Treatment of positive catheter tip culture without bloodstream infections in critically ill patients. A case-cohort study from the OUTCOMEREA network

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Electronic supplementary material: Treatment of positive catheter tip culture without bloodstream infections in critically ill patients. A case cohort study from the OutcomeRéa network.

Results of the survey by experts

In the absence of high-quality evidence on the management of positive catheter-tip cultures, we conducted a survey to identify variables associated with antimicrobial treatment that should be included in the propensity score.

A questionnaire was sent to 75 attending experts (*i.e.*, intensivists, infectious diseases specialists, infection prevention and control specialists) from participating centers of the database or national experts from two countries (*i.e.*, France and Switzerland) on which factors influence the management of positive catheter tip cultures. We received 45 responses to 14 questions (eTable 1 and eTable 2).

Only 6 respondents (13%) stated that they would never treat a positive catheter tip culture without a concomitant positive blood culture. Severity of the patient, shock, occurrence of fever, decrease in temperature after catheter removal, presence of immunosuppression, presence of vascular and non-vascular prostheses, duration of catheter maintenance before removal, presence of exit signs of infection were all considered important in the therapeutic decision. Twelve out of 17 respondents mentioned that catheter venous thrombosis was also an important point for starting antimicrobial treatment. Therefore, we decided to include mostly of these risk factors for treatment in the same logistic regression model to determine the individual propensity to treat for each patient.

In which situation would you start an antimicrobial treatment?		Never N (%)	Rarely N (%)	Sometimes N (%)	Often N (%)	Always N (%)
	1-A catheter tip colonization with a culture threshold ≥10^3 CFU/ml, without positive blood culture except coagulase negative staphylococci	6 (13.3)	13 (28.9)	23 (51.1)	3 (6.7)	0
	2-In case of concomitant fever > 38.5°C	1 (2.2)	13 (28.9)	15 (33.3)	12 (26.7)	4 (8.9)
	3-According to the microorganism identified					
	Staphylococcus aureus	3 (6.7)	9 (20)	9 (20)	15 (33.3)	9 (20)
	Pseudomonas aeruginosa	3 (6.7)	14 (31.1)	8 (17.8)	14 (31.1)	6 (13.3)
	Candida albicans	3 (6.7)	8 (17.8)	10 (22.2)	15 (33.3)	9 (20)
	Streptococcus spp	8 (17.8)	10 (22.2)	21 (46.7)	3 (6.7)	3 (6.7)
	Enterococcus faecalis or *faecium*	8 (17.8)	12 (26.7)	19 (42.2)	3 (6.7)	3 (6.7)
	Acinetobacter baumannii	6 (13.3)	17 (37.8)	13 (28.9)	6 (13.3)	3 (6.7)
	Anaerobic bacteria	12 (26.7)	11 (24.4)	20 (44.4)	1 (2.2)	1 (2.2)
	Staphylococcus lugdunensis	5 (11.1)	8 (17.8)	19 (42.2)	9 (20)	4 (8.9)
	4-In case of immunosuppression	2 (4.4)	16 (35.6)	11 (24.4)	14 (31.1)	2 (4.4)
	5-In case of local signs	2 (4.4)	10(22,2)	4 (8.9)	20 (44.4)	9 (20)

eTable 1 Summary of the first part of the panel answers

Which of the following elements, in addition to those discussed above, do you consider to start an antimicrobial treatment?		Not at all relevant N (%)	Not relevant N (%)	No opinion N (%)	Relevant N (%)	Highly relevant N (%)	Mandatory N (%)
	6-Duration of insertion of the catheter suspected at the time of removal	5 (11.1)	22 (48.9)	4 (8.9)	9 (20)	5 (11.1)	
	7-Fever reduced by 0.5 degrees after catheter removal	2 (4.4)	9 (20)	3 (6.7)	18 (40)	11 (24.4)	2 (4.4)
	8-A high SOFA score at catheter removal	5 (11.1)	11 (24.4)	5 (11.1)	17 (37.8)	6 (13.3)	1 (2.2)
	9-Presence of septic shock at catheter removal	2 (4.4)	1 (2.2)	1 (2.2)	8 (17.8)	22 (48.9)	11 (24.4)
	10- Presence of sepsis at catheter removal	2 (4.4)	3 (6.7)	4 (8.9)	19 (42.2)	12 (26.7)	5 (11.1)
	12- Presence a non-vascular prothesis	3 (6.7)	6 (13.3)	3 (6.7)	17 (37.8)	10 (22.2)	6 (13.3)
	13- Presence of a vascular prosthesis	2 (4.4)	2 (4.4)	5 (11.1)	16 (35.6)	12 (26.7)	8 (17.8)

eTable2: Summary of the second part of panel answers

eTable 3: Microorganisms identified in positive intravascular catheter tip cultures.

Microorganism group	Total	With adequate treatment within 48h (n=279)	Without adequate treatment within 48h (n=222)
Non-fermenting Gram-negative, n (%)	123 (24.6)	60 (21.5)	63 (28.4)
Candida spp, n (%)	14 (2.8)	7 (2.5)	7 (3.2)
S. aureus, n (%)	59 (11.8)	44 (15.8)	15 (6.8)
Enterobacterales, n (%)	220 (43.9)	123 (44.1)	97 (43.7)
Enterococcus spp, n (%)	72 (14.4)	35 (12.5)	37 (16.7)
Other Gram-positive microorganisms, n (%)	13 (2.6)	10 (3.6)	3 (1.4)

Legend. We illustrated more than one microorganism per episode. Spp: species.

eTable 4: Logistic regression model used to develop the propensity score for adequate antimicrobial therapy within 48 hours.

Parameter	OR	CI 95%		p-value
Sepsis				0.5967
Without sepsis	1			
Sepsis	1.265	0.751	2.128	
Septic shock	1.458	0.657	3.238	
Temperature >38.5°C	2.075	1.194	3.608	0.0097
SOFA score at time of catheter tip colonization	0.973	0.906	1.046	0.4615
Number of days before catheter tip colonization	0.985	0.969	1.001	0.0594
Immunosuppression	2.583	1.413	4.725	0.0021
Thrombosis at time of catheter colonization	0.605	0.091	3.999	0.6016
Decrease in temperature of >0.5° after catheter removal	1.112	0.65	1.902	0.6988
S. aureus	2.69	1.375	5.261	0.0039
P. aeruginosa	0.959	0.574	1.601	0.8717
Candida spp	1.095	0.361	3.319	0.8721
Streptococcus spp	2.546	0.655	9.9	0.1774
Enterococcus spp	0.766	0.439	1.336	0.3469
Acinetobacter spp	0.676	0.232	1.97	0.4733

Legend. SOFA: Sequential Organ Failure Assessment. OR: Odds ratio. CI: Confidence interval. Spp: species. The AUC was 0.675. For our variables of interest, no missing values were observed. For SOFA and number of days before catheter tip colonization log-linearity was checked.

eTable 5: Microorganisms recovered in subsequent infections

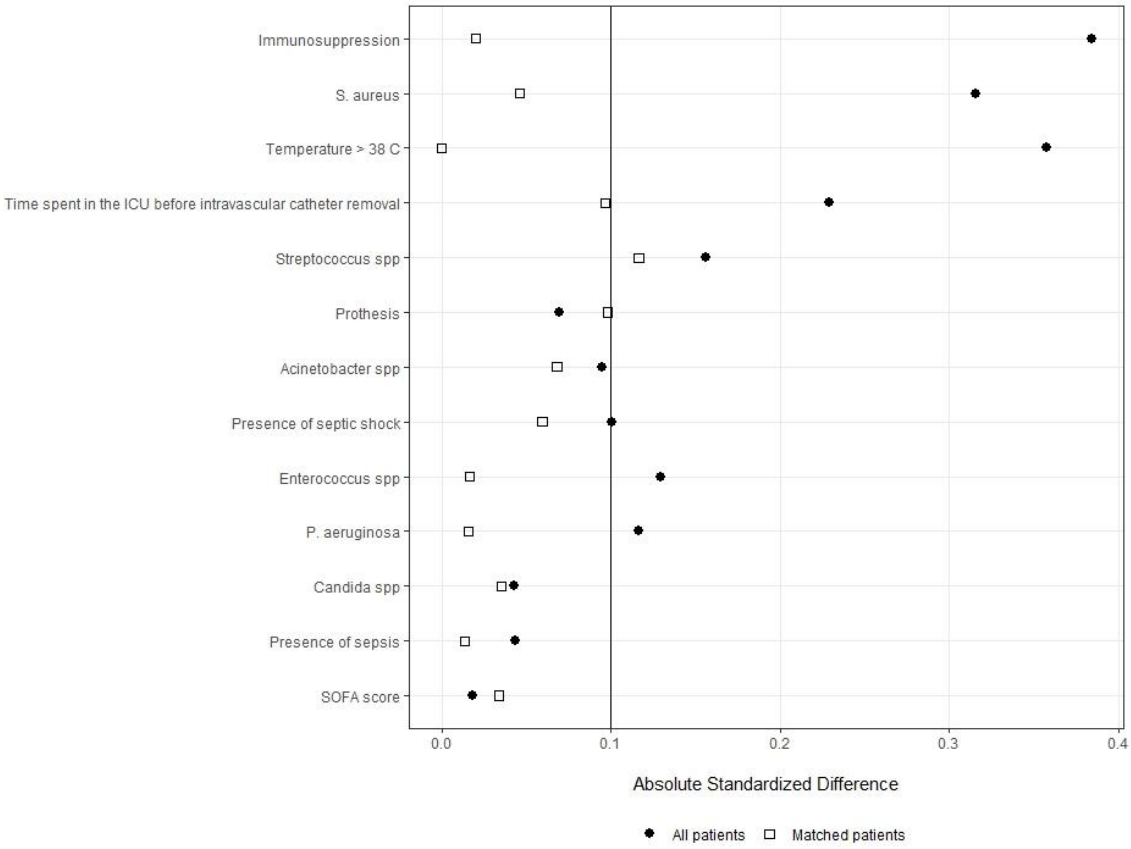
	Matched population (n=30)		**With adequate therapy within 48h (n=15)**		**Without adequate therapy within 48h (n=15)**	
Microorganisms	Bloodstream infections (n=8)	Other (n=22)	Bloodstream infections (n=5)	Other (n=10)	Bloodstream infections (n=3)	Other (n=12)
Staphylococcus aureus	1	0	1	0	0	0
Enterococcus faecalis	0	1	0	1	0	0
Enterococcus faecium	0	2	0	2	0	0
Proteus mirabilis	0	4	0	2	0	2
Serratia	1	0	1	0	0	0
Citrobacter freundii	0	3	0	0	0	3
Escherichia coli	2	4	1	2	1	2
Enterobacter cloacae	1	3	0	0	1	3
Klebsiella pneumoniae	1	2	1	2	0	0
Pseudomonas aeruginosa	1	4	0	3	1	1
Stenotrophomonas maltophilia	0	1	0	0	0	1
Corynebacterium JK.	1	0	1	0	0	0
Polymicrobial	0	2	0	2	0	0

eTable 6: Subsequent infection and mortality risk for patients treated with and without adequate therapy within 48 hours after catheter removal.

	n/N adequate therapy within 48h	n/N without adequate therapy within 48h	sHR or HR	CI 95%	p-value
Subsequent infection risk at Day 30 with adequate antimicrobial therapy, n (%)					
Matched population	15/150	15/150	1.083	(0.622-1.887)	0.778
In patients with high-risk microorganisms	7/64	3/64	2.333	(0.833-6.536)	0.107
In patients with sepsis	11/83	12/83	0.833	(0.459-1.512)	0.549
Subsequent infection risk at Day 15 with adequate antimicrobial therapy, n (%)					
Matched population	15/150	14/150	1.182	(0.669-2.089)	0.566
In patients with high-risk microorganisms	7/64	3/64	2.333	(0.833-6.536)	0.107
In patients with sepsis	11/83	11/83	0.909	(0.496-1.667)	0.758
30-day mortality with adequate antimicrobial therapy, n (%)					
Matched population	33/150	29/150	0.889	(0.453-1.743)	0.732
In patients with high-risk microorganisms	17/64	14/64	1.222	(0.506-2.949)	0.655
In patients with sepsis	27/83	20/83	1.200	(0.605-2.381)	0.602
15-day mortality with adequate antimicrobial therapy, n (%)					
Matched population	25/150	20/150	1.000	(0.489-2.046)	1.000
In patients with high-risk microorganisms	13/64	9/64	1.250	(0.493-3.167)	0.638
In patients with sepsis	20/83	14/83	1.167	(0.540-2.522)	0.695

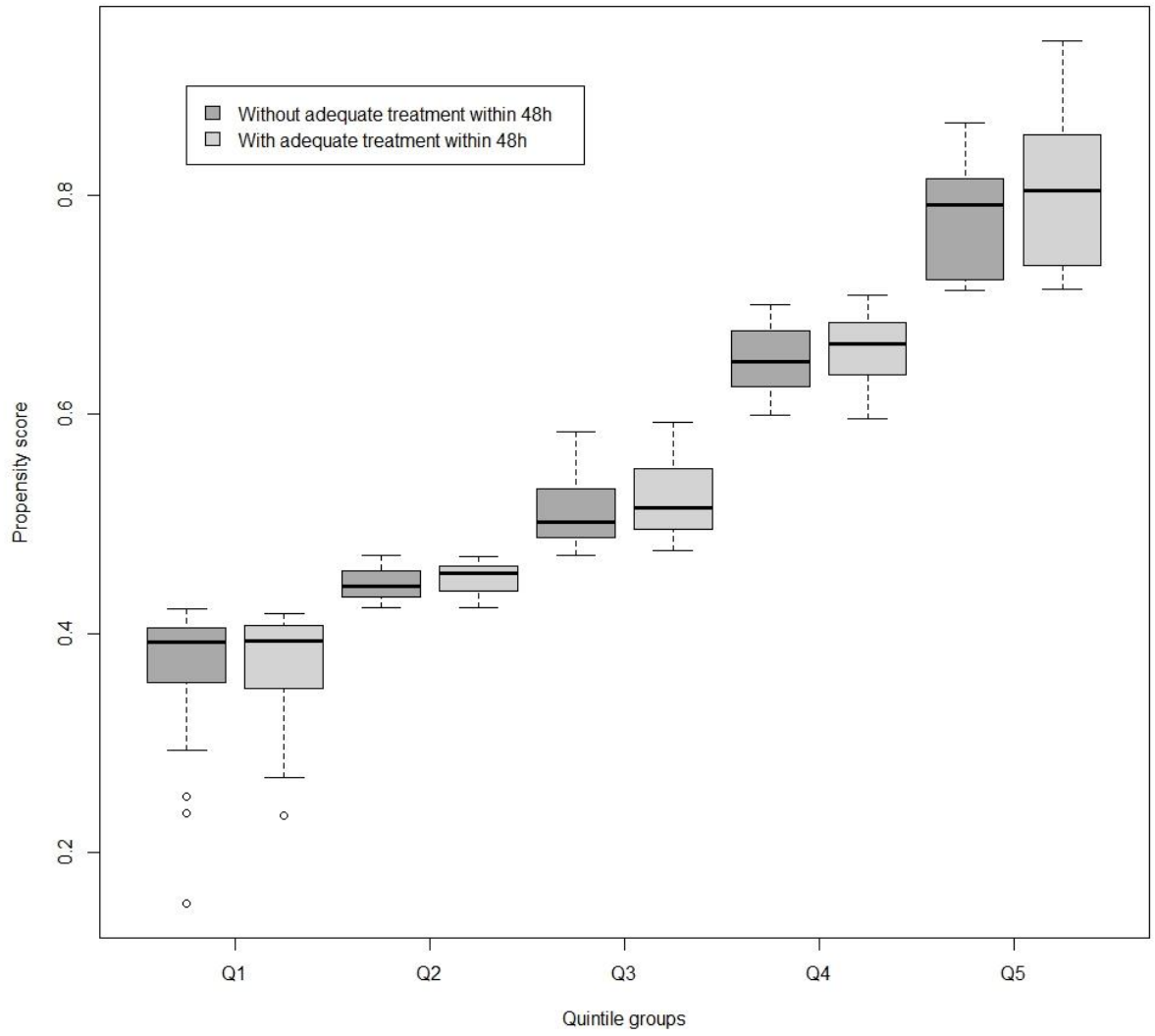
Legend. CI: Confidence Interval. HR: Hazard ratio. SHR: subdistribution hazard ratio.

eFigure 1: Standardized mean difference (SMD) before and after matching process of the main patient' and catheter' characteristics.



Legend: a SMD <0.1 after matching is considered to be optimal. Spp: species. SOFA: Sequential Organ Failure Assessment. ICU: intensive care unit.

eFigure 2: Distribution of propensity scores according to the adequacy of antimicrobial therapy within 48 hours, stratified by the quintile of propensity score.



Legend. This figure illustrated the distribution of propensity scores. We graphically observed a good overlap between patients with and without adequate treatment within 48 hours.

Supplementary analysis for patients with and without delayed antibiotic therapies

The impact of absence of treatment or delayed treatment (i.e., within 96 hours) was not assessed in our study. For this reason we performed a post-hoc analysis including controls without an adequate antibiotic therapy within 96h (n=119) and matched cases (n=119) with an adequate therapy within 48 hours. Using Cox proportional hazard models, the 30-day mortality risk was similar between patients non treated patients within 96h and treated within 48h (HR 0.86, 95% CI 0.40–1.85, p=0.70). Using subdistribution hazard models, the daily risk to develop subsequent infection up to Day-30 was similar between patients non-treated within 96h and treated within 48h (sHR 1.22, 95% CI 0.65–2.29, p=0.53). Moreover, we performed a sensitivity analysis including controls who received an adequate therapy between 48 and 96 hours (n=31) and matched cases with an adequate therapy within 48 hours. Using Cox proportional hazard models, the 30-day mortality risk was similar between patients treated between 48h and 96h and treated within 48h (HR 1.00, 95% CI 0.25–4.00, p=1.00). Using subdistribution hazard models, the daily risk to develop subsequent infection up to Day-30 was non-significantly reduced between patients treated between 48h and 96h and treated within 48h (sHR 0.33, 95% CI 0.09–1.18, p=0.09).

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