) and subsequent (right panel) TDM assessments for those antimicrobials with a total number of delivered ECPAs ≥10 during the study period (July 2021 to June 2022) grouped by admission ward (haematology, intensive care unit, paediatrics, medical wards and surgical wards). ECPA, expert clinical pharmacological advice; Pip/Taz, piperacillin/tazobactam; TDM, therapeutic drug monitoring.

are frequently affected by underlying diseases and/or pathophysiological conditions causing huge pharmacokinetic variability [14,15]. The awareness of clinicians of this programme was favoured by the daily attendance of both the MD clinical pharmacologist and the infectious diseases (ID) consultant at the ICU and at the haematology bedside morning multidisciplinary briefings during the study period.

Overall, the proportion of ECPAs recommending dosage adjustments was quite high in all of the hospital settings at first TDM assessment, but decreased by one-third to one-half at subsequent TDM assessments. This suggests, on the one hand, a good compliance of clinicians in promptly implementing dosing recommendations and, on the other hand, the usefulness of the ECPA programme in achieving antimicrobial exposure optimisation. The very short overall median TAT was crucial in making the ECPA programme reliable and successful.

The prevalent types of delivered ECPAs varied in the different hospital settings. In haematology, ECPAs were requested mainly for azole antifungals and β-lactams. Most concerned posaconazole for IFI prophylaxis [15], and dosing adjustments were recommended in around one-sixth of cases, almost equally distributed between increases and decreases. Dosing increases were recommended to avoid the risk of breakthrough infections related to underexposure mainly in patients co-treated with corticosteroids and/or proton pump inhibitors [16]. Dosing decreases were provided in the presence of overexposure for preventing the risk of pseudo-hyperaldosteronism, which is a dose-dependent adverse event of posaconazole [17]. The ECPAs for meropenem and piperacillin/tazobactam were provided for optimising empirical treatment of FN [18] and recommended dosing adjustments in almost one-half of cases. Augmented renal clearance is a rather frequent occurrence among onco-haematological patients and may represent a major cause of accelerated elimination of β-lactams with the need for dosing increases [19]. Noteworthy, the ECPAs delivered for optimising IFI treatment with voriconazole [15] recommended dosage increases in as many as three-quarters of first TDM assessments. This stresses once more the mandatory role that TDM-guided dosing of voriconazole should have in the Caucasian population [20]. In this ethnicity, the prevalence of CYP2C19 ultrarapid genotype promoting fast voriconazole biotransformation may be as high as 30–40% [21]. An additional cause of the need for dose increase may be co-treatment with the anti-cytomegalovirus agent letermovir, which is a strong inducer of CYP2C19-mediated voriconazole biotransformation [22]. Conversely, the ECPAs delivered for isavuconazole recommended dosing adjustments only in very few cases. This confirms that the need for tailoring therapy with this novel azole antifungal is quite limited and may be restricted only to some peculiar cases [23,24].

In the ICU, ECPAs were primarily requested for tailoring therapy with β-lactams, voriconazole and linezolid. Most of the ECPAs delivered for piperacillin/tazobactam and meropenem were requested for tailoring targeted therapy of Gram-negative-related BSI and ventilator-associated pneumonia and/or for empirical treatment of septic shock. The high rate of ECPAs recommending dosing reduction at first TDM assessment may be explained by several reasons. First, initial dosages of β-lactams for treating septic shock were aggressive even in patients with acute kidney injury. This was done to confer maximal effectiveness in the golden hours even in those patients who could have experienced acute kidney injury transiently, with a return to baseline renal function within the first 48 h [25]. Second, the option to switch to targeted therapy based

on a minimum inhibitory concentration (MIC)-driven approach occurred rather frequently in this setting and allowed for consistent dose reduction in the presence of very susceptible clinical isolates. This was made especially reliable by continuous-infusion administration of β-lactams, which allowed attaining PK/PD targets with lower doses compared with intermittent infusion. Besides, renal function may be changeable in critically ill patients during the ICU stay and may affect the likelihood of attaining optimal PK/PD targets [26]. This may explain the frequent need for recommending dosing adjustments even at the subsequent TDM assessments. In this setting, the ECPAs for voriconazole recommended more dosing decreases than increases. This may seem in contrast to what was observed in haematology. Indeed, the findings may be explained by a downregulation of the CYP450-mediated metabolism of voriconazole, which could have been caused by the hyperinflammation occurring during septic shock [27,28]. The ECPAs for linezolid recommended dosing adjustments in almost one-half of first TDM assessments. This confirms that nowadays TDM should be considered a mandatory tool for optimising linezolid treatment [29,30], especially among critically ill patients [31,32]. Important causes of linezolid overexposure were severe renal dysfunction and co-treatment with some drugs, such as cardiovascular agents and cyclosporine [32–34].

In paediatrics, most of the ECPAs were provided for voriconazole, piperacillin/tazobactam and vancomycin both in onco-haematological and critically ill children. Of note, the ECPAs recommended dosing increases in as many as 40–70% of first TDM assessments. For piperacillin/tazobactam and vancomycin, which are hydrophilic antibiotics, this may be explained by the frequent occurrence of augmented renal clearance in this setting [35,36]. For voriconazole, the need might have been linked to the age-related increase in CYP-mediated clearance occurring in the first years of life [37].

In the medical wards, most of the ECPAs concerned piperacillin/tazobactam, teicoplanin, meropenem and linezolid, and at first TDM assessment recommended dosing reductions in up to 30–60% of cases. This is in agreement with the fact that these patients were the oldest and had the lowest eGFR [38]. Interestingly, the medical wards were the only setting in which ECPAs were requested quite frequently for tailoring levofloxacin therapy [39]. Indeed, in our hospital nowadays levofloxacin use is consistently restricted and is limited essentially to the targeted therapy of methicillin-susceptible *Staphylococcus aureus* bone and joint infections.

In the surgical wards, most of the ECPAs were provided for teicoplanin, piperacillin/tazobactam, meropenem and ganciclovir. The ECPAs for teicoplanin were provided mainly for tailoring treatment of IAIs, and most of these recommended a dosing decrease at first TDM assessment. Major reasons for this were underlying renal dysfunction and/or inappropriate extension of loading dose administration during the maintenance period. This confirms once more the usefulness that this approach may have in counteracting the wide pharmacokinetic variability of teicoplanin [40].

Overall, applying for ECPAs every 48–72 h was crucial in timely tailoring of TDM-guided antimicrobial treatments in all of the settings, especially among those patients having changeable pathophysiological conditions and/or interacting co-treatments.

We recognise that this study has some limitations. The retrospective study design and lack of assessment of the relationship between tailored antimicrobial exposure and clinical/microbiological outcome must be acknowledged. Conversely, the very large sample size, the huge number of ECPAs delivered hospital-wide for the vast majority of the 18 antimicrobials included in the programme, and the remarkable proportion of dosing adjustment recommendations coupled with the optimal TATs strengthen the contention that this novel TDM-based ECPA programme was successful and had a great clinical impact in tailoring antimicrobial therapies.

In conclusion, our study showed that a TDM-guided ECPA programme may be extensively and successfully applied for tailoring treatment with a wide panel of antimicrobials hospital-wide. Expert interpretation of TDM results by the MD clinical pharmacologist with rapid TATs and strict interaction with ID consultants and clinicians were crucial in achieving these objectives. Prospective studies investigating the impact of the programme on clinical and microbiological outcomes in the different patient settings are warranted.

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Competing interests: P.G.C. has participated in speakers' bureaux for Angelini, Shionogi, Pfizer and MSD outside of the submitted work; M.G. has participated in speakers' bureaux for Angelini and Shionogi outside of the submitted work; F.P. has participated in speakers' bureaux for Angelini, BeiGene, Gilead, InfectoPharm, Menarini, Merck Sharp & Dohme, Pfizer and Sanofi Aventis and on advisory boards for Advanz Pharma, Angelini, BeiGene, Gilead, Merck Sharp & Dohme and Pfizer outside of the submitted work; P.V. has participated in speakers' bureaux for Correvio, Gilead, Merck Sharp & Dohme, Nordic Pharma and Pfizer and on advisory boards for bioMérieux, Gilead, Merck Sharp & Dohme, Nabriva, Nordic Pharma, Pfizer, Thermo Fisher and Venatorx outside the submitted work. All other authors declare no competing interests.

Ethical approval: This study was approved by the Ethics Committee of IRCCS Azienda Ospedaliero–Universitaria of Bologna (Bologna, Italy) [no. 442/2021/Oss/AOUBo, approved on 28 June 2021]. Written informed consent was waived due to the retrospective and observational nature of the study.

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