Critical Care

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Further considerations on the clinical applicability of time to positivity as a prognostic tool for catheter-related *Pseudomonas aeruginosa* bloodstream infections

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To the Editor,

We appreciate the thoughtful comments by Liao et al. [1] regarding our study [2] on "Time to positivity (TTP) as a predictor of catheter-related bacteremia and mortality in *Pseudomonas aeruginosa* bloodstream infections (PAE-BSI)". Their insights highlight important aspects that warrant further discussion, particularly regarding additional variables that could influence the TTP, and about long-term outcome.

In response to the first point, we acknowledge the potential influence of resistance on TTP. We found that susceptible *P. aeruginosa* strains had a significantly shorter TTP (Table 1). Moreover, this property was consistent across all antibiotic families. Since no clinically relevant TTP cut-off for predicting resistance was identified, this data was not included in the main article due to length limitation. This finding supports that resistant strains may decelerate their replication rates because resistance mechanisms affect one or more metabolic pathways involved in bacterial replication. A previous study in *Staphylococcus aureus* bacteremia also demonstrated shorter TTP for methicillin-susceptible strains compared to methicillin-resistant ones [3]. However, we have to recognize that other studies focused in Enterobacterales and other non-fermenting gram-negative bacilli have shown contradictory results [4, 5].

The authors raise another point regarding immune suppression and comorbidities as potential modifiers of TTP. Although the role of host immunity seems reasonable, our data (Table 1) did not support this statement. In the univariable analysis, chronic kidney disease (CKD) in hemodialysis, neutropenia and corticosteroid therapy were significantly associated with shorter TTP. However, no one was finally included in the multivariable analysis. In the case of CKD in hemodialysis the reason to be excluded is that the majority of these cases were catheter-related bacteremia that is a significant determinant of shorter TTP. Neutropenia reduces the host capacity to clear bacteria from infected tissue resulting in higher bacterial loads in the bloodstream and corticosteroid therapy impair the reticuloendothelial system located at the liver and the spleen, both responsible of rapid bacterial clearance from the blood [6, 7]. Therefore, weak immune system increases the inoculum at the infectious foci and that is the variable

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Table 1 Factors associated with shorter TTP. Univariate and multivariate analysis.

Characteristics	TTP < 15 h (N = 600)	TTP > 15 h (N = 577)	*p*-value	Multivariate analysis	
				OR	*p*-value
Age > 64 years	297 (49.5)	314 (54.4)	0.1		
Sex (female)	233 (38.8)	164 (28.4)	< 0.001		
Comorbidities					
Foreign body	239 (39.8)	268 (46.4)	0.025		
Diabetes mellitus	116 (19.3)	129 (22.4)	0.22		
Chronic pneumopathy	63 (10.5)	68 (11.8)	0.52		
CKD	96 (16)	75 (13)	0.16		
CKD hemodialysis	41 (6.8)	21 (3.6)	0.02		
Chronic liver disease	40 (6.7)	34 (5.9)	0.63		
Solid neoplasm	147 (24.5)	148 (25.6)	0.7		
Hematologic malignancy	127 (21.2)	107 (18.5)	0.27		
Neutropenia	131 (21.8)	84 (14.9)	0.013		
Solid organ transplantation	78 (13)	97 (16.8)	0.07		
Stem cell transplantation	38 (6.3)	30 (5.2)	0.45		
HIV	21 (3.5)	19 (3.3)	0.9		
Corticosteroids	224 (37.3)	169 (29.3)	< 0.001		
Admission data					
Previous admission (< 1 month)	183 (31.5)	199 (35.5)	0.15		
Nosocomial bacteremia	550 (53.5)	478 (46.5)	< 0.001		
Bladder catheterization	193 (33)	225 (40.1)	0.02		
Intravascular catheter	489 (81.5)	370 (64.1)	< 0.001	2.4 [1.5–3.7]	< 0.001
Microbiologic data					
PAE isolated in aerobic 2/2 vials	352 (58.8)	236 (40.1)	< 0.001	1.5 [1.2–1.8]	< 0.001
Sensible to ceftazidime	458 (81.6)	377 (72.4)	< 0.001		
Sensible to piperacillin	402 (81.4)	337 (69.2)	< 0.001		
Sensible to gentamycin	381 (81.2)	330 (73.3)	0.005		
Sensible to amikacin	548 (97.3)	526 (96.9)	0.7		
Sensible to ciprofloxacin	411 (72.4)	348 (64.9)	0.01		
Sensible to meropenem	355 (73.8)	297 (63.2)	< 0.001		
Susceptible PAE	377 (63.9)	317 (56.7)	0.01		
MDR PAE	55 (9.2)	88 (15.3)	0.002	0.4 [0.2–0.7]	< 0.001
Active antibiotic (during bacteremia)	66 (11)	90 (15.6)	0.02	0.35 [0.2–0.5]	< 0.001
Source of infection					
Primary bacteremia	127 (21.5)	127 (22.3)	0.8		
Catheter-related	281 (47.5)	112 (19.6)	< 0.001	2.9 [2.1–4]	< 0.001
Respiratory	77 (12.8)	84 (14.6)	0.4		
Abdominal	14 (2.4)	33 (5.8)	0.004		
Biliary tract	19 (3.2)	42 (7.4)	0.002		
Urinary tract	49 (8.3)	130 (22.8)	< 0.001	0.5 [0.3–0.8]	0.008

CKD, chronic kidney disease, HIV; Human immunodeficiency virus; MDR, Multi—drug resistant strain; PAE, *Pseudomonas aeruginosa*

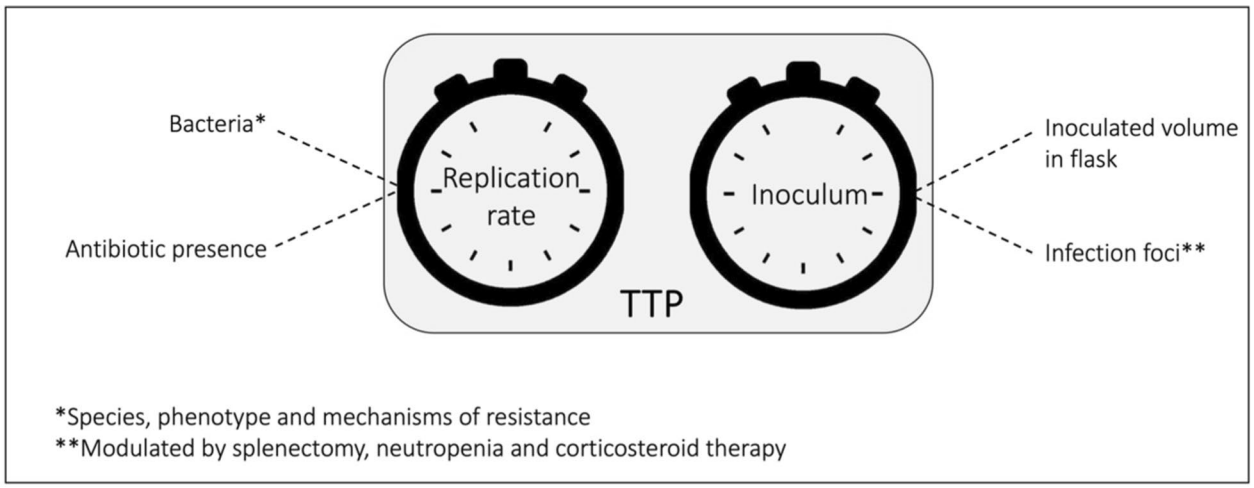

Fig. 1 Diagram displaying the main determinants of time to positivity (TTP). The figure also represents the microbiological and clinical variables which in turn affect the two main determinants

superior in the multivariable analysis. According to our findings, we have summarized the main determinants of TTP in Fig. 1.

While we agree that evaluating long-term mortality and post-infection complications would provide a more comprehensive perspective, this was not the primary scope of our study, and this information was not captured in our database.

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Author contributions
D.N.M., À.S., and S.H. contributed to the conception and design of the study. D.N.M. conducted the data collection and statistical analysis, with guidance from À.S. and S.H. The manuscript was drafted by D.N.M. and SH and critically revised by À.S. for important intellectual content. S.H. and A.S supervised the project and provided final approval of the version to be published. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

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Declarations

Competing interests
The authors declare no competing interests.

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