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Personalization of antimicrobial dosing regimens: indicators of performance

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ABSTRACT

BACKGROUND: the present study aims to assess the efficiency and effectiveness of the organizational system of a Clinical Pharmacological Service of an Italian tertiary care teaching hospital in providing advices (CPAs) to clinicians within timeframes useful for the personalization of antimicrobial dosing regimens in different patients' populations according to the clinical benefit for patient care.

METHODS: the frequency per week of the various typologies of CPA was defined on the basis of prior evaluations aimed at estimating the clinical benefit for patient care (high priority level, for antimicrobials used to treat acute infections in the critically ill patients; moderate priority level, for those used to treat cytomegalovirus infections in solid organ transplant recipients; mild priority level, for those used to treat chronic infections). The CPAs provided between December 2011 and June 2012 represented the starting database. The measured turnaround time (TAT) of each CPA typology was used as an indicator of the performance of the organizational system according to a predefined scale (high, when within agreed timeframe; acceptable, when 1-2 days overdue; low, when > 2 days overdue).

RESULTS: 6601 CPAs were provided (77.4% for AOUD and 22.6% for other hospitals), mainly for antimicrobials with high priority. The mean TAT was of < 24 hours for the CPAs provided 3 to 5 times per week, of < 48 hours for those provided 2 times per week, and of < 6 days for those provided once weekly every other week. Overall, the performance was high, the percentage of overdue advices always less than 5%, irrespective of the CPA type.

CONCLUSIONS: our study confirms the suitability of the organizational system of our Service to provide a thousand per month TDM-based CPAs within timeframes clinically useful for the individualization of the dosing regimens of several antimicrobials.

Key words: Personalized antimicrobial therapy; Clinical pharmacological advice; Therapeutic drug monitoring

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INTRODUCTION

Clinical pharmacology is the discipline devoted to improving the safe and effective use of medicines (1). Therapeutic drug monitoring (TDM) has became an invaluable tool for optimizing drug therapy in some clinical settings (2). Noteworthy, the usefulness of TDM may become of utmost importance for clinicians when drug levels are interpreted

by the clinical pharmacologist in the light of the patient's characteristics (i.e. age, weight, pathophysiological conditions and co-treatments), and a motivated clinical pharmacological advice (CPA) suggesting how and when to modify drug dosage in order to achieve optimal plasma exposure is provided to clinician within a reasonably brief timeframe.

This is especially true for those drugs whose effectiveness must be maximized within few hours after starting therapy and is titrated to drug exposure, as is the case with antimicrobial agents for the treatment of severe infections in the critically ill patients (3).

Notably, the dose adjustment of antibiotic regimen on the basis of real time CPAs can meet the dual goal of maximizing clinical efficacy and of preventing the emergence of antimicrobial resistance in the environment (4).

It has been shown that achieving therapeutic concentrations with antimicrobials since the first hours of therapy is of paramount importance in terms of favourable clinical outcomes for the critically ill patients with severe sepsis or septic shock (5). Accordingly, providing clinicians with TDM-based CPAs for the optimization of dosing regimens of antimicrobials within few hours from their request represents a key strategy to improve clinical outcomes in this scenario.

The aim of the present study was to assess the efficiency and effectiveness of the organizational system of a Clinical Pharmacological Service of an Italian tertiary care teaching hospital in providing helpful CPAs to clinicians within timeframes useful for the personalization of antimicrobial dosing regimens in different patients' populations according to the clinical benefit for patient care.

METHODS

Organizational aspects

AOUD is a 950-bed tertiary care teaching hospital which is organized in 13 departments. The Institute of Clinical Pharmacology belongs to the Department of Internal Medicine, is the hub centre for clinical pharmacology of the Friuli Venezia Giulia Region, and provides CPAs for both inpatients and outpatients region wide.

The TDM-based CPAs for the individualization of antimicrobial dosing regimens are provided by the clinical pharmacologists on the basis of the patient's peculiar characteristics (weight, height, biochemical parameters of renal and hepatic function, causative organism, infection site, date of starting antimicrobial therapy, drug dose and frequency of administration, time of blood sample collection, co-administered drugs), which must be supplied by the physician who have in charge the patient. An example of this is depicted in Figure 1.

CPAs are produced electronically through the hospital online intranet system with the intent of increasing the efficiency of the process and of shortening the latency time. This enables in-hospital clinicians to view them immediately after completion of the process and application of the digital signature. In presence of applications coming from other hospitals, a printed copy of the CPA is promptly anticipated by fax to the applicant hospital ward, with the original document subsequently sent by ordinary mail.

As far as the organizational aspects of the implemented system are concerned, the execution plan with the frequency per week of the various typologies of CPAs for antimicrobials (Table 1) was based on prior evaluations aimed at estimating their clinical benefit for patient care in different clinical settings (acute or chronic infections or prevention). The CPAs for antimicrobials used to treat acute infections in the critically ill patients (amikacin, ceftazidime, daptomycin, fluconazole, gentamicin, levofloxacin, linezolid, meropenem, piperacillin, teicoplanin and vancomycin) were classified at high priority level, and they were provided five or three times in a week; those for antimicrobials used to prevent or to treat cytomegalovirus infections in solid organ transplant recipients (ganciclovir) were classified at moderate priority level, and they were scheduled twice in a week; those for antimicrobials used to treat chronic infections (isoniazid, voriconazole) were considered at mild priority level and were provided once weekly or every other week.

In order to measure the efficiency of the process, different turnaround times (TATs) for each typology of antimicrobial CPA were agreed with the Medical Directorate of the AOUD by taking into account their clinical benefit for patient care. TAT was defined as the timeframe elapsing between the receipt of the TDM sample and the production of the definitive TDM-based CPA made available to the applicant clinician. The agreement had also

to take into account the fact that the available laboratory instrumentations [6 high pressure liquid chromatography (HPLC) instruments, 1 capillary electrophoresis and 1 LC-mass spectrometry, 1 immunoassay and clinical chemistry analyser] are not fully devoted to these purposes, but have to be used for other TDM purposes, too (i.e. for immunosuppressants and antiepileptics). Additionally, it had to be considered that some TDM procedures are more time-consuming than others (most of them are not fully automated and require operators for drug extraction and sample injections).

Assessment of performance

The TDM-based CPAs provided between December 2011 and June 2012 represented the starting database. The TAT for each type of CPA was used as an indicator of the performance of our organizational system, and was categorized according to a predefined scale: high performance, when the measured TAT was within agreed timeframe; acceptable performance, when it was 1-2 days overdue; low performance, when it was > 2 days overdue.

RESULTS

The number of CPAs for individualization of antimicrobial therapy provided during the seven-month study period was 6601. They concerned mainly antimicrobials with high priority and were addressed to AOUD inpatients in 77.4% of the cases and to inpatients of other hospitals in 22.6 % of the cases (Figure 2). Overall, medical wards were the most frequent applicant units (n=2 966, 58.0% for AOUD; n=823, 55.2% for other hospitals) followed by the surgical wards (n=1 233, 24.1% for AOUD; n=424, 28.5% for other hospitals) and by the intensive care units (n=912, 17.9% for AOUD; n=243, 16.3% for other hospitals).

Mean ± SD of measured TATs for each typology of antimicrobial CPA plotted against the agreed TATs threshold of 48 or 96 hours are shown in Figure 3 and Figure 4, respectively. Overall, the performance level was high, the percentage of overdue advices being always less than 5%, irrespective of the typology of CPA. Interestingly, the mean TAT was of less than 24 hours for all the typologies of CPAs provided 3 to 5 times per week (amikacin, daptomycin, fluconazole, gentamicin, levofloxacin, linezolid, meropenem, teicoplanin, vancomycin), whereas it was of less than 48 hours for those provided 2 times per week (ceftazidime, ganciclovir, piperacillin), and of 4.7 and 5.9 days for those provided once weekly (voriconazole) or every other week (isoniazid), respectively.

DISCUSSION

Our findings showed an overall high performance level for the organizational system of our Service in providing 900-to-1000 TDM-based CPA per month within timeframes

TABLE 1

WEEKLY-BASED SCHEDULE OF CLINICAL PHARMACOLOGICAL ADVICES FOR PERSONALIZED ANTIMICROBIAL THERAPY

5 TIMES WEEKLY			3 TIMES WEEKLY			2 TIMES WEEKLY			ONCE WEEKLY OR EVERY OTHER WEEK		
Drug	TD (h)	TATt of CPA (days)	Drug	TD (h)	TATt of CPA (days)	Drug	TD (h)	TATt of CPA (days)	Drug	TD (h)	TATt of CPA (days)
Gentamicin*	0.5	2	Daptomycin°	4.9	4	Ceftazidime°	5.5	4	Voriconazole°	5.9	5
Amikacin*	0.5	2	Fluconazole°	4.1	4	Ganciclovir°	5.2	4	Isoniazid°	4.3	11
Teicoplanin*	0.5	2	Linezolid°	3.4	4	Piperacillin°	6.3	4			
Vancomycin*	0.5	2	Meropenem°	4.2	4						
Levofloxacin°	3.3	2									

CPA, clinical pharmacological advice; TATt, turnaround time threshold agreed with the Medical Directorate; TD, temporal duration of the analytical procedure for 10 TDM samples; *fully automated analytical procedure; ° non automated analytical procedure

FIG. 1

EXAMPLE OF CLINICAL PHARMACOLOGICAL ADVICE

AZIENDA OSPEDALIERO UNIVERSITARIA
Santa Maria della Misericordia di Udine

DEPARTMENT of INTERNAL MEDICINE

Institute of Clinical Pharmacology

Applicant hospital/ward: .....

Mr.....
Birth Date: ..... Age: .... yrs Sex: .....
Request n°: ..... Request date:.....

Patient Weight	78	kg
Patient Height	178	cm
Sampling day and time	03.08.2012 h8:00	
MEROPENEM concentration	17.51	mg/L
Day for TDM reassessment	Monday 06.08.2012	

Comment:
Highly efficacious concentration for the treatment of bloodstream infection caused by the identified pathogen (*K. pneumoniae* with an MIC for meropenem of 0.5 mg/L). According to an estimated creatinine clearance of 0.98 mL/min/kg and to the observed concentration, in order to prevent drug accumulation and to optimize the time-dependent pharmacodynamic activity of meropenem, it is advisable to adjust dosage to 500 mg every 6 h administered by continuous infusion (total daily dose of 2 000 mg) and to reassess TDM on next Monday.

Warning: Meropenem is stable in aqueous solution maximum 6 hours; therefore it is mandatory that the solution is reconstituted every maximum six hours, next to each single administration.

Example of clinical pharmacological advice based on the TDM of the antibacterial agent meropenem administered at a dose of 1 000 mg every 6 hours by continuous infusion (4 000 mg daily) in a male patient (age: 66, weight: 78 kg, creatinine: 1.05 mg/dL) with a bloodstream infection caused by a *K. pneumoniae* strain with a minimum inhibitory concentration (MIC) for meropenem of 0.5 mg/L

clinically useful to individualize the dosing regimens of several antimicrobials.

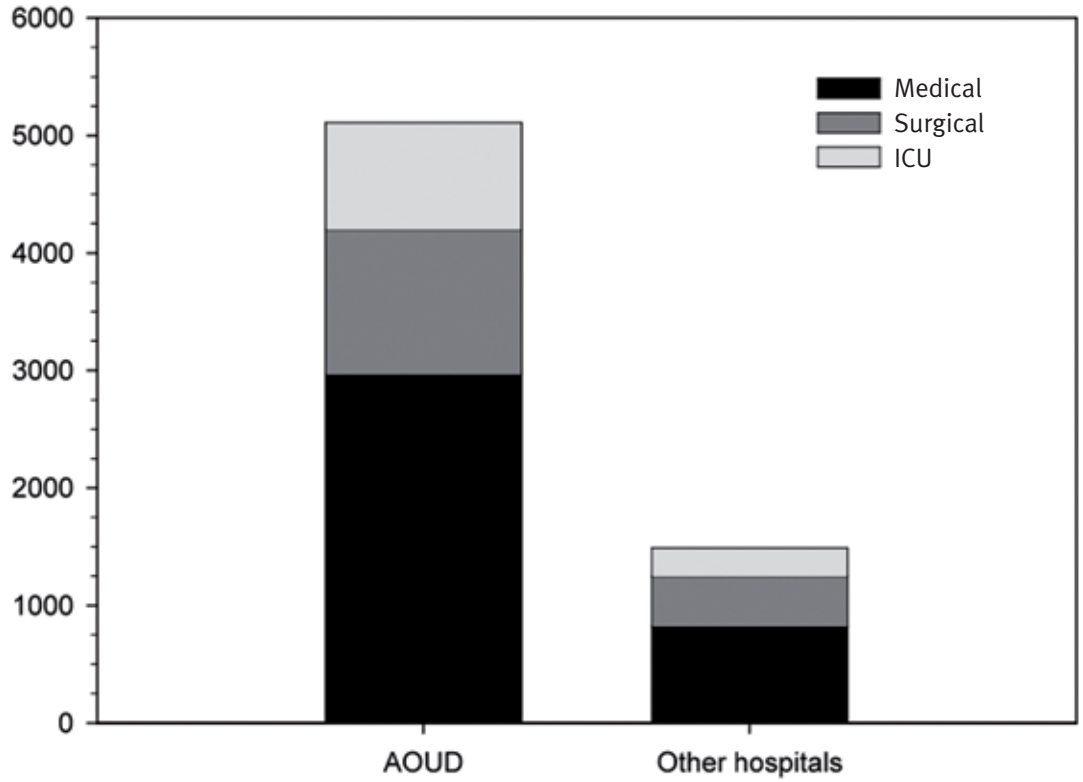
The CPAs provided during the study period concerned especially antimicrobials classified at high priority level which are frequently used to treat critically ill patients with acute severe infections. Notably, the high unpredictability of plasma drug exposure when fixed antimicrobial dosages are used in these patients challenges clinicians in individualizing dosing regimens in order to optimize efficacy (6, 7). In recent years, TDM-based CPA has emerged as an invaluable tool for individualizing antimicrobial drug exposure in the critically ill patients (4, 8-10). The interpretation of TDM results by the clinical pharmacologist is mandatory in these cases, since it has been shown that TDM services providing test results without appropriate interpretation and dosage recommendations generate costs without obtaining great clinical benefits (11).

Interestingly, most of our high priority level CPAs were completed within 1 to 2 days from request, this enabling clinicians for prompt dosage adjustments. The weekly plan of the different TDM-based CPAs and the prompt availability of the CPAs in the online intranet system which allowed for real-time viewing by clinicians have revealed of utmost importance in obtaining these results.

Most of the CPAs were provided within the agreed TATs, and this emphasizes that the choice of defining the priority level according

FIG. 2

NUMBER OF CLINICAL PHARMACOLOGICAL ADVICES



ICU: intensive care unit

Number of clinical pharmacological advices (CPAs) for individualization of antimicrobial therapy provided during the seven month study period in relation to the applicant hospital

to the clinical benefit for patient care has proven worthwhile. This allowed most of the CPAs to be provided to clinicians within the timeframe useful for dosing adjustment just before the subsequent day of the week in which an application for the same typology of CPA could be resubmitted. Thanks to this approach, it is expected that the period of time with inappropriate drug exposure in patients treated with these antimicrobials may be minimized. This is in line with the recommendations of the Survival Sepsis Campaign guidelines suggesting the need for frequent reassessment of antimicrobial dosing regimen in patients with severe sepsis and/or with septic shock (3).

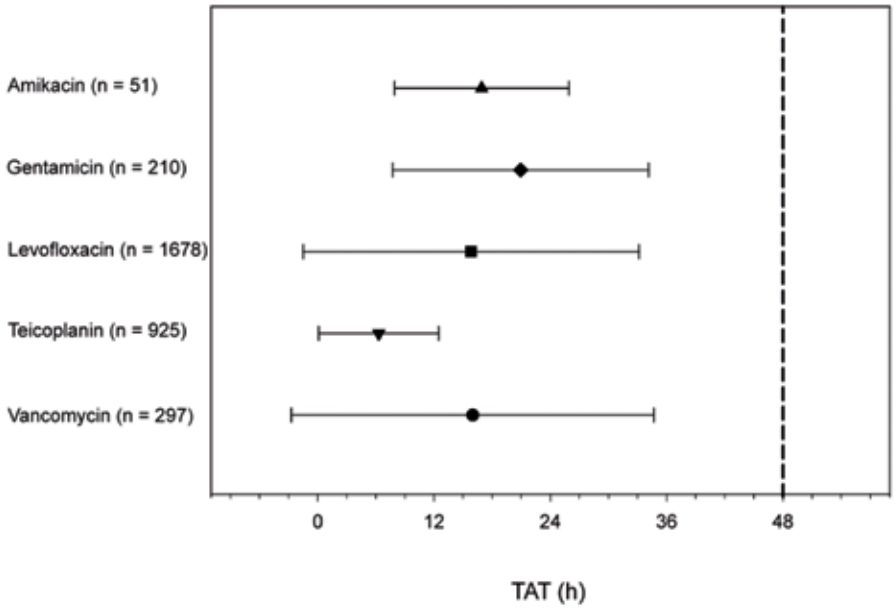
Indeed, to date it's mandatory that tertiary referral hospitals providing the highest level of care to patients with the highest complexity push towards the implementation of antimicrobial stewardship programs devoted to optimize antimicrobial drug exposure through TDM-based CPAs (12).

Although this could be easily implemented for drugs analyzed through fully automated procedures, it becomes more challenging in presence of non-automated analytical procedures, as it is the case with most of our activities, which, other than being more time consuming in daily practice, need additional technical skill and appropriate knowledge. Roberts et al. (10) stated that an issue still to be addressed concerning the TDM of the β-lactams, namely one of the most widely used class of antimicrobials, is the slow turnaround time of the results, as analytical methods are typically long and don't keep up the pace of clinical variability. Indeed, our organizational efforts allowing for average TATs of less than 24 h for most types of CPAs suggest that good performance may be achieved anyway.

In conclusion, our study confirms the suitability of the organizational system of our Service in providing a thousand per month TDM-based CPAs within timeframes clinically useful

FIG. 3

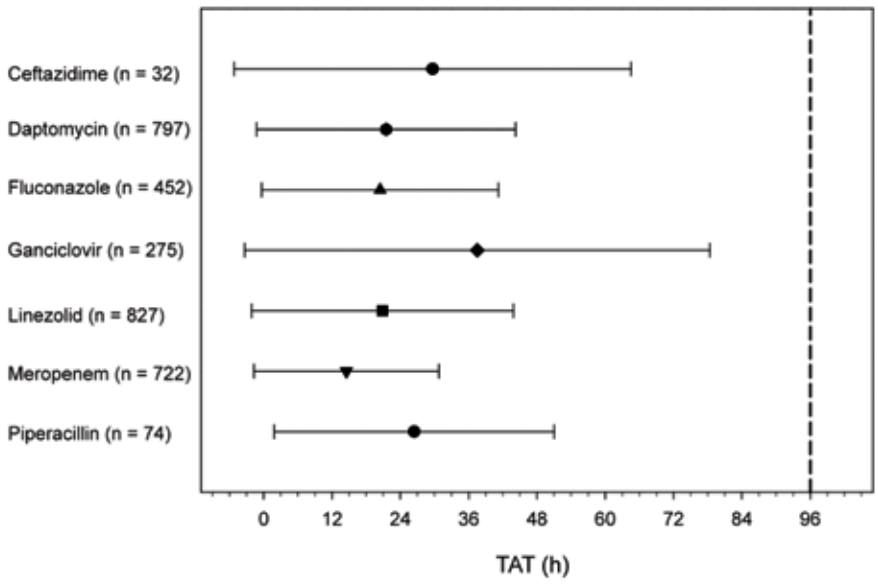
MEAN ± SD OF TURNAROUND TIME (TAT) OF CLINICAL PHARMACOLOGICAL ADVICES (CPA)



Mean ± SD of turnaround time (TAT) of clinical pharmacological advices (CPA) for dosing regimen individualization of those antimicrobials classified at high priority level, scheduled 5 times weekly and with agreed threshold of TAT of 48 hours. Short dash line identifies agreed threshold of TAT (48 hours)

FIG. 4

MEAN ± SD OF TURNAROUND TIME (TAT) OF CLINICAL PHARMACOLOGICAL ADVICES (CPA)



Mean ± SD of turnaround time (TAT) of clinical pharmacological advices (CPA) for dosing regimen individualization of those antimicrobials classified at high or moderate priority level, scheduled 3 or 2 times weekly and with agreed threshold of TAT of 96 hours. Short dash line identifies agreed threshold of TAT (96 h)

to the individualization of the dosing regimens of several antimicrobials. The relevance that these CPAs may have in maximizing the efficacy of antimicrobial therapy while containing the emergence of resistance in the hospital settings remains to be demonstrated and is the subject of an ongoing study.

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