Barriers And Facilitators For Therapeutic Drug Monitoring Of Beta-Lactams And Ciprofloxacin In The ICU: A Nationwide Cross-Sectional Study

Tim M.J. Ewoldt (t.ewoldt@erasmusmc.nl)
Erasmus University Medical Center
Alan Abdulla
Erasmus University Medical Center
Puck van den Broek
Utrecht University
Nicole Hunfeld
Erasmus University Medical Center
Soma Bahmany
Erasmus University Medical Center
Anouk E. Muller
Erasmus University Medical Center
Diederik Gommers
Erasmus University Medical Center
Suzanne Polinder
Erasmus University Medical Center
Henrik Endeman
Erasmus University Medical Center
Inge Spronk
Erasmus University Medical Center
Birgit C.P. Koch
Erasmus University Medical Center

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Abstract

Background: Recent studies demonstrated that failure of achieving pharmacodynamic targets of commonly used antibiotics is common in critically ill patients. Therapeutic drug monitoring (TDM) can contribute to optimize the exposure of beta-lactams and ciprofloxacin. While evidence for TDM of these antibiotics is growing, translation into clinical implementation remains limited. Therefore, perceived barriers and facilitators are important for implementing TDM in this population. The primary aim of this study was to identify healthcare professionals' barriers and facilitators for the implementation of TDM of beta-lactams and ciprofloxacin in Dutch intensive care units (ICU).

Methods: We conducted a nationwide cross-sectional online survey among healthcare professionals (HCPs) involved in antibiotic treatment of ICU patients. An adapted version of the Measurement Instrument for Determinants of Innovations was sent out. Items were considered barriers when ≥ 20% of participants responded with a negative answer. If ≥ 80% of the participants responded with a positive answer, the item was considered a facilitator.

Results: Sixty-four HCPs completed the survey, of which 14 were from academic hospitals, 25 from general hospitals, and 25 from teaching hospitals. Most participants were hospital pharmacists (59%) or medical specialists (23%). Eleven barriers and four facilitators for implementation of TDM of beta-lactams were identified; 17 barriers for TDM of ciprofloxacin and no facilitators. The most important barriers were a lack of conclusive evidence, organizational support, and low availability of assays. Additional barriers were a lack of consensus on which specific patients to apply TDM and which pharmacodynamic targets to use. Identified facilitators for beta-lactam TDM implementation are low complexity and high task perception, combined with the perception that TDM is important to prevent side effects and to adequate treat infections. Twenty-eight percent of participants reported that flucloxacillin could be analyzed in their hospital. Availability of other beta-lactams and ciprofloxacin varied (3-17%).

Conclusion: Several barriers were identified that could obstruct the implementation of TDM of beta-lactams and ciprofloxacin in the ICU. In particular, education, clear guidelines, and organizational support in particular should be considered when creating tailored implementation strategies. Finally, evidence of beneficial clinical outcomes on TDM of beta-lactams and ciprofloxacin can enhance further implementation.

Background

Beta-lactams and ciprofloxacin are frequently prescribed antibiotics in intensive care units (ICU) to treat severe infections (1, 2). The standard dosing regimen of these drugs is not based on their pharmacokinetics in the critically ill. Failure to achieve the pharmacodynamic target (PDT) of these antibiotics is a common problem, which might result in therapeutic failure and antibiotic resistance (3-5). To increase the efficacy of beta-lactams and ciprofloxacin in critically ill patients, individualizing dosing

by measuring drug and active metabolite concentrations is proposed, which is called therapeutic drug monitoring (TDM) (6).

TDM has been increasingly used for antimicrobial drugs over the past decades (7). TDM-guided dosing is traditionally used to monitor the toxicity and the efficacy of drugs with a small therapeutic range, such as glycopeptides and aminoglycosides. The focus has recently been extended to the use of TDM for improving the efficacy of drugs with a wider therapeutic range in critically ill patients, like beta-lactams and ciprofloxacin (8, 9). Although beta-lactams have broad therapeutic indices, toxic adverse effects have been described (10, 11). The risk of serious adverse events is especially high for patients with renal impairment or a history of neurological disorders, which are both prevalent in ICU patients (12). Conversely, underexposure can lead to therapeutic failure (3). Furthermore, high inter-individual variability of the pharmacokinetic (PK) profile of beta-lactams and ciprofloxacin has been reported in critically ill patients (13, 14). These arguments have led to an increasing number of studies aiming at improving the efficacy of beta-lactams and ciprofloxacin for ICU patients (15-17).

TDM-guided dosing of beta-lactams and ciprofloxacin for efficacy is currently under investigation and proposed as routine care in multiple countries (18, 19). However, the translation into clinical implementation of this multifaceted strategy is only sparingly reported (1, 20-22). A recent review suggested that several barriers need to be overcome, such as assay availability, clinical evidence, and proof of cost-effectiveness, to facilitate the optimal implementation of beta-lactams TDM in critically ill patients (23). However, no study included in this review used a systematic method to identify barriers and facilitators. The authors recommended to reach consensus regarding clear and practical targets.

To successfully implement TDM-guided dosing of beta-lactams and ciprofloxacin, developing an implementation strategy can contribute to good adaptation in clinical practice (24). An important first step is to understand barriers and facilitators that influence the implementation (25, 26), to ensure that the implementation strategy contains relevant determinants, is feasible, and tailored to the context (27). Therefore, the primary aim of this study was to identify the barriers and facilitators for the implementation of TDM of beta-lactams and ciprofloxacin in Dutch ICUs. The secondary aim was to assess the availability of TDM in Dutch hospitals. This study provides an opportunity to create targeted strategies for implementing TDM of beta-lactams and ciprofloxacin.

Methods

Study design and participants

A cross-sectional online survey was distributed to healthcare professionals (HCP) including hospital pharmacists, physician microbiologists, and intensivists. All HCPs involved in the treatment of ICU patients were eligible for inclusion. All data and methods were handled in accordance with the GDPR.

Setting

In the Netherlands, general and teaching hospitals usually co-operate with larger academic care centers. General hospitals mostly provide basic and less complicated care. Teaching hospitals usually perform more complex care and commonly have access to more resources. However, in severe or particularly complicated cases, a referral to academic hospitals is provided. Nearly all hospitals in the Netherlands have an ICU, sometimes combined with a post-operative care unit (PACU) or cardiac care unit (CCU) and are all capable of providing respiratory and circulatory support.

Antibiotic teams (A-teams) are prevalent in the Netherlands. Ever since 2012, having an A-team is strongly advised by Dutch guidelines to ensure proper antibiotic prescribing practices (28). These A-teams guard the quality of antibiotic prescription practices in hospitals and include at least a physician-microbiologist, an internist-infectiologist, and a hospital pharmacist.

Data collection

The online survey was programmed and distributed using LimeSurvey (version 2.06, 2021, Hamburg, German). The survey invitation was distributed to the members of the Dutch association of clinical pharmacists (NVZA) and the Dutch association of critical care (NVIC). Personalized invitations were also sent via our extensive network. After three weeks, a reminder e-mail was sent to heighten the response rate. Data was collected in June 2021 and was analyzed anonymously.

Survey

The survey consisted of 51 questions, most were asked separately for beta-lactams and ciprofloxacin. The Measurement Instrument for Determinants of Innovations (MIDI) formed the basis of our survey (25, 29). MIDI is an evidence-based survey to identify factors influencing the implementation and uptake of interventions and is used to develop tailored implementation strategies. It consists of 29 questions on common determinants of implementation in the healthcare setting. According to the survey regulations, MIDI items were adapted to the context of this study (29). Twenty-five MIDI items were included in our survey, as well as one item of the Barriers and Facilitators Assessment Instrument (BFAI) (30), and twenty-five items that were developed after consultation with healthcare professionals. We did not include MIDI items 11 and 12 because they are on expectations of patients. In the targeted patient population, the patients are usually sedated or too ill to be informed about this specific procedure. We also did not include items 20 and 29 as these questions were not considered relevant.

Nineteen additional questions covered the availability of TDM in the respective hospitals, namely the PDT that is being used, and other potential barriers and facilitators. Four open-ended questions addressed the main important barriers and facilitators perceived by the participant. Two questions regarding the effect of the ongoing COVID-19 pandemic were also included. Most questions were scaled from 1 (“totally disagree”) to 5 (“totally agree”), and some 1 (No), 2 (Not applicable/Do not know) and 3 (Yes).

Finally, several questions were included about the participants’ characteristics (age, sex, profession, discipline, and years of experience in the current profession).

This survey was tested before distribution by a panel consisting of an intensive care specialist, a physician microbiologist, and a hospital pharmacist. The wording of some questions was altered to prevent ambiguity.

The complete survey, in Dutch and translated to English, is available in the Appendix (supplementary table 2).

Statistical analysis

'R' (version 4.0.4, Vienna, Austria, 2021) was used for analysis with packages 'likert' (version 1.3.5) and 'tidyverse' (version 1.3.0). Descriptive statistics were reported in mean and standard deviation, or counts and percentages. Positively worded items were considered barriers when ≥20% of participants responded with a negative answer ("totally disagree" or "disagree"). If ≥80% of the participants responded with a positive answer ("agree" or "totally agree"), the item was considered a facilitator (31, 32). For negatively worded items, the opposite was applied: if ≥80% disagreed, the statement was considered a barrier, whereas statements to which ≥20% agreed were considered facilitators. A general inductive approach was used for analyzing the qualitative data (33).

Results

Participants

Sixty-four participants completed the survey, of which 14 (22%) were from academic hospitals, 25 (39%) from general hospitals, and 25 (39%) from teaching hospitals (Table 1). The median duration of professional work experience was 10 years (range 1–35). Most participants were hospital pharmacists (n = 38, 59%) or medical specialists (n = 15, 23%). The department of the participants was most frequently the hospital pharmacy (n = 45), followed by intensive care (n = 10) and microbiology and infectious diseases (n = 9).

Table 1
Characteristics of the participants

Department	Intensive Care (n = 10)	MMB and infect dis (n = 9)	Hospital Pharm. (n = 45)	Total (n = 64)
Age (year)				
26–35	1 (10%)	0 (0%)	17 (37.8%)	18 (28.1%)
36–45	3 (30%)	6 (66.7%)	15 (33.3%)	24 (37.5%)
46–55	4 (40%)	3 (33.3%)	10 (22.2%)	17 (26.6%)
> 55	2 (20%)	0 (0%)	3 (6.7%)	5 (7.8%)
Hospital beds				
301–500	2 (20%)	1 (11.1%)	10 (22.2%)	13 (20.3%)
501–700	3 (30%)	2 (22.2%)	9 (20.0%)	14 (21.9%)
> 900	2 (20%)	2 (22.2%)	8 (17.8%)	12 (18.8%)
Missing	3 (30%)	4 (44.4%)	18 (40.0%)	25 (39.1%)
ICU beds				
9–16	4 (40%)	3 (33.3%)	16 (35.6%)	23 (35.9%)
17–23	2 (20%)	0 (0%)	8 (17.8%)	10 (15.6%)
24–30	1 (10%)	2 (22.2%)	4 (8.9%)	7 (10.9%)
> 30	1 (10%)	2 (22.2%)	7 (15.6%)	10 (15.6%)
Missing	2 (20%)	2 (22.2%)	10 (22.2%)	14 (21.9%)
Type of Hospital				
Academic	2 (20%)	4 (44.4%)	8 (17.8%)	14 (21.9%)
General	4 (40%)	3 (33.3%)	18 (40.0%)	25 (39.1%)
Teaching	4 (40%)	2 (22.2%)	19 (42.2%)	25 (39.1%)
Profession				
Physician-assistant	1 (10%)	0 (0%)	0 (0%)	1 (1.6%)
Resident	0 (0%)	0 (0%)	5 (11.1%)	5 (7.8%)
Physician-microbiologist	0 (0%)	5 (55.6%)	0 (0%)	5 (7.8%)

Abbreviations: TDM: therapeutic drug monitoring, BLA: beta-lactam antibiotics, MMB and infect dis: Medical microbiology and infectious diseases, Hospital Pharm: Hospital Pharmacy

Department	Intensive Care (n = 10)	MMB and infect dis (n = 9)	Hospital Pharm. (n = 45)	Total (n = 64)
Medical Specialist	8 (80%)	4 (44.4%)	3 (6.7%)	15 (23.4%)
Hospital Pharmacist	1 (10%)	0 (0%)	37 (82.2%)	38 (59.4%)
Experience (years)				
Mean (SD)	10.7 (8.5)	9.7 (3.9)	12 (9.10)	11.4 (8.42)
Median [Min, Max]	10.5 [1, 25]	10 [5, 15]	10.0 [1, 35]	10.0 [1, 35]
Use of BLA TDM				
Never	3 (30%)	3 (33.3%)	13 (28.9%)	19 (29.7%)
Rare	2 (20%)	2 (22.2%)	16 (35.6%)	20 (31.2%)
Sometimes	3 (30%)	2 (22.2%)	9 (20.0%)	14 (21.9%)
Regularly	2 (20%)	0 (0%)	3 (6.7%)	5 (7.8%)
Often	0 (0%)	2 (22.2%)	4 (8.9%)	6 (9.4%)
Use of Ciprofloxacin TDM				
Never	6 (60%)	5 (55.6%)	32 (71.1%)	43 (67.2%)
Rare	2 (20%)	3 (33.3%)	8 (17.8%)	13 (20.3%)
Sometimes	1 (10%)	0 (0%)	4 (8.9%)	5 (7.8%)
Regularly	0 (0%)	1 (11.1%)	1 (2.2%)	2 (3.1%)
Often	1 (10%)	0 (0%)	0 (0%)	1 (1.6%)
BLA TDM Experience				
Beginner	2 (20.0%)	2 (22.2%)	13 (28.9%)	17 (26.6%)
Average	5 (50.0%)	2 (22.2%)	13 (28.9%)	20 (31.2%)
Advanced	1 (10.0%)	4 (44.4%)	4 (8.9%)	9 (14.1%)
Expert	1 (10.0%)	0 (0%)	6 (13.3%)	7 (10.9%)
Unknown	1 (10.0%)	1 (11.1%)	9 (20.0%)	11 (17.2%)

Abbreviations: TDM: therapeutic drug monitoring, BLA: beta-lactam antibiotics, MMB and infect dis: Medical microbiology and infectious diseases, Hospital Pharm: Hospital Pharmacy

Department	Intensive Care (n = 10)	MMB and infect dis (n = 9)	Hospital Pharm. (n = 45)	Total (n = 64)
Ciprofloxacin TDM Experience				
Beginner	1 (10%)	3 (33.3%)	13 (28.9%)	17 (26.6%)
Average	4 (40%)	1 (11.1%)	4 (8.9%)	9 (14.1%)
Advanced	1 (10%)	3 (33.3%)	3 (6.7%)	7 (10.9%)
Expert	1 (10%)	0 (0%)	4 (8.9%)	5 (7.8%)
Unknown	3 (30%)	2 (22.2%)	21 (46.7%)	26 (40.6%)
Abbreviations: TDM: therapeutic drug monitoring, BLA: beta-lactam antibiotics, MMB and infect dis: Medical microbiology and infectious diseases, Hospital Pharm: Hospital Pharmacy				

Only 70% ever came into contact with TDM of beta-lactams with 31% of them indicating that this was seldom. With ciprofloxacin only 33% of the participants ever came into contact with TDM, of which 20% only seldom did.

Table 1: *Characteristics of the participants*

Barriers And Facilitators

For the implementation of beta-lactams TDM, 11 barriers and 4 facilitators were identified. For the implementation of ciprofloxacin TDM, 17 barriers and no facilitators were found. All beta-lactams barriers were also ciprofloxacin barriers. Table 2 describes all identified barriers and facilitators, and is a summary of all the questions described in supplementary table 1.

Table 2
Identified barriers and facilitators influencing the implementation of therapeutic drug monitoring for ICU patients (n = 64)

Factors	Barriers (question number)	Beta-lactams (%)	Ciprofloxacin (%)
Procedure	Completeness of materials (3)	39	47
	Knowledge (10/9)	28/23*	36/30*
	Procedural clarity (1)		28
	Experience with TDM (45)		27
	Observability of outcomes (6)		20
Beliefs	Outcome expectations: TDM saves costs (20/44)	36/20*	38/22*
	Personal benefits: TDM increases my workload (23)	30	25
	Normative beliefs (15)		25
	Importance outcome expectations: TDM shortens ICU length of stay (29)		20
Organization	Formal ratification by management (30)	55	72
	Unsettled organization (32)	36	39
	Assigned coordinator (31)	28	39
Literature	Evidence of effectiveness (41)	53	58
	Evidence of cost-effectiveness (42)	31	30
	Facilitators (question number)		
Procedure	Importance outcome expectations: TDM treats infection (18)	92	
Beliefs	Professional obligation (12)	84	
	Low complexity (4)	81	
	Importance outcome expectations: TDM prevents side effects (19)	81	

Data expressed as percentages representing the fraction of respondents that indicated that that the statement was a barrier or facilitator. The results of all questions are found in supplementary table 1.

TDM, therapeutic drug monitoring; ICU, intensive care unit

*Multiple questions addressed the same barrier

Barriers

Multiple barriers were identified for the implementation of TDM of beta-lactams and ciprofloxacin in critically ill patients (Table 2). A substantial proportion of the participants indicated that they did not have all the information and materials to apply TDM for these antibiotics (39% beta-lactams, 47% ciprofloxacin). From the perspective of the participants, they explained that they did not have enough practical experience (28% beta-lactams, 36% ciprofloxacin) or, to a lesser degree, the required knowledge (23% beta-lactams, 30% ciprofloxacin). The respondents believed that TDM would not result in cost reduction (36% beta-lactams, 38% ciprofloxacin), would not be cost-effective (20% beta-lactams, 22% ciprofloxacin), and would increase their workload (30% beta-lactams, 25% ciprofloxacin). Furthermore, they indicated that lack of clear evidence of effectiveness (53% beta-lactams, 58% ciprofloxacin) and cost-effectiveness (31% beta-lactams, 30% ciprofloxacin) prohibits implementation. From the organization perspective, they further replied that there are mainly no formal agreements made by management (55% beta-lactams, 72% ciprofloxacin) followed by other factors in the organization preventing implementation (36% beta-lactams, 39% ciprofloxacin). A smaller number responded that there is no coordinator for the implementation of TDM for these antibiotics (28% beta-lactams, 39% ciprofloxacin).

More barriers were identified for ciprofloxacin TDM implementation: the responders found that the procedural clearness of TDM is unclear and that the procedures are unclear (both 28%) They also indicated that they felt hindered by little experience (27%). Furthermore, they responded that colleagues do not expect them to use TDM (25%), indicated that the outcome of TDM is not visible, and did not expect that it shortens ICU length of stay (both 20%).

Facilitators

The facilitators identified for implementation of beta-lactams TDM were that TDM is not complex to carry out (81%), that they perceived TDM to be one of their tasks (84%), that they believed that beta-lactams TDM prevent side-effects (81%), and that it improves treatment of infections (91%) (Table 2). There were no facilitators identified for implementation of ciprofloxacin TDM.

Eight respondents (13%) indicated that the COVID-19 pandemic increased the requests for beta-lactams TDM, whereas six respondents (9%) claimed that this increased for ciprofloxacin. Additionally, some responders (n = 9; 14%) indicated that the implementation of beta-lactams TDM was hampered by the COVID-19 pandemic, whereas 11% (n = 7) argued that this was a case for ciprofloxacin.

Qualitative Analysis

We also asked responders what they consider the greatest benefit and the main disadvantage of TDM of beta-lactams and ciprofloxacin combined. The most often mentioned disadvantages were ’the low availability of assays’ and ‘the absence of convincing evidence’ (both: n = 14; 21%). The greatest benefit was ‘the possible increased effectivity’(n = 29; 45%). The availability of assays, the costs and the

complexity of sending blood samples to other laboratories were mostly named as the most important barriers for implementation. Eleven participants (17%) responded that patients with enhanced or diminished renal clearance should be considered for TDM. Eleven responded that all ICU patients should be considered, five participants indicated patients with overweight or underweight and four noted that it should be considered based on the micro-organism.

Availability Of Analysis

Around 28% of the participants reported that flucloxacillin could be analyzed for TDM purposes in their hospital (Fig. 1). Ceftazidime with 17% and meropenem with 16% followed closely. Ciprofloxacin was available in 14% of all hospitals. Cefotaxime was the least available of the beta-lactams with only 8% availability. None of the assays were available in general hospitals, except for flucloxacillin. In academic hospitals, the availability of assays was much more prevalent, with 41% availability compared to 6% in other hospitals.

Figure 1: Availability of therapeutic drug monitoring of beta-lactams and ciprofloxacin.

Pharmacodynamic Targets (Pdt)

Of all the participants, 21 answered possible PDT's (Table 3). There was a great amount of variability in the answers for both beta-lactams and ciprofloxacin. For dosing TDM of beta-lactams 43% of the respondents indicate that 100% (f)T > 4xMIC should be achieved, compared to 38% that indicated that 100% (f)T > MIC should be targeted.

For ciprofloxacin, 57% indicated that they did not know what target to achieve. Of the responses, 29% answered that the target of AUC/MIC > 120 should be targeted, while 14% preferred to target fAUC/MIC > 100.

Table 3
Reported pharmacodynamic targets for therapeutic drug monitoring of beta-lactams and ciprofloxacin in ICU patients (n = 21)

Beta-lactams	
50% (f)T > MIC	14%
100% (f)T > MIC	38%
100% (f)T > 4xMIC	43%
100% (f)T > MIC ECOFF	10%
Do not know	24%
Ciprofloxacin	
AUC/MIC > 120	29%
(f)AUC/MIC > 100	14%
(f)AUC/MIC > 90	5%
Cmax/MIC > 10	10%
fCmax/MIC > 8	5%
Do not know	57%

AUC, Area under the curve; (f), free fraction; T, time; MIC, Minimal inhibitory concentration, ECOFF, EUCAST epidemiological cut-off values; Cmax, Maximum concentration

Discussion

This nationwide study provides comprehensive coverage of barriers and facilitators that influence the implementation of TDM of beta-lactams and ciprofloxacin in critically ill patients. More barriers than facilitators were identified. Barriers were mostly related to the lack of clinical evidence of TDM of beta-lactams and ciprofloxacin, lack of practical experience, low availability of assays, and no organizational support for implementation. Furthermore, only 40% of the participants had experience with beta-lactams TDM, and even fewer had experience with ciprofloxacin TDM (13%). TDM of beta-lactams was associated with a high task perception, relative ease of use, and the ability to use TDM to treat infections more effectively.

The barriers identified in our study were in line with those uncovered by Sandaradura et al. (34) that investigated barriers to the implementation of beta-lactams TDM in Australia, including Lack of timely assays, a lack of training and a lack of guidelines. They also observed that the participants expected fewer clinical effects of TDM of ciprofloxacin than of other antibiotics. In the current study, we also found that ciprofloxacin TDM was less often applied and more obscure than beta-lactams TDM. Abdulla et al. reviewed current barriers and facilitators for the clinical implementation of beta-lactams TDM in critically

ill patients (23). They noted that important barriers were the limited availability of assays and a lack of guidelines. This is also reflected in our results. An ongoing study by Barreto et al. aims to identify more perspectives of HCPs in the USA on what is needed for the implementation of beta-lactams TDM using a mixed-model approach (35).

We showed that TDM of beta-lactams is not often applied, and ciprofloxacin TDM being even less often. These results are in line with other studies (21, 34, 36). Assays for determining beta-lactams and ciprofloxacin concentrations are not yet widely available, and are mostly centered in academic hospitals. This is most likely due to the high cost and high complexity of chromatography. Mass-spectrometry (MS) has the advantage of determining a wide variability of drug concentrations but requires well-trained personnel. Continuous availability of MS is therefore costly to implement due to the need of personnel and MS-devices. Immunoassays could be a straightforward alternative but are currently unavailable for determining beta-lactams and ciprofloxacin concentrations. Another option is the transport of patient material towards a center that can analyze these drugs but requires a strong and fast infrastructure.

Although evidence on the efficacy of beta-lactams TDM with clinical outcomes is growing (37), these studies are mostly observational. To address the lack of evidence of effectiveness, a large multi-center trial is being conducted researching the efficacy of TDM of beta-lactams and ciprofloxacin in ICU patients (38). Making clear guidelines on how to perform TDM of beta-lactams and ciprofloxacin and on which pharmacodynamic breakpoints to target are most important for implementing these procedures. Creating organizational support and organizing education are the next steps to further clear most barriers.

Identifying patients at risk for low concentrations may help to consider and implement more individualized dosing regimens using TDM (39). Decision aids and strong cooperation between specializations such as clinicians, pharmacists, and microbiologists can help to find the optimal population for optimizing the dosing of beta-lactams and ciprofloxacin.

TDM targets were also assessed in our study. The responses indicate that there is not yet a clear consensus for what to target during TDM. Most evidence of these targets in ICU patients is from observational trials. The ONTAI trial questioned German physicians for targets for TDM (21). They observed a great amount of variability of what to target for beta-lactams, with most answers of experienced HCP answering 100% (f)T > 4xMIC and 100% (f)T > MIC. In a study by Wong et al., a target of 100% (f)T > MIC was most prevalent (20). These studies have a similar conclusion, as there seems to be no clear consensus on which target to aim for.

Strengths and limitations

Using the widely-used MIDI questionnaire is an accepted approach to identify barriers and facilitators is a strength of this study. Another strength is that this questionnaire has reached a wide range of HCP in different hospital sizes. However, a possible limitation is that due to the methodology of this study, multiple HCPs that filled in the survey may work in the same hospital. There was, however, a clear distinction between the participants concerning the hospital size, ICU size, category of the hospital, and

departments. Secondly, only Dutch HCPs were included, which should be taken into consideration when applying our results in other healthcare settings. Finally, the cutoff point of 80% in combination with the relatively small sample size may lead to some potential facilitators not being identified as such. For example, 78% indicated that there was enough personnel available in their organization for beta-lactams TDM, but this was not included in our results.

Future research

Implementation strategies for TDM of beta-lactams and ciprofloxacin should focus on assay availability, creating clear working instructions, education of HCPs, agreement on pharmacodynamic breakpoints, and organizational support. Future research should consider repeating this questionnaire on an international level, possibly after implementation in several hospitals has been attempted.

Conclusion

In conclusion, we identified several factors that obstruct the implementation of TDM of beta-lactams and ciprofloxacin in critically ill patients. The discussed barriers will need to be considered when implementing TDM of these antibiotics. In particular, creating clear guidelines, assay availability, HCP education, and organizational support should all be considered when creating tailored implementation strategies. Also, further quality evidence of clinical outcomes on TDM of beta-lactams and ciprofloxacin can enhance further implementation.

List Of Abbrevations

A-teams: Antibiotic Teams

BFAI: Barriers and Facilitators Assessment Instrument

HCP: Health Care Professional

ICU: Intensive Care Unit

MS: Massa-spectrometry

MIDI: Measurement Instrument for Determinants of Innovations

PDT: Pharmacodynamic Target

TDM: Therapeutic Drug Monitoring

Declarations

Ethics approval and consent to participate

All participants gave digital informed consent to store and process the entered data. No ethics approval was needed according to the Dutch law “medical-scientific research regarding humans” and the guidelines of the Dutch central commission of human research (CCMO) due to the nature of our research. (40, 41)

Consent for publication

Not applicable

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Authors contributions

AA and TE created the study conception and design. AA, TE, SP and IS took first responsibility in setting up the survey. All authors then aided in achieving the final survey. IS and PB set up the final survey and sent it out to the participants. PB, TE, and AA analyzed the results. TE and IS wrote the first draft of the manuscript. All authors contributed to subsequent drafts and gave final approval of the version to be published.

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Figures

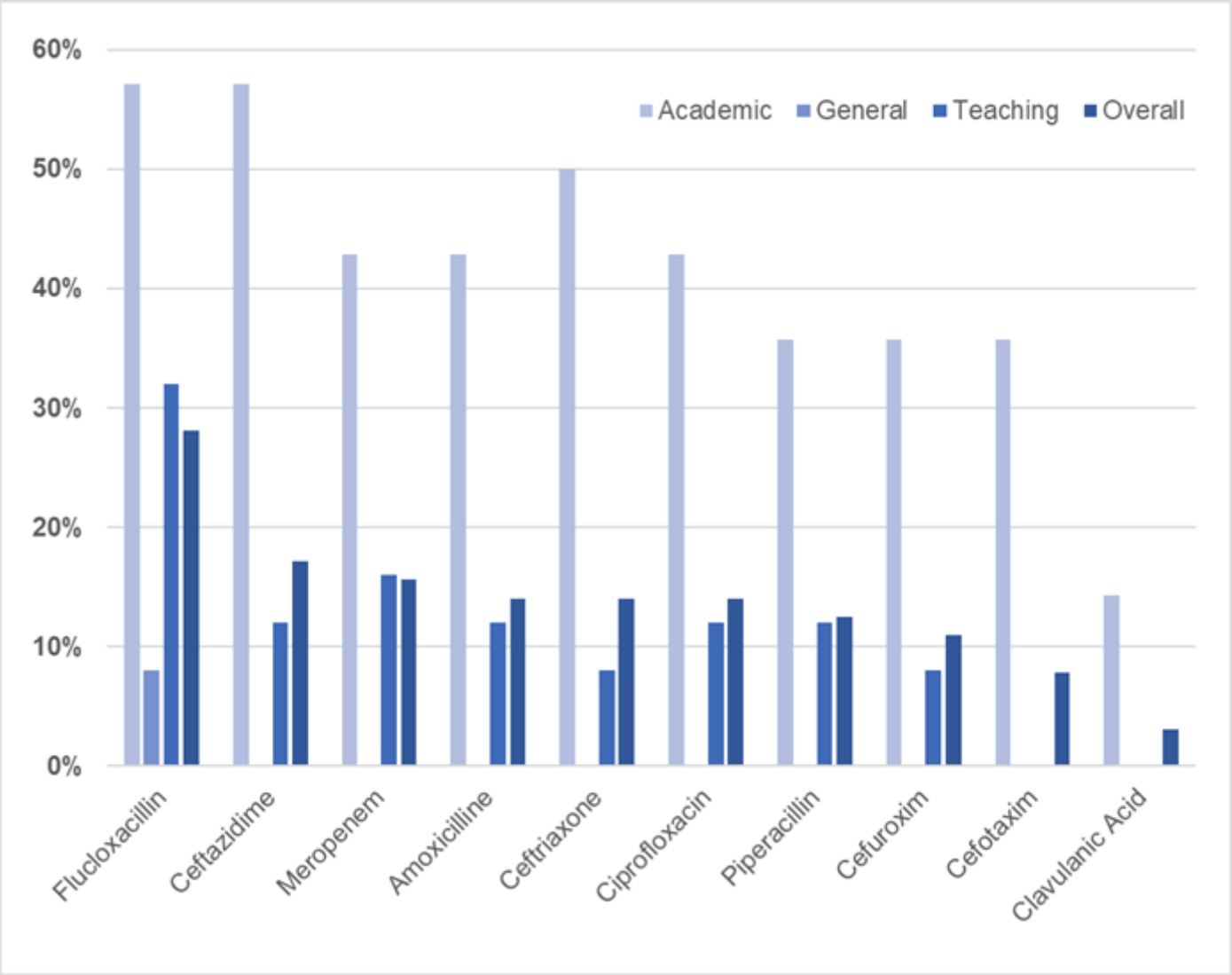

Figure 1

Availability of therapeutic drug monitoring of beta-lactams and ciprofloxacin.

Supplementary Files

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- SupplementaryTable1.docx
- SupplementaryTable2.docx