Journal of Clinical Anesthesia 103 (2025) 111826

Contents lists available at ScienceDirect

Journal of Clinical Anesthesia

journal homepage: www.elsevier.com/locate/jclinane

Original Contribution

Regional analgesia catheter-related infections and the effectiveness of antibiotic prophylaxis in immunocompromised patients: A retrospective multicenter registry analysis

Lukas M. Müller-Wirtz, MD [a,b,c,*], William M. Patterson, MPH [a], Sascha Ott, MD MHBA [a,d,e,f], Kurt Ruetzler, MD [a,g], Alparslan Turan, MD [a,h], Daniel I. Sessler, MD [a,h], Thomas Volk, MD [a,b], Christine Kubulus, MD [a,b], the net-ra investigators[1]

[a] Outcomes Research Consortium, Houston, TX, USA
[b] Department of Anaesthesiology, Intensive Care and Pain Therapy, Saarland University Medical Center and Faculty of Medicine, Homburg, Saarland, Germany
[c] Department of Anesthesiology, Friedrich-Alexander-Universität Erlangen-Nürnberg, Universitätsklinikum Erlangen, Erlangen, Germany
[d] Department of Cardiac Anesthesiology and Intensive Care Medicine, Deutsches Herzzentrum der Charité, Berlin, Germany
[e] Department of Cardiothoracic and Vascular Surgery, Deutsches Herzzentrum der Charité, Berlin, Germany
[f] Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin, Germany
[g] Ordensklinikum Linz, Department of Anesthesiology and Intensive Care Medicine, Linz, Austria
[h] Center for Outcomes Research, Department of Anesthesiology, Critical Care and Pain Medicine, McGovern Medical School, Health Sciences Center at Houston, University of Texas, Texas, USA

HIGHLIGHTS

- Regional analgesia catheter-related infections occur slightly earlier and are more frequent in immunocompromised patients.
- Antibiotics are marginally effective in delaying and preventing catheter-related infections but are more effective in immunocompromised patients.
- With antibiotic prophylaxis, risk of regional analgesia catheter-related infections is similar in immunocompromised and immunocompetent patients.
- Prophylactic antibiotics may be considered for rare cases of severe immunocompromise with additional infection risks.

ARTICLE INFO

Keywords:
Anesthesia
Regional anesthesia
Analgesia
Catheters
Infection
Immunocompromise
Immune function

ABSTRACT

Background: The risk of regional analgesia catheter-related infections in immunocompromised patients remains uncertain. We therefore tested the hypotheses that catheter-related infections appear earlier and are more severe, and that antibiotic prophylaxis is more effective in immunocompromised than immunocompetent patients.
Methods: Data were extracted from the Network for Safety in Regional Anesthesia and Acute Pain Therapy (net-ra) registry from 2007 to 2022. We used multivariable cox and ordinal regression to assess the effect of immune function and antibiotic prophylaxis indicated by surgery on infection onset and severity.
Results: We analyzed data from 196,711 catheters, including 1347 in immunocompromised patients. Infection severities in immunocompetent patients were none (190,220 (97.4 %)), mild (4517 (2.3 %)), and moderate/severe (627 (0.3 %)). In immunocompromised patients, infection severities were none (1285 (95.4 %)), mild (58 (4.3 %)), and moderate/severe (4 (0.3 %)). Immunocompromised patients who were not given antibiotics had a 29 % greater infection hazard (HR 1.29 [95 %CI: 0.95, 1.76], $p = 0.1$) and 91 % greater odds of higher infection severities (OR 1.91 [95 %CI: 1.39, 2.63], $p < 0.001$). Antibiotics were more effective in delaying infection onset (HR 0.65 [95 %CI: 0.38, 1.12], $p = 0.12$) and preventing infection (OR 0.54 [95 %CI: 0.31, 0.94], $p = 0.029$) in immunocompromised than immunocompetent patients. The number of patients needed-to-treat to prevent an infection with antibiotics was 55 in immunocompromised patients versus 83 in immunocompetent patients.

* Corresponding author at: Department of Anesthesiology, Friedrich-Alexander-Universität Erlangen-Nürnberg, Universitätsklinikum Erlangen, 91054 Erlangen, Germany.
E-mail address: lukas.mueller-wirtz@uk-erlangen.de (L.M. Müller-Wirtz).

https://doi.org/10.1016/j.jclinane.2025.111826
Received 19 August 2024; Received in revised form 5 March 2025; Accepted 26 March 2025
Available online 4 April 2025

Conclusions: Regional analgesia catheter-related infections occur slightly earlier and are more frequent in immunocompromised patients. Antibiotics are marginally effective for catheter infection prophylaxis and should be restricted to patients who are severely immunocompromised with and at special risks.

1. Introduction

Regional analgesia catheters provide prolonged postoperative analgesia. Although rare, severe catheter-related infections are potentially disastrous [1–4], especially when catheters are inserted neuraxially [5,6]. Most infections of catheter insertion sites are mild and resolve when catheters are removed [2,7]. Nevertheless, any severity of catheter-related infection promotes premature termination of a highly effective pain therapy, and thus compromises quality of care.

Nearly 3 % of US adults receive immunosuppressants and previous epidemiological reports indicate that patients with severe infectious complications after epidural catheter placement are often immunocompromised [2,8–11]. Moreover, immunocompromised patients are at special risk for postoperative wound infections and central venous catheter-related infections [12,13]. For example, diabetes mellitus – which impairs immune function – is consistently identified as an risk factor for regional analgesia catheter-related infections [14,15]. Immunocompromise thus presumably augments the risk of regional analgesia catheter-related infections, but the magnitude of the association remains unclear [11,16].

Antibiotics may lower the incidence of regional analgesia catheter infections [17,18], but the overall low infection incidence may not justify antibiotic prophylaxis for catheter insertion in all patients [18]. However, the risk of catheter-related infections is presumably higher in immunocompromised patients so they may especially benefit from antibiotic prophylaxis.

We therefore tested the hypotheses that regional analgesia catheter-related infections appear earlier and are more severe in immunocompromised surgical patients than in those with presumed normal immune function. And second, that antibiotics for prevention of regional analgesia catheter-related infections are more effective in immunocompromised surgical patients than in those with presumably normal immune function.

2. Methods

Ethical approval with waived informed consent was obtained by the responsible ethics committee (date of approval: 01/11/2021, identification number: 324/20). The final study protocol was reviewed and approved by the scientific committee of the German Network for Safety in Regional Anesthesia and Acute Pain Therapy (net-ra) registry and registered at the German Clinical Trials Register (DRKS00031272) prior to data access (**Supplemental File 1, Study Protocol**). This manuscript adheres to the STROBE guideline.

2.1. Study design

This is a retrospective multicenter observational cohort study designed to compare infection risk from regional analgesia catheters in patients with and without immunocompromise, and the extent to which antibiotic prophylaxis reduces infection risk in immunocompromised and immunocompetent patients. Data were obtained from the net-ra registry which was established in 2007 by the German Society for Anaesthesiology and Intensive Care Medicine (DGAI) and the Professional Association of German Anesthetists (BDA). The registry data includes preoperative, intraoperative, and postoperative data on regional anesthesia procedures from 26 German centers collected by a standardized data entry [19].

2.2. Study population, measurements, and data handling

We included all registry patients who had a regional analgesia catheter inserted from 2007 to 2022, all of whom were inpatients. Our analysis was based on catheters instead of patients, and data for each catheter were restricted to the initial 14 days after insertion. We included peripheral and central catheters (**Supplemental File 2, Table S1**). We performed plausibility checks for sex (i.e., male designation excludes obstetrics), age range: 0–120 year, height range: 30–249 cm, weight range: 1–249 kg, body mass index (BMI) range: 12 to 85 kg/m^2, creatinine range: 0–10 mg/dL or < 884 μmol/L, and discrepancies between the variable renal insufficiency and the calculated glomerular filtration rate (eGFR, <60 mL/min/1.73m^2 = renal insufficiency; CKD-EPI formula). Implausible data were blanked and imputed as specified in the statistical analysis section. In addition to specified exposure and outcome variables, we extracted patient demographic characteristics and patient-, surgery-, and block-specific risk factors for infection (Table 1).

2.3. Exposures

As pre-specified in the registry, we considered patients to be immunosuppressed when they: 1) took corticosteroids at a dose exceeding the Cushing threshold (≥7.5 mg/day prednisolone equivalents) longer than 7 days; 2) took immunosuppressant medications other than corticosteroids; 3) were organ transplant recipients; or 4) had immunodeficiency diseases such as HIV. We also considered whether patients were given preoperative antibiotic prophylaxis. In general, antibiotic prophylaxis was given for surgical reasons, at the discretion of the attending surgeon, without regard to catheter insertion.

2.4. Outcomes

The *primary outcome* was infection onset, defined by the number of days since catheter insertion. Our *secondary outcome* was infection severity which the net-ra registry grades as: *no infection*; *mild infection* (presence of two of redness, swelling, and pain); *moderate infection* (mild infection plus two of elevated C-reactive protein, leucocytosis, fever, or pus at the punctured site); and *severe infection* (need for surgical intervention including incisions or revisions). The routine across the participating centers is to assess catheter insertion sites at least daily for infection signs.

2.5. Statistical analysis

Statistical analyses were conducted with R (version 4.2.1, R Core Team 2023) using the mice package for imputation [20]. Missing and implausible data were imputed using multivariate imputation by chained equations, resulting in 20 synthetic datasets. Any variable with at least one missing value had the value imputed, and there was no minimum threshold of 'missingness' to be considered eligible for imputation. BMI and eGFR were recalculated from available or imputed raw data. Model estimates were pooled across the datasets according to Rubin's rules [21]. All analyses were conducted at the catheter level. A two-sided $p < 0.05$ was set as level of significance.

Population demographics and potential confounders were summarized as means ± standard deviations (SD) and frequencies (%). The distribution of potential confounders between exposure groups was assessed as absolute standardized differences (SMD), with values <0.1 considered well balanced. We adjusted our analyses for both patient-

Table 1
Patient demographics and catheter characteristics on the catheter level.

	Immunocompromised		
n_{total} = 196,711	No n = 195,364	Yes n = 1347	SMD
Age (years)			0.064
Mean (SD)	57 (18)	56 (16)	
Missing/Implausible	275 (<1 %)	3 (<1 %)	
Sex			0.132
Male	110,249 (56 %)	671 (50 %)	
Female	85,057 (44 %)	676 (50 %)	
Missing/Implausible	58 (<1 %)	0 (0 %)	
Weight (kg)			0.27
Mean (SD)	81 (18)	76 (17)	
Missing/Implausible	5367 (3 %)	77 (6 %)	
Height (cm)			0.039
Mean (SD)	171 (9)	171 (9)	
Missing/Implausible	81,389 (42 %)	394 (29 %)	
Body mass index (kg/m^2)			0.373
Mean (SD)	28 (6)	26 (6)	
Missing/Implausible	82,456 (42 %)	427 (32 %)	
Creatinine (mg/dL)			0.506
Mean (SD)	0.943 (0.60)	1.60 (1.72)	
Missing/Implausible	75,648 (39 %)	487 (36 %)	
eGFR (mL/min) [a]			0.464
Mean (SD)	87 (28)	71 (37)	
Missing/Implausible	75,914 (39 %)	491 (37 %)	
Renal failure, eGFR < 60			0.398
Yes	22,185 (11 %)	361 (27 %)	
No	173,179 (89 %)	986 (73 %)	
Diabetes			0.195
Yes	23,314 (12 %)	256 (19 %)	
No	172,050 (88 %)	1091 (81 %)	
Active malignancy			0.159
Yes	510 (<1 %)	26 (2 %)	
No	194,854 (99.7 %)	1321 (98 %)	
Active alcohol use			0.035
Yes	1265 (<1 %)	13 (1 %)	
No	194,099 (99.4 %)	1334 (99 %)	
Active drug use			0.159
Yes	589 (<1 %)	27 (2 %)	
No	194,775 (99.7 %)	1320 (98 %)	
ASA Physical Status			0.664
1	20,344 (10 %)	34 (3 %)	
2	64,264 (33 %)	335 (25 %)	
3	48,401 (25 %)	639 (47 %)	
4	2198 (1 %)	73 (5 %)	
Missing/Implausible	60,157 (31 %)	266 (20 %)	
Pre-existing infection [b]			0.126
Yes	3738 (2 %)	55 (4 %)	
No	191,626 (98 %)	1292 (96 %)	
Pre-existing antibiotic therapy			0.228
Yes	14,072 (7 %)	192 (14 %)	
No	181,292 (93 %)	1155 (86 %)	
Antibiotic prophylaxis [c]			0.015
Yes	109,312 (56 %)	764 (57 %)	
No	86,052 (44 %)	583 (43 %)	
Medical/surgical specialty			0.693
Cardiac surgery	1194 (<1 %)	19 (1 %)	
General surgery	36,794 (19 %)	500 (37 %)	
Gynecology	14,813 (8 %)	42 (3 %)	
Internal medicine	630 (<1 %)	17 (1 %)	
Neurosurgery	156 (<1 %)	0 (0 %)	
Obstetrics	15,000 (8 %)	75 (6 %)	
Trauma/orthopedics	94,448 (48 %)	311 (23 %)	
Urology	10,877 (6 %)	117 (9 %)	
Vascular surgery	1362 (<1 %)	4 (<1 %)	
Other	19,969 (10 %)	259 (19 %)	
Pediatric surgery	99 (<1 %)	2 (<1 %)	
Missing/Implausible	22 (<1 %)	1 (<1 %)	
Catheter target [d]			0.314
Central	100,892 (52 %)	902 (67 %)	
Peripheral	94,355 (48 %)	444 (33 %)	
Missing/Implausible	117 (<1 %)	1 (<1 %)	
Tunneled catheter			0.205
Yes	54,867 (28 %)	511 (38 %)	
No	138,399 (71 %)	832 (62 %)	
Missing	2098 (1 %)	4 (<1 %)	
Sterile procedure			0.024
Yes	136,869 (70 %)	962 (71 %)	
No	56,087 (29 %)	374 (28 %)	
Missing/Implausible	2408 (1 %)	11 (<1 %)	
Bacterial filter used			0.068
Yes	188,449 (97 %)	1315 (98 %)	
No	6190 (3 %)	28 (2 %)	
Missing/Implausible	725 (<1 %)	4 (<1 %)	
Multiple skin punctures			0.175
Yes	32,427 (17 %)	320 (24 %)	
No	161,027 (82 %)	1023 (76 %)	
Missing/Implausible	1910 (1 %)	4 (<1 %)	
Infection (any severity)			0.105
Yes	5144 (3 %)	62 (5 %)	
No	190,220 (97 %)	1285 (95 %)	
Infection severity			0.115
None	190,220 (97.4 %)	1285 (95.4 %)	
Mild	4517 (2.3 %)	58 (4.3 %)	
Moderate	534 (0.3 %)	4 (0.3 %)	
Severe	93 (<0.1 %)	0 (0 %)	
Catheter indwelling time (days)			0.394
Median [Q1, Q3]	3.5 [2.4–5.4]	4.5 [3.4–6.6]	

[a] eGFR values are calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.
[b] Catheters in patients with pre-existing systemic infections.
[c] The indication of preoperative antibiotic prophylaxis was entirely at the discretion of the attending surgeon, and not determined by catheter placement.
[d] Central blocks were defined as any nerve block administered near the central nervous system.

related confounders (age, sex, BMI, ASA physical status, diabetes, renal insufficiency, alcohol abuse, pre-existing systemic infection, antibiotic prophylaxis, ongoing antibiosis prior to surgery, active malignancy) and catheter-related confounders (catheter target, sterile procedure, tunneled catheter, use of bacterial filter, multiple skin punctures). We included a pre-specified interaction term between immunocompromise and antibiotic prophylaxis, and calculated cluster-robust standard errors to account for correlation within study centers for all analyses.

2.5.1. Primary analysis

Hazards for infection onset were estimated with multivariable Cox regression. The proportional hazards assumption was validated through visual inspection of Schoenfeld residuals.

2.5.2. Secondary analysis

Odds for progression of infection severity by one level were calculated using a proportional-odds cumulative logit model. Because higher infection severities were sparse, we collapsed moderate and severe infections into a single category. The proportional odds assumption was validated with the Brant-Wald test, and by sequential logistic regressions for each step increase in infection severity (i.e., none vs. mild/moderate/severe, mild vs. moderate/severe).

2.5.3. Sensitivity analyses

We repeated the above-described analyses restricted to catheters with prolonged use, defined as catheters remaining in situ for at least four days. Additionally, we performed a subgroup analysis to test our hypotheses in centrally versus peripherally placed catheters.

The adjusted number of patients who needed be given antibiotic prophylaxis to prevent a single catheter-related infection was estimated using an adjusted logistic regression model (i.e., none vs. any infection).

2.6. Sample size considerations

We planned to consider all available patients, but nonetheless estimated power with G*Power (version 3.1.9.6) [22]. We assumed the effect of immunocompromise on the catheter infection incidence to be at least as strong as the effect of diabetes mellitus. Previous data revealed a 1.2 % higher infection incidence in patients with diabetes mellitus (no diabetes: 3.0 %, $n = 32,891$ versus any diabetes: 4.2 %, $n = 3990$) [23]. We assumed that there were at least 10-times more immunocompetent patients available than immunocompromised patients, resulting in an allocation ratio of 0.1.

An a priori sample size estimate for a z test statistic with 90 % power and a two-tailed alpha of 0.05 yielded into a total required sample size of 29,647 patients (immunocompromised: $n = 2695$, immunocompetent: $n = 26,952$). Because the treatment effect proved to be greater than initially estimated, we had sufficient power even though there were fewer immunocompromised cases than expected.

3. Results

3.1. Data preparation

We retrieved data characterizing 196,711 regional analgesia catheters of which 1347 were inserted into immunocompromised patients. Plausibility checks and missing data led to incomplete data entries for 133,306 catheters (823 in immunocompromised patients); however, 98,971 (74 %) had three or fewer missing values: 12,756 (10 %) were missing one value, 50,360 (26 %) two values, and 35,855 (38 %) three values. All incomplete cases were usable for analysis after imputation of weight, height, BMI, creatinine, eGFR, and ASA physical status (Fig. 1).

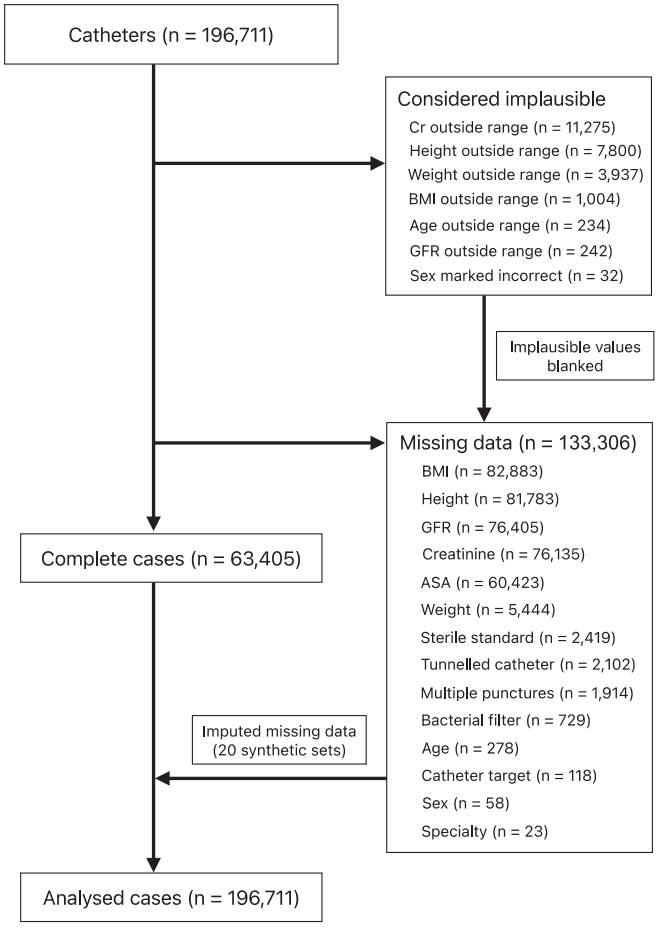

Fig. 1. Flow chart for implausible/missing data and imputation.

3.2. Patient and catheter characteristics

Immunocompromise was attributed to corticosteroids in 37 % of the catheters ($n = 576$), other immunosuppressants in 40 % ($n = 621$), previous organ transplantation in 22 % ($n = 342$), and by immunodeficient diseases in 17 % ($n = 264$). Immunocompromised patients had more comorbidities and mostly had general surgeries. In contrast, immunocompetent patients were comparably healthier and most often had trauma/orthopedic surgeries. The frequency of preoperative antibiotic prophylaxis was similar in each group (Table 1). A table presenting patient demographics and catheter-related characteristics stratified by receipt of preoperative antibiotic prophylaxis is presented in the supplement **(Supplemental File 2, Table S2)**.

3.3. Immune function and catheter-related infections

190,220 of 195,364 (97.4 %) catheter insertion sites in immunocompetent patients had no infections, 4517 (2.3 %) had mild, 534 (0.3 %) had moderate, and 93 (<0.1 %) had severe infections. In contrast, 1285 of 1347 (95.4 %) catheter insertion sites in immunocompromised patients had no infections, 58 (4.3 %) had mild, 4 (0.3 %) had moderate, and none had severe infections (Table 1). After adjustment for multiple block- and patient-related infection risk factors, catheters in immunocompromised patients who were not given antibiotic prophylaxis had a 29 % greater hazard for infection (HR: 1.29 [95 % CI: 0.95, 1.76], $p = 0.1$) and 91 % greater odds of developing higher infection severity (OR: 1.29 [95 % CI: 1.39, 2.63], $p < 0.001$) than immunocompetent patients, although the difference in hazards did not reach statistical significance (Table 2). The time to 10 % catheter-related infections was about one day shorter for catheters in immunocompromised than immunocompetent patients (Fig. 2).

The proportional odds assumption of our ordinal regression model for the association of immune function with infection severity was validated with two separate logistic regression models, revealing no substantial differences in effect sizes between level increases in infection severity (none versus any infection: OR: 1.91 [95 %CI: 1.39, 2.64], $p < 0.001$.; mild versus moderate-to-severe infection: OR: 2.02 [95 %CI: 0.64, 6.35], $p = 0.23$).

Table 2
Association of immunocompromise with infection onset and severity.

Immune function		Total regional analgesia catheters *n = 196,711*		Immunocompromised versus immunocompetent	
		competent *n = 195,364*	compromised *n = 1347*	Effect estimates (95 %CI)	p
Infection onset (days to 10 % infection, 95 %CI)		9.4 (8.4, 11)	8.3 (7.4, 10)	HR: 1.29 (0.95, 1.76)	0.10
Infection severity (n, %)	none	190,220 (97.4)	1285 (95.4)	OR: 1.91 (1.39, 2.63)	<0.001
	mild	4517 (2.3)	58 (4.3)		
	moderate/ severe	627 (0.3)	4 (0.3)		

Effect estimates were adjusted for patient-related confounders (age, sex, BMI, ASA physical status, diabetes, renal insufficiency, alcohol abuse, pre-existing systemic infection, antibiotic prophylaxis, ongoing antibiosis prior to surgery, active malignancy) and catheter-related confounders (catheter target, sterile procedure, tunneled catheter, use of bacterial filter, multiple skin punctures). Cluster robust standard errors were calculated to account for within center and surgical specialty correlations. Abbreviations: HR, hazard ratio; OR, odds ratio; 95 %CI, 95 % confidence interval; BMI, body mass index; ASA, American Society of Anesthesiologists.

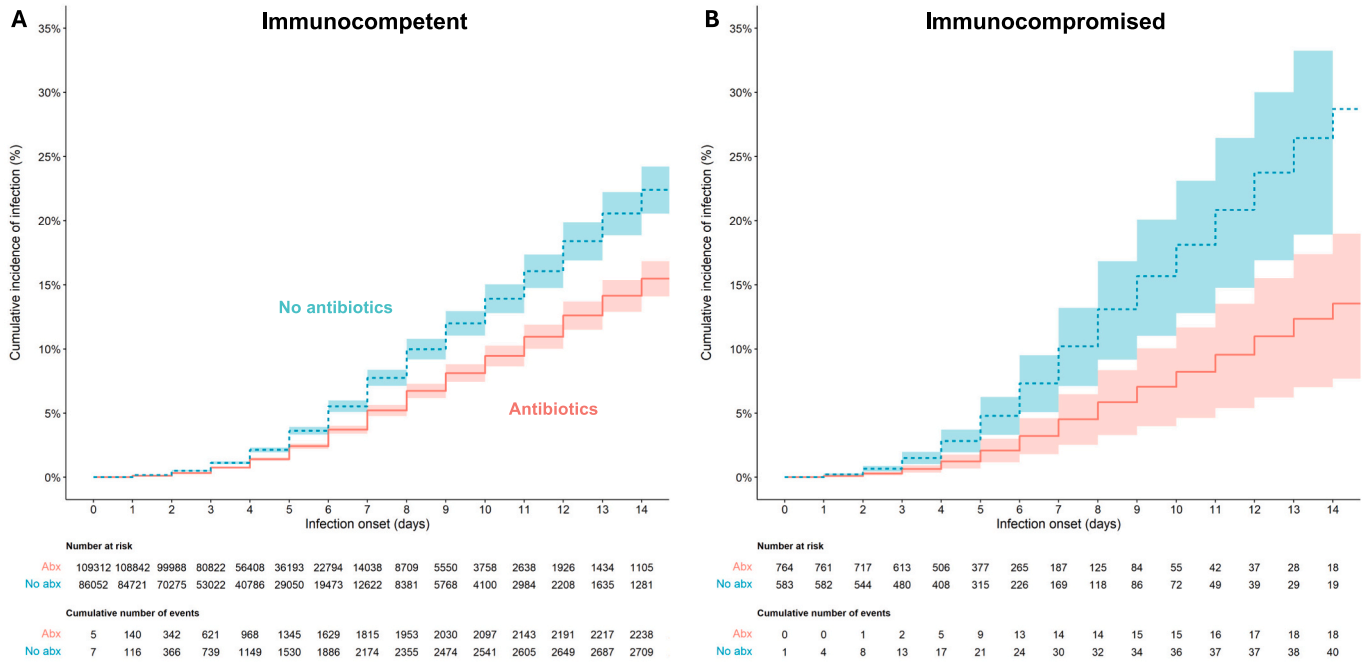

Fig. 2. Cumulative incidence of catheter-related infection stratified by immune function and antibiotic prophylaxis.

3.4. Antibiotic prophylaxis and catheter-related infections

There was a significant interaction between immune function and antibiotic prophylaxis for infection onset and severity. Specifically, antibiotic prophylaxis was more effective in immunocompromised than immunocompetent patients in delaying and preventing infection (Table 3, Fig. 3). Consequently, the hazards for infection onset and odds for infection severity were similar for catheters in immunocompromised and immunocompetent patients receiving antibiotic prophylaxis (Fig. 3). The adjusted number of patients needed to treat with antibiotics to prevent a single catheter-related infection in immunocompromised patients was 55 [95 %CI: 28, 82], whereas it was 83 [95 %CI: 75, 91] in immunocompetent patients.

3.5. Sensitivity analyses

Restriction of the study population to catheters with indwelling times of at least 4 days reduced sample size to a total of 119,899 catheters, with 118,855 placed in immunocompetent patients and 1044 in immunocompromised patients. Infection severities in immunocompetent patients were none 114,621 (97 %), mild 3788 (3 %), and moderate/severe 446 (<1 %). In immunocompromised patients, infection severities were none 994 (95 %), mild 47 (5 %), and moderate/severe 3 (<1 %) **(Supplemental File 2, Table S3)**.

The infection incidence for short-term catheters (<4 days) was 4 % in immunocompromised versus 1.2 % immunocompetent patients. Consequently, our sensitivity analysis excluded disproportionately more catheter-related infections in immunocompromised patients, thereby attenuating the effects observed in our original analyses to the point of statistical insignificance. **(Supplemental File 2, Table S4–5)**.

We additionally stratified our main analysis by catheter target, resulting in a reduced sample size of 101,797 centrally placed and 94,796 peripherally placed catheters. Centrally placed catheters had greater odds for more severe infections in immunocompromised compared to immunocompromised patients (OR: 1.63 [95 %CI: 1.21, 2.05], $p = 0.021$), but did not differ significantly in the time to infection (HR: 1.08 [95 %CI: 0.72, 1.61], $p = 0.69$). Peripherally placed catheters in immunocompromised patients had both a significantly greater hazard of infection (HR: 1.73 ([95 %CI: 1.07, 2.80], $p < 0.001$) and odds of more severe infections (OR: 2.41 [95 %CI: 1.90, 2.91], $p < 0.001$) than those in immunocompetent patients **(Supplemental File 2, Table S6–8)**.

4. Discussion

Unsurprisingly, immunocompromised patients were at higher risk for regional analgesia catheter-related infections than immunocompetent patients when no antibiotic prophylaxis was given. Infections developed earlier and were more frequent in immunocompromised patients. Antibiotic prophylaxis was minimally effective in both groups,

Table 3
Interaction effect of immune function and antibiotic prophylaxis on infection onset and severity.

Immune function	Total regional analgesia catheters *n = 196,711*		With versus without antibiotic prophylaxis			
			Infection onset		Infection severity	
	With antibiosis *n total/events*	Without antibiosis *n total/events*	HR (95 % CI)	*p* value for interaction	OR (95 % CI)	p value for interaction
competent	109,312/2308	86,502/2836	0.67 (0.64, 0.72)	0.12	0.53 (0.5, 0.56)	<0.001
compromised	764/20	583/42	0.44 (0.26, 0.75)		0.29 (0.16, 0.49)	

Effect estimates were adjusted for patient-related confounders (age, sex, BMI, ASA physical status, diabetes, renal insufficiency, alcohol abuse, pre-existing systemic infection, ongoing antibiosis prior to surgery, active malignancy) and catheter-related confounders (catheter target, sterile procedure, tunneled catheter, use of bacterial filter, multiple skin punctures). Cluster robust standard errors were calculated to account for within center and surgical specialty correlations. Abbreviations: HR, hazard ratio; OR, odds ratio; 95 %CI, 95 % confidence interval; BMI, body mass index; ASA, American Society of Anesthesiologists.

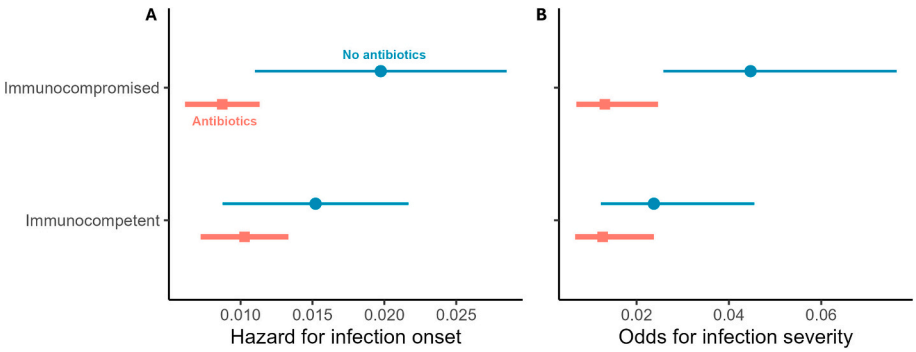

Fig. 3. Effects of immune function and antibiotic prophylaxis on infection onset (A) and severity (B).
Data are presented as hazards and odds with the corresponding 95 % confidence intervals, which were calculated based on the adjusted cox and ordinal models presented in Table 3. Antibiotic prophylaxis was more effective in immunocompromised patients (top row) than immunocompetent patients (bottom row) both in prolonging infection onset and preventing progression to higher infection severities. The hazard for catheter-associated infection onset decreased more with antibiotic prophylaxis in immunocompromised than immunocompetent patients (A). Similarly, the odds for catheter-associated infection severity decreased much more with antibiotic prophylaxis in immunocompromised than immunocompetent patients (B). Consequently, both the hazard and odds for infection in patients treated with antibiotics were similar in both immunocompromised and immunocompetent patients.

but slightly more protective in immunocompromised patients to the point of equalizing infection risk in immunocompromised and immunocompetent patients.

We are not aware of previous studies on the risk of regional analgesia catheter-related infections in immunocompromised patients, but the effect of immune function on the risk of central venous catheter-related and postoperative wound infections has been characterized [12,13]. For example, a retrospective cohort analysis that compared 1021 immunocompromised and 5473 immunocompetent patients from 51 intensive care units reported that the odds of central venous catheter-related infections were 42 % greater (1.42 [95 %CI: 1.03–1.9], $p = 0.016$). Furthermore, prolonged corticosteroid use increased the odds for wound infections by 21 % (1.21 [95 %CI: 1.03, 1.41], p = 0.01) [13]. Our finding that immunocompromised patients are at increased risk for regional catheter-related infections is thus generally consistent with previous reports on infection risks in immunocompromised patients.

Whether regional analgesia catheters should be avoided in immunocompromised patients has been unclear [11]. Our analysis suggests that catheters inserted in immunocompromised patients without antibiotic prophylaxis are more likely to become infected, although severe infections were rare. However, the overall low incidence of moderate-to-severe regional analgesia catheter-related infections suggests that catheter-based analgesic techniques remain appropriate in these patients. Long-term use of regional analgesia catheters in immunocompromised patients remains reasonable but should be accompanied by frequent monitoring of catheter-insertion sites for signs of infection. From previous net-ra registry analyses, we know that severe infections are commonly preceded by mild or moderate infection signs at the catheter insertion site [2,7]. Thus, immediate removal of catheters with initial infection signs should effectively prevent significant harm in immunocompromised patients.

The average number of patients who need to be treated with preoperative antibiotic prophylaxis to prevent one surgical site infection is 34, which is much lower than the 83 treated immunocompetent patients we found were needed to prevent one regional analgesia catheter-related infection [24]. In immunocompromised patients though, antibiotics were more effective, with only 55 patients needing to receive antibiotics to prevent a catheter-related infection. Consequently, immunocompromised patients treated with preoperative prophylactic antibiotics had infection risks similar to immunocompetent patients who were or were not given antibiotics. Clinicians should thus not refrain from catheter-based analgesic techniques in immunocompromised patients given prophylactic antibiotics anyway.

Antibiotics in our patients were nearly always given for surgical reasons. Whether antibiotics are indicated solely for insertion of regional analgesia catheters remains debatable. A recent meta-analysis suggests that one in every 100 patients experiences significant side-effects from prophylactic antibiotics, corresponding to a number-needed-to-harm of 100 [24]. Given the number-needed-to-treat of 55 and the low incidence of catheter-related infections immunocompromised patients, prophylactic antibiotics seem not well justified in such patients. However, our study did not assess the severity of immunocompromise; presumably risk is greatest in patients with severe immunocompromise, and antibiotics might be especially effective in such patients. Previously reported risk factors are prolonged catheter use [7], neuraxial catheters [2], femoral catheters [25], non-tunneled catheters, multiple skin punctures during insertion [26], obesity [26], diabetes mellitus [14], ASA physical score ≥ 3 [18], and age more than 65 years [18]. Clinicians should thus aim for puncture sites with low infection risk, avoid multiple skin punctures, and tunnel catheters in immunocompromised patients, especially when prolonged catheter-based pain therapy is required. Administration of prophylactic antibiotics solely indicated by catheter insertion may be considered in patients who are severely immunocompromised, present other special risks for infection, and especially when prolonged catheter use is indicated. We note though that patients with these characteristics and in whom prophylactic antibiotics are not already indicated for surgical reasons are rare.

We performed a sensitivity analysis focusing on catheters with prolonged use (>3 days), based on previous findings indicating that catheter-related infections are unlikely to occur within the first few days of insertion [7]. However, excluding short-term catheters disproportionately removed more infected catheters in immunocompromised than immunocompetent patients, likely due to early removal of infected catheters. As a result, the effects observed in our original analyses were reduced to the point of statistical insignificance. This suggests that the increased infection risk in immunocompromised patients is not limited to prolonged catheter use but is evident from the day of insertion. We also compared centrally and peripherally placed catheters and found results that largely mirrored that of our main analysis – with one notable exception. Peripherally placed catheters appear to have a significantly greater hazard of infection when placed in immunocompromised patients, compared to immunocompetent patients. This finding comes from a post-hoc sub-group analysis and should be interpreted with caution.

A limitation of our analysis is that the reported prevalence of immunocompromise is about 3 % in US adults whereas it was <1 % in our population. Our registry was restricted to German patients so regional differences could be present, but it may also indicate under-reporting of immunocompromise in the net-ra registry or that clinicians were reluctant to insert catheters in immunocompromised

patients. While we were able to adjust for patient-, block- and specialty-specific factors, we did not have access to surgery-specific factors that may also influence immune function. Prophylactic antibiotics are more likely to be prescribed for major than minor surgeries. Despite this potential selection bias, we found that antibiotics prevented catheter-related infections. Due to missing data, we had to use imputation methods which may have introduced bias. Finally, progress of medicine during the 15-year observation period (2007–2022) could have caused time-related bias; however, inclusion of the year of surgery did not improve model fit nor did it meaningfully alter primary effect estimates.

5. Conclusions

Regional analgesia catheter-related infections occur earlier and more frequently in immunocompromised patients. Therefore, catheter insertion sites should be closely monitored in these patients. Antibiotic prophylaxis provided marginal benefit in immunocompetent patients but were more protective in immunocompromised patients. Consequently, the hazard for infection onset and odds for severity were similar in immunocompetent patients with or without antibiotics and in immunocompromised patients given antibiotics, with risk being greater in immunocompromised patients who were not given antibiotics. Most infections were mild, though, and previous work suggests that simply removing infected catheters usually prevents progression. Prophylactic antibiotics for catheter infection prophylaxis should be restricted to patients who are severely immunocompromised and are at special infection risks.

CRediT authorship contribution statement

Lukas M. Müller-Wirtz: Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **William M. Patterson:** Visualization, Investigation, Formal analysis, Data curation. **Sascha Ott:** Writing – review & editing, Investigation. **Kurt Ruetzler:** Writing – review & editing, Investigation. **Alparslan Turan:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Daniel I. Sessler:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Thomas Volk:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Christine Kubulus:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Thorsten Steinfeldt:** Visualization, Investigation, Formal analysis, Data curation. **Dieter Fröhlich:** Visualization, Investigation, Formal analysis, Data curation. **Claudia Spies:** Visualization, Investigation, Formal analysis, Data curation. **Wolf Armbruster:** Visualization, Investigation, Formal analysis, Data curation. **Michael Przemeck:** Visualization, Investigation, Formal analysis, Data curation. **André Gottschalk:** Visualization, Investigation, Formal analysis, Data curation. **Arnd Timmermann:** Visualization, Investigation, Formal analysis, Data curation. **Stefan Wirtz:** Visualization, Investigation, Formal analysis, Data curation. **Andreas Meier-Hellmann:** Visualization, Investigation, Formal analysis, Data curation. **Gerald Burgard:** Visualization, Investigation, Formal analysis, Data curation. **Lars Fischer:** Visualization, Investigation, Formal analysis, Data curation. **Michael Adamzik:** Visualization, Investigation, Formal analysis, Data curation. **Jens Döffert:** Visualization, Investigation, Formal analysis, Data curation. **René Schmidt:** Visualization, Investigation, Formal analysis, Data curation. **Frederic Böttcher:** Visualization, Investigation, Formal analysis, Data curation. **Paul Kessler:** Visualization, Investigation, Formal analysis, Data curation. **Thomas Standl:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Werner Hering:** Visualization, Investigation, Formal analysis, Data curation. **Thea Koch:** Visualization, Investigation, Formal analysis, Data curation. **Thomas Volk:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Christian Zöllner:** Visualization, Investigation, Formal analysis, Data curation. **Hartmut Bürkle:** Visualization, Investigation, Formal analysis, Data curation. **Winfried Meißner:** Visualization, Investigation, Formal analysis, Data curation. **Hinnerk F.W. Wulf:** Visualization, Investigation, Formal analysis, Data curation. **Jörg Winckelmann:** Visualization, Investigation, Formal analysis, Data curation. **Patrick Meybohm:** Visualization, Investigation, Formal analysis, Data curation. **Peter Kranke:** Visualization, Investigation, Formal analysis, Data curation.

Ethics approval

Approval for this retrospective cohort study was provided by the Ethics Committee of the Saarland Medical Chamber, Saarbrücken, Germany (Chairperson Prof. Dr. U. Grundmann) on January 11, 2021 (identification no. 324/20). Written informed consent was waived as the registry data are completely anonymous (regularly proof of protection of data privacy, Saarland commissioner, March 12, 2014).

Author statements

LMMW was the driving force of the project, wrote the first drafts of the study protocol and manuscript, applied for ethics approval, acquired funding, and ensured technical prerequisites were in place to conduct the analysis. WMP helped with the statistical analysis and the creation of tables and figs. AT, DIS, TV, and CK helped with writing the study protocol. SO, KR, AT, DIS, TV, and CK critically revised the manuscript for important intellectual content and helped with the interpretation of the results. TV provided departmental funds to cover the costs of an online server-based analysis platform to ensure GDPR-conform data access. CK was the primary senior physician-scientist overseeing the process of data cleaning and preparation, and the statistical analysis. All authors critically revised and approved the final version of this manuscript before submission.

Funding

Funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) – 466655093. The Network for Safety in Regional Anesthesia and Acute Pain Therapy (net-ra) registry is supported by the Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin (DGAI) and Berufsverband Deutscher Anästhesisten (BDA).

Declaration of competing interest

Lukas Martin Mueller-Wirtz reports financial support was provided by German Research Foundation. Alparslan Turan and Daniel Sessler reports a relationship with Pacira BioSciences Inc. that includes: consulting or advisory and funding grants. Thomas Volk reports a relationship with Pajunk that includes: speaking and lecture fees. Thomas Volk reports a relationship with CSL Behring that includes: speaking and lecture fees. Daniel I. Sessler, Thomas Volk, Kurt Ruetzler, and Alparslan Turan serve as editors for the Journal of Clinical Anesthesia, but were not involved in the peer review of this article. All other authors have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Drs. Kurt Ruetzler, Alparslan Turan, Daniel. I. Sessler and Thomas Volk are editors of this journal and were not involved in the peer-review process and the decision making for this article.

Acknowledgements

We thank all hospital centers that are/were part of the net- ra registry and particularly those providing data for the current analysis (see net-ra investigator list).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinane.2025.111826.

Data availability

Data are available from the authors upon reasonable request and after approval by the net-ra registry's organizational committee.

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