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The impact of the revised EUCAST definitions of susceptibility testing categories on the use of antibiotics for Pseudomonas aeruginosa infections: a matched cohort study

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Summary

STUDY AIMS: In January 2019, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) redefined the categories classifying the clinical effectiveness of antibiotics, changing the meaning of the "I" category from "intermediate" to "susceptible at increased exposure". We aimed to estimate the effect of this change on the likelihood of carbapenem prescriptions to treat infections caused by wild-type *Pseudomonas aeruginosa*.

METHODS: We performed a matched cohort study at University Hospital Basel, Switzerland, including patients with urinary or respiratory tract infection caused by wild-type *P. aeruginosa*. Patients hospitalised between October 2020 and December 2021 (exposure period after implementation of EUCAST criteria) were matched 1:2 by ward and sample type to patients hospitalised between January 2016 and September 2020 (control period). In multivariable conditional logistic regression analysis, we calculated odds ratios (OR) for meropenem use.

RESULTS: During the study period, 32 and 64 patients were included in the exposure and control periods, respectively. After implementation of the new EUCAST criteria, meropenem prescriptions increased from 3.1% (2/64) to 15.6% (5/32). In the multivariable analyses, we observed increased odds for receiving meropenem in the exposure period as first treatment (adjusted OR: 5.22; 95% confidence interval: 0.87–31.41), although not statistically significant, and as first treatment or treatment change (adjusted OR: 11.10; 95% confidence interval: 2.94–41.85).

CONCLUSIONS: At our institution, the implementation of the revised EUCAST criteria was associated with an increased likelihood of meropenem prescription overall for wild-type *P. aeruginosa* infection. This highlights the need for comprehensive antimicrobial stewardship efforts to promote and ensure adequate implementation of such reclassifications.

Introduction

In January 2019, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) redefined the categories classifying the clinical effectiveness of antibiotics. The abbreviation "I" was previously used to define an intermediate category referring to an area of uncertainty in terms of clinical effectiveness, thus commonly interpreted as "resistant" for treatment decisions: the revised classification scheme now uses the abbreviation "I" to define the category "susceptible, increased exposure" indicating clinical effectiveness of the corresponding compound given adjusted dosing [1]. In addition, based on the revision of breakpoints for key antimicrobials, EUCAST reclassified wild-type *Pseudomonas aeruginosa* isolates (i.e. isolates with no acquired resistance mechanisms) from "S" (susceptible at standard dose) to "I" (susceptible at increased exposure) [2] for cefepime, ceftazidime and piperacillin-tazobactam. It has previously been shown that susceptibility reporting rules may significantly influence prescribing behaviour, with antibiotics presented on lab-

oratory susceptibility reports more likely to be prescribed both empirically and for directed therapy [3–5]. Therefore, without comprehensive communication of the revised EUCAST definitions of susceptibility testing categories on the use of antibiotics for *P. aeruginosa* infections, there is a risk that uninformed healthcare providers may opt for prescribing meropenem or other carbapenems, given its classification as "S" among the limited beta-lactam options, leading to an increase in meropenem consumption and thus promotion of carbapenem resistance.

In October 2020, at University Hospital Basel, the Division of Clinical Microbiology and the Division of Infectious Diseases, in close collaboration, adapted their interpretation categories and advised physicians to prescribe antibiotic therapies according to the new EUCAST recommendations, favouring beta-lactams other than carbapenems if categorised as "I". We hypothesised that despite these efforts, carbapenem use may have increased and thus aimed to estimate the effect of the 2019 EUCAST modifications on the likelihood of carbapenem prescription to treat infections caused by wild-type *P. aeruginosa* at our institution.

Methods

Setting

This study was performed at University Hospital Basel, Switzerland, a tertiary academic care centre admitting >40,000 patients annually.

Study design and population

We performed a retrospective, matched cohort study. Adult inpatients hospitalised between January 2016 and December 2021 with a urinary tract or respiratory tract infection caused by wild-type *P. aeruginosa* were eligible for study inclusion. Patients hospitalised between October 2020 and December 2021 (exposure period after introduction of the revised EUCAST classification at our institution) were matched 1:2 by ward and sample type to patients hospitalised between January 2016 and September 2020 (control period before introduction of the revised EUCAST classification). A longer control period was chosen to enable 1:2 matching by ward and sample type. Exclusion criteria were as follows: age below 18 years; *P. aeruginosa* infection with acquired resistance mechanisms (non-wild-type); polymicrobial infection; positive blood culture; documented allergy to beta-lactam antibiotics; patient's documented refusal of subsequent use of their data.

Data collection

Pertinent clinical data was collected from electronic patient records (clinic information systems Meona®, v92.566×64_c7, and IsMed®, v21.02b) including demographic data, weight, height, renal function (creatinine, creatine clearance and glomerular filtration rate as estimated using the CKD-EPI equation) [6] and comorbidities to calculate the Charlson Comorbidity Index (CCI). Further, information on antimicrobial therapy – such as choice of agent, dosage, treatment duration and any changes of treatment – was assessed. Information on sample type (respiratory or urinary), microbiology results (wild-type *P. aeruginosa*) and consultation with an infectious disease specialist was collected.

All data was entered into an electronic clinical report form using the REDCap® platform (Research Electronic Data Capture, Vanderbilt University, Nashville, TN, USA) [7].

Outcomes

The primary outcome was empirical or targeted meropenem treatment for patients with wild-type *P. aeruginosa* urinary and respiratory tract infections as compared to other beta-lactam treatments. Antimicrobial treatment was classified as empirical or targeted according to whether the prescription preceded or followed receipt of susceptibility testing results. The secondary outcome was the frequency of infectious disease consultations.

Statistics

Categorical and numeric variables were compared between the matched control and exposure period using standardised differences (Stata package *STDDIFF*; version dated 12/2022); rank-based comparisons were used for numeric variables. Absolute standardised differences of ≥0.10 were considered to be imbalanced [8]. Crude and adjusted relationships between the study periods and the administration of meropenem were estimated using conditional logistic regression. Models were fitted separately for the first antibiotic treatment and for the first three antibiotic treatments

including treatment changes. To avoid overadjustment bias given the matched data structure, the multivariable selection strategy was guided by a directed acyclic graph with 56 potential causal paths (http://dagitty.net/; release 2019-01-09). Adjustments were made for patient's age, sex, Charlson Comorbidity Index, glomerular filtration rate, medical/surgical wards and empirical/targeted therapies. All models were based on complete cases. All analyses were performed on a multicore system with Stata/MP version 16 (Stata Corp., College Station, TX, USA). Reported p-values are two-sided.

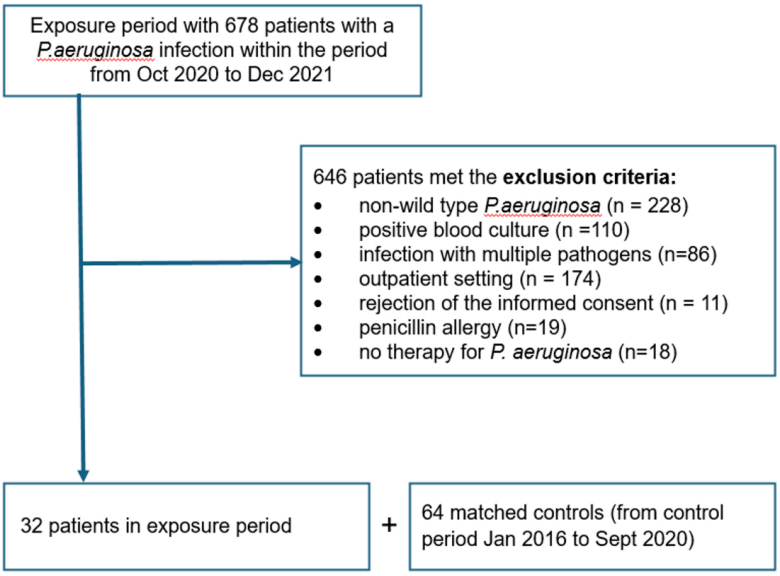
Ethics

The Nordwest- und Zentralschweiz Ethics Committee (EKNZ) considered the study to be a quality assurance project (Project-ID Req-2022-00460).

Results

After implementation of the revised EUCAST definitions of susceptibility testing categories, *P. aeruginosa* was detected in samples collected from 678 patients. Patients with detection of non-wild-type *P. aeruginosa* (n = 228), detection of *P. aeruginosa* in blood culture (n = 110) and polymicrobial infections (n = 86) were excluded. Other exclusion criteria were met by 222 patients, as further detailed in figure 1, resulting in 32 patients during the case period.

Figure 1: Flowchart of the study selection process.



After applying the same inclusion and exclusion criteria, 64 patients in the control period were matched to patients of the exposure period. Patients in the exposure and control period were imbalanced regarding age, Charlson Comorbidity Index, renal function, treatment, ward type and infectious disease consultations (table 1).

Table 1: Patient characteristics.

Variable		Control period (n = 64)	Exposure period (n = 32)	Total (n = 96)	Missing	Standardised difference
		n (%) or median (IQR)	n (%) or median (IQR)	n (%) or median (IQR)	n (%)	
Age		72.5 (60.0–80.8)	76.0 (65.0–86.8)	74.5 (62.3–82.8)	0/96 (0%)	–0.286
Sex					0/96 (0%)	0.067
	Male	42(65.6%)	22(68.8%)	64(66.7%)		
	Female	22(34.4%)	10(31.3%)	32(33.3%)		
Charlson Comorbidity Index		5.0 (3.0–6.0)	5.0 (3.3–7.0)	5.0 (3.0–7.0)	0/96 (0%)	–0.230
GFR		64.0 (39.0–98.5)	53.5 (33.5–91.3)	61.5 (38.0–93.5)	0/96 (0%)	0.206
Ward (matched)					0/96 (0%)	0
	ICU	4 (6.3%)	2 (6.3%)	6 (6.3%)		
	Normal ward	60 (93.8%)	30 (93.8%)	90 (93.8%)		
Sample (matched)					0/96 (0%)	0
	Bronchial secretion	4 (6.3%)	2 (6.3%)	6 (6.3%)		
	BAL	4 (6.3%)	2 (6.3%)	6 (6.3%)		
	Sputum	8 (12.5%)	4 (12.5%)	12 (12.5%)		
	Tracheal secretion	2 (3.1%)	1 (3.1%)	3 (3.1%)		
	Urine	46 (71.9%)	23 (71.9%)	69 (71.9%)		
Therapy (first antibiotic)					0/96 (0%)	0.095
	Empirical	25 (39.1%)	14 (43.8%)	39 (40.6%)		
	Targeted	39 (60.9%)	18 (56.3%)	57 (59.4%)		
Active compound (first antibiotic)					0/96 (0%)	0.731
	Piperacillin-tazobactam	31 (48.4%)	15 (46.9%)	46 (47.9%)		
	Ceftazidime	1 (1.6%)	1 (3.1%)	2 (2.1%)		
	Cefepime	2 (3.1%)	0 (0.0%)	2 (2.1%)		
	Meropenem	2 (3.1%)	5 (15.6%)	7 (7.3%)		
	Ciprofloxacin	5 (7.8%)	1 (3.1%)	6 (6.3%)		
	Ceftriaxone	19 (29.7%)	5 (15.6%)	24 (25.0%)		
	Amoxicillin-clavulanic acid	4 (6.3%)	4 (12.5%)	8 (8.3%)		
	Cotrimoxazole	0 (0.0%)	1 (3.1%)	1 (1.0%)		
Prescriber (first antibiotic)					0/96 (0%)	0.107
	Medical ward	49 (76.6%)	23 (71.9%)	72 (75.0%)		
	Surgical ward	15 (23.4%)	9 (28.1%)	24 (25.0%)		
ID consultation?		n = 62	n = 31		3/96 (3.1%)	0.476
	No	54 (87.1%)	21 (67.7%)	75 (80.6%)		
	Yes	8 (12.9%)	10 (32.3%)	18 (19.4%)		

BAL: bronchoalveolar lavage; GFR: glomerular filtration rate; ICU: intensive care unit; ID: infectious disease; IQR: interquartile range; NA: not applicable.

After the implementation of the new EUCAST criteria, meropenem prescriptions increased from 3.1% (2/64) to 15.6% (5/32). In the multivariable analyses, we observed increased odds for receiving meropenem in the exposure period as first treatment (adjusted OR: 5.22; 95% confidence interval: 0.87–31.41), although not statistically significant, and as first treatment or treatment change (adjusted OR: 11.10; 95% confidence interval: 2.94–41.85) (table 2). The proportion of patients with infectious disease consultations was higher during the exposure period (32.3% [10/31] vs 12.9% [8/62]).

Table 2: Association of study periods with administration of meropenem.

Period		OR	95% CI	p-value	Number of patients/observations
Univariable model (first antibiotic treatment)	Control	1.00 (reference)		0.054	96/96
	Exposure	5.00	0. 97–25.77		
Adjusted model[a] (first antibiotic treatment)	Control	1.00 (reference)		0.071	96/96
	Exposure	5.22	0.87–31.41		
Univariable model (first antibiotic treatment and treatment changes)	Control	1.00 (reference)		0.010	96/160[c]
	Exposure	7.99	1.65–38.74[b]		
Adjusted model[a] (first antibiotic treatment and treatment changes)	Control	1.00 (reference)		<0.001	96/153[d]
	Exposure	11.10	2.94–41.85[b]		

CI: confidence interval; OR: odds ratio.
a Adjusted for patient age (linear increments), sex, Charlson Comorbidity index (linear increments), glomerular filtration rate (linear increments), medical/surgical ward and empirical/targeted therapy.
b Based on robust standard errors.
c Antibiotic treatments 1 + 2 + 3 (96 + 53 + 11 observations).
d Missing data on therapy status in 7 of 160 observations.

Discussion

This matched cohort study revealed a trend towards an increase in meropenem prescriptions for managing *P. aeruginosa* infections after the revised 2019 EUCAST criteria were implemented at our hospital in 2020. The findings support concerns raised by experts that the new criteria may influence meropenem prescribing practice for *P. aeruginosa* infections [9, 10]. We also observed a slight increase in the number of infectious disease consultations, possibly pointing to challenges regarding treatment choices based on susceptibility testing results. We acknowledge that the exposure period (after introduction of the revised EUCAST classification at our institution) was during the COVID-19 pandemic, which may have contributed to an increased use of antibiotics, particularly broad-spectrum ones [11].

The use of multiple communication channels (e.g. email, intranet, meetings), focused education (e.g. e-learnings, training), technological integration (e.g. clinical decision support tools) and ongoing support from infectious disease specialists or an antimicrobial stewardship team [12] is proposed to facilitate the implementation of new guidelines and to change long-term prescribing behavior. Pharmacist-driven programmes have been established to optimise antibiotic therapy and to guide clinicians in improving antibiotic therapy and reducing expenditure [13, 14]. More recently, machine learning algorithms have been shown to potentially reduce the inappropriate use of broad-spectrum antibiotics [15]. Specifically, patients are screened for inappropriate use of meropenem early and proactively with electronic decision support systems to optimise therapy whenever possible. Also, selective reporting of laboratory testing only to infectious disease specialists might optimise antibiotic therapy [16]. At our hospital, a newsletter with background information and recommendations was sent to every healthcare professional to raise awareness of the EUCAST revisions. In addition, microbiology laboratory reports included a note to draw attention to the changes and a very low threshold was used for referrals for infectious disease consultations.

Our findings are reinforced by other reports pointing to an increase in meropenem prescription after the EUCAST revision [17].

Our study has important limitations. Generalisation of the findings may not be possible due to the monocentric study design, the small sample size and the relatively short exposure phase (after introduction of the revised EUCAST classification). The tertiary-care setting cannot be compared directly to small hospitals without pharmacological and infectious disease specialists onsite. The short study period limited the number of patients with meropenem prescriptions. Meropenem was prescribed to seven patients – a sample too small to draw robust conclusions –, thus limiting the significance of our findings. The study period included the COVID-19 pandemic, which may have contributed to an increased use of antibiotics, particularly broad-spectrum ones [11], possibly additionally challenging the implementation of the revised classification system and thus the increased use of meropenem during the exposure period.

Conclusions

At our hospital, the implementation of the revised EUCAST criteria was associated with an increased use of meropenem in patients with *P. aeruginosa* infections, given the limitation of our small sample size. Although the specific factors influencing the choice of meropenem remain unclear, the observed increase suggests that the revised EUCAST criteria may not have been fully or effectively adopted in clinical practice. This highlights the need for clear and consistent communication across multiple channels. An interdisciplinary antimicrobial stewardship team may play a critical role in facilitating and sustaining the implementation of such reclassifications.

Data sharing statement

The datasets used and analysed during this study are available from the corresponding author on reasonable request.

Acknowledgments

Author contributions: DH supported data collection, interpreted the data and critically revised the manuscript. CK and EWW analysed and interpreted the data and wrote the first draft of the manuscript. FA collected the data. MW and PMK supported data collection, interpreted the data and critically revised the manuscript. JR analysed and interpreted the data and critically revised the manuscript. STS conceived, initiated and supervised the study, and critically revised the manuscript.

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Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. MW reports support for attending meetings and/or travel from Gilead. No other potential conflict of interest related to the content of this manuscript was disclosed.

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