NOVEL DATA ON NEW AND OLD EPIDEMICS

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Predictive factors of persistent *Staphylococcus aureus* bloodstream infections: a retrospective study in northern Italy

PerSAB study – an interim analysis

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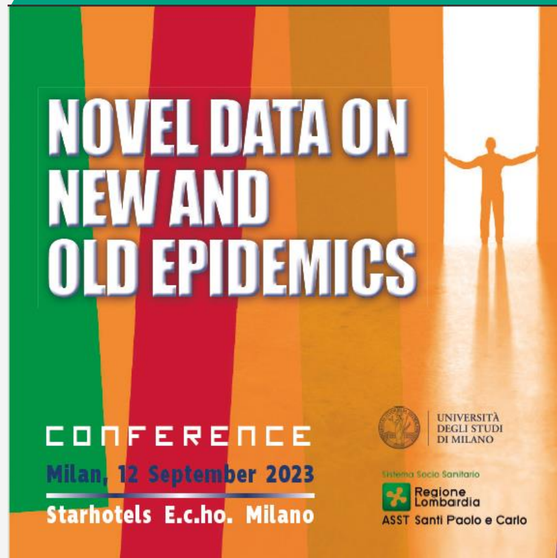


Rational of the study

- S. aureus bacteremia (SAB) is a high mortality condition (20-40%) with a high rate of morbidity due to its potential dissemination

- Persistent bacteremia is defined by the presence of positive follow-up blood coltures (FU-BC) starting 48/72 hours after the beginning of an effective anti-staphylococcus antibiotic therapy, with an incidence estimated between 6 and 38%

- Mortality risk raises everyday of positive FU-BC with a cut-off of 72 hours as the limit to the higher incrementation of mortality

- Some risk factors for persistent SAB, in literature, have been identified but its determinants are still not completely defined

Aims

to analyse:

- epidemiology and clinical features of SAB from 2019 to 2022 (4 years) at San Paolo Hospital
- prevalence of persistent SAB and risk factors associated
- mortality and risk factors associated

Material and methods

- Retrospective observational study

- Inclusion criteria: All patients with monobicrobic SAB, from January 1st 2019 to December 31st 2022 in San Paolo Hospital, age>18 yrs

- Persistent SAB were evaluated in patients with at least one follow-up blood culture performed after 72h and within 7 days of effective antibiotic therapy:
  -Persistent bacteremia >=72h: at least one positive blood culture after 72h of effective therapy **(PB >= 72h)**
  -Persistent bacteremia >7 days: at least one positive blood culture after 7 days of effective therapy **(PB > 7days)**
  -Risk factors associated with both outcomes were evaluated by univariate and multivariate logistic regression analysis

- Mortality at 30 days was evaluated by Kaplan-Meier curves, risk factors associated were evaluated by Cox regression analysis.

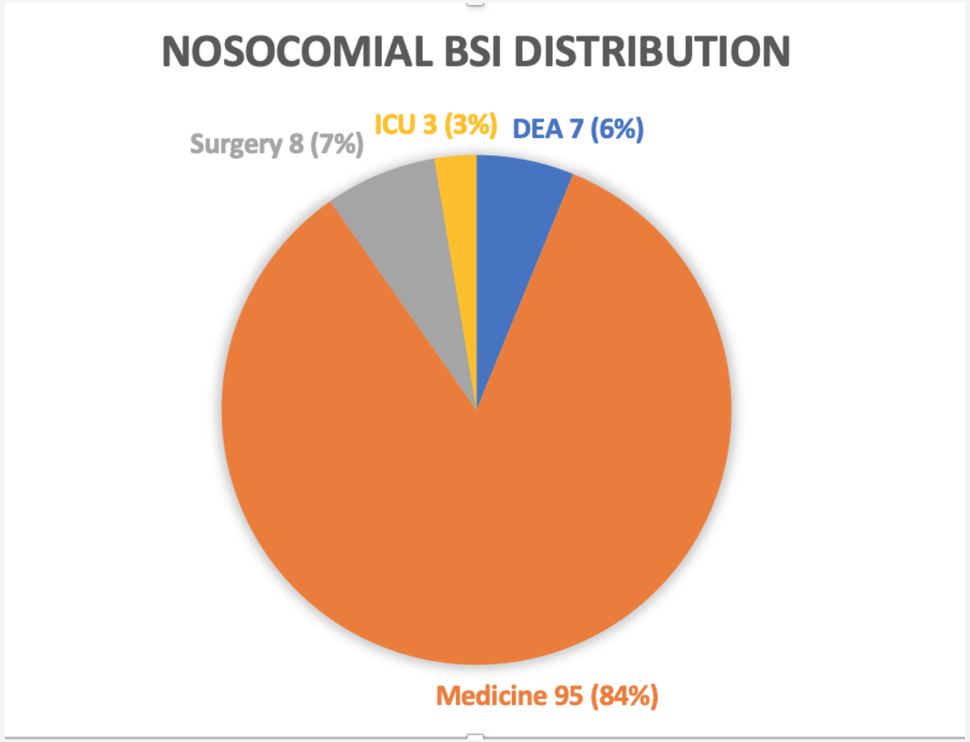
Demographic and patient characteristics

	Overall (219)
Male (%)	129 (58.9%)
Age (IQR)	75 (61-83)
Charlson (IQR)	6 (5-9)
PITTs	0 (0-1)
Dialysis (%)	27 (12%)
Permanent endovascular devices (%)	51 (23%)
Orthopedic devices (%)	17 (8%)
CVC (%)	64 (30%)
MRSA (%)	66 (30%)

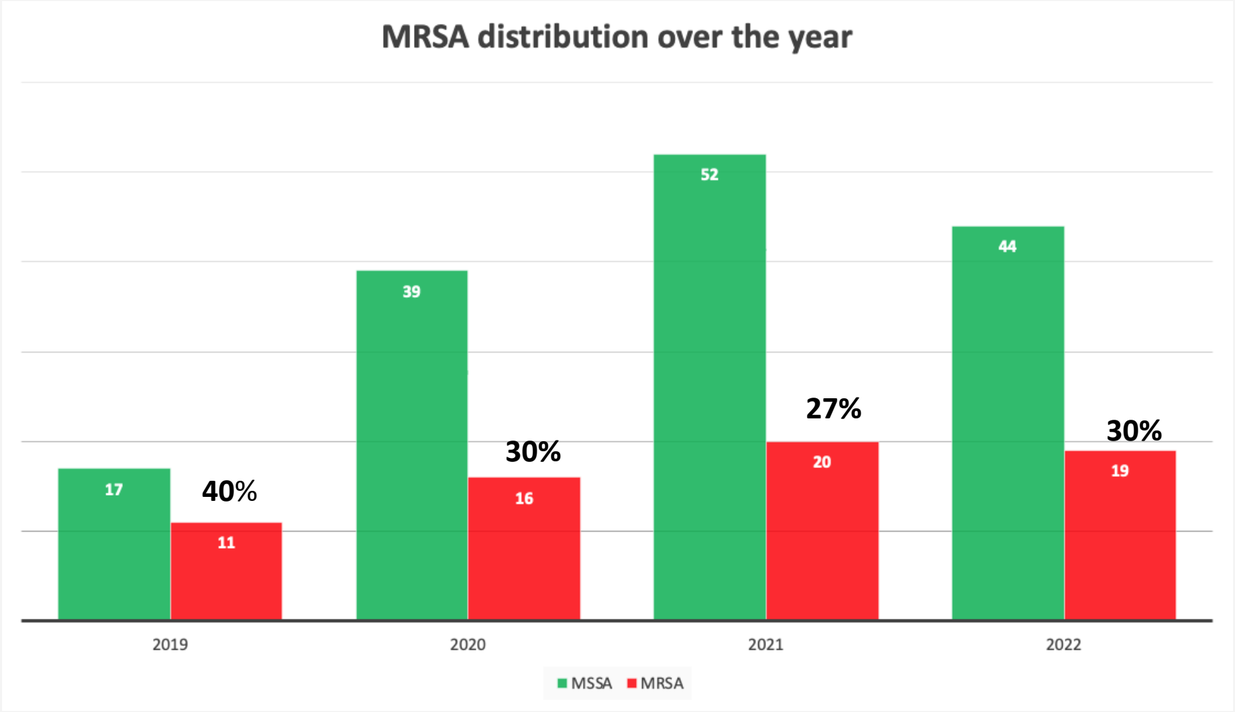
*Charlson Comorbidity Index: Predicts 10-year survival in patients with multiple comorbidities (0 – 33 pts)
*PITT score: severity of acute illness index (0 – 14 pts)

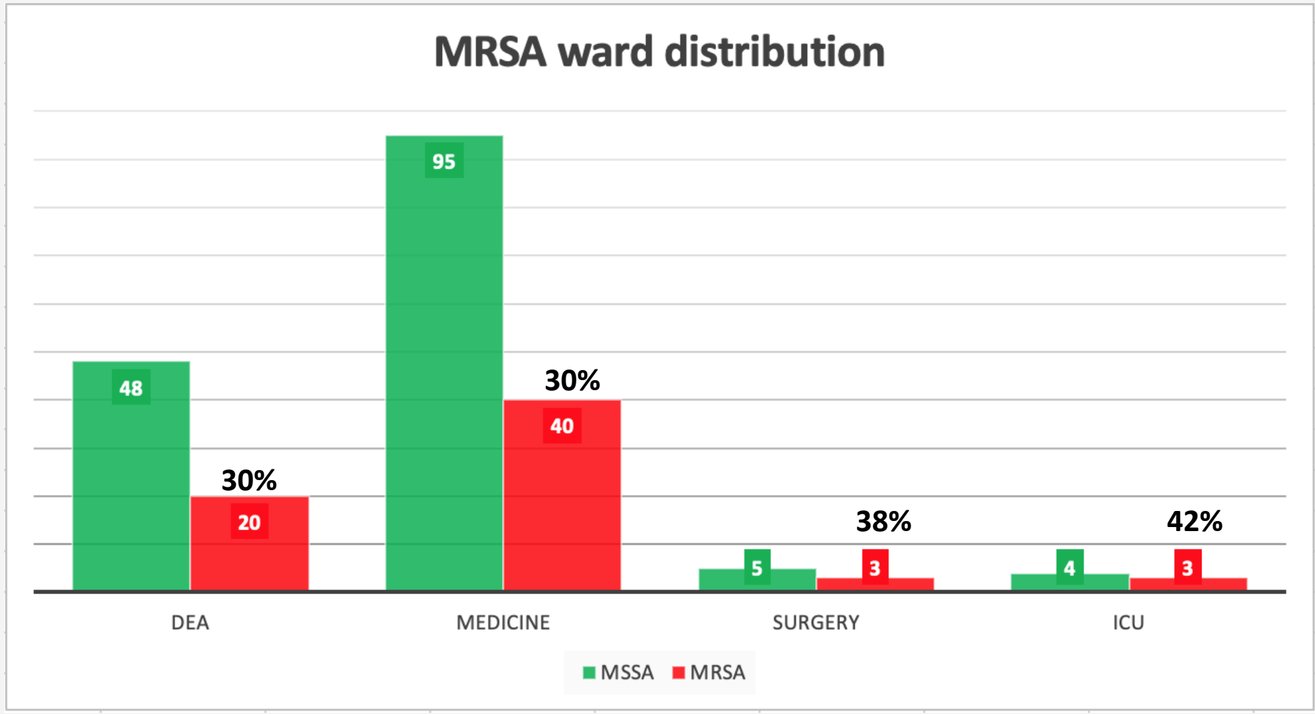
- Nosocomial BSI defined by positive BC after 72h from the admission: 113 nosocomial SAB were found **(52%).**

- Average time of nosocomial BSI: 9 days from the admission (IQR 5-14 days).



MRSA prevalence 66 cases (30%)



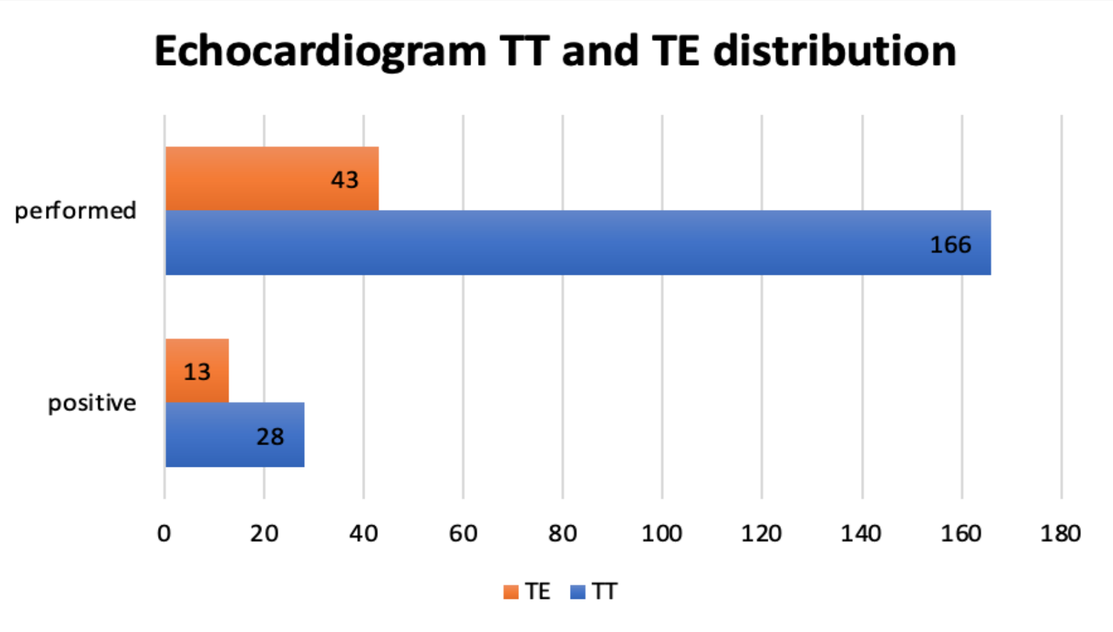


Risk factors associated with MRSA

	MSSA (152)	MRSA (66)	p
Male (%)	90 (59%)	39 (59%)	0.98
Age (IQR)	75 (60-83)	77 (64-83)	0.73
Charlson (median, IQR)	6.5 (4.5-8.0)	6.5 (5-9)	0.17
Permanent endovascular devices	39 (25)	12 (18)	0.23
Dialysis	19 (12)	18 (12)	0.93
Orthopedic prosthesis	**7 (4%)**	**10 (15%)**	**0.007**
CVC	44 (29)	20 (30)	0.9
Ward DEA Medicine Surgery ICU	 48 (31%) 95 (62%) 5 (3.2%) 4 (2.6%)	 20 (30.3%) 40 (60.6%) 3 (4.5%) 3 (4.5%)	0.85
Nosocomial BSI	77 (50%)	36 (54.5%)	0.59
TD	18 (11.8%)	2 (3%)	0.11
Time onset BSI	3 (0-9)	3.5 (0-11)	0.6

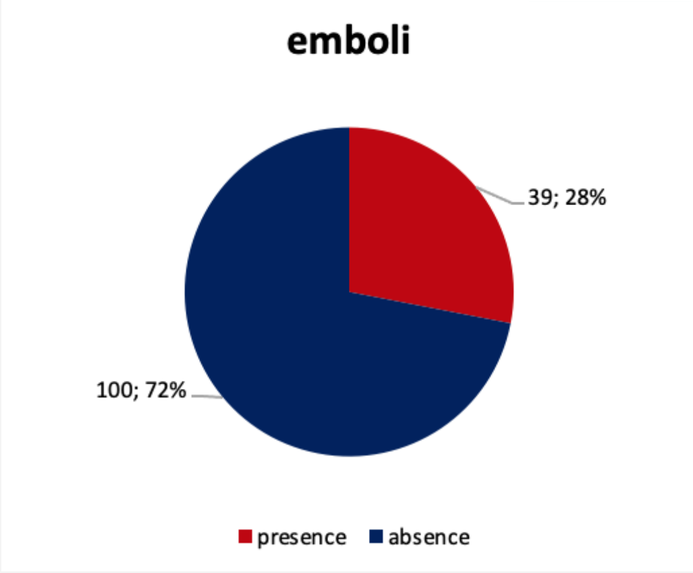
	OR of MRSA	p
Orthopedic prosthesis	3.6 (1.3-10.1)	0.015

Diagnostic work-up



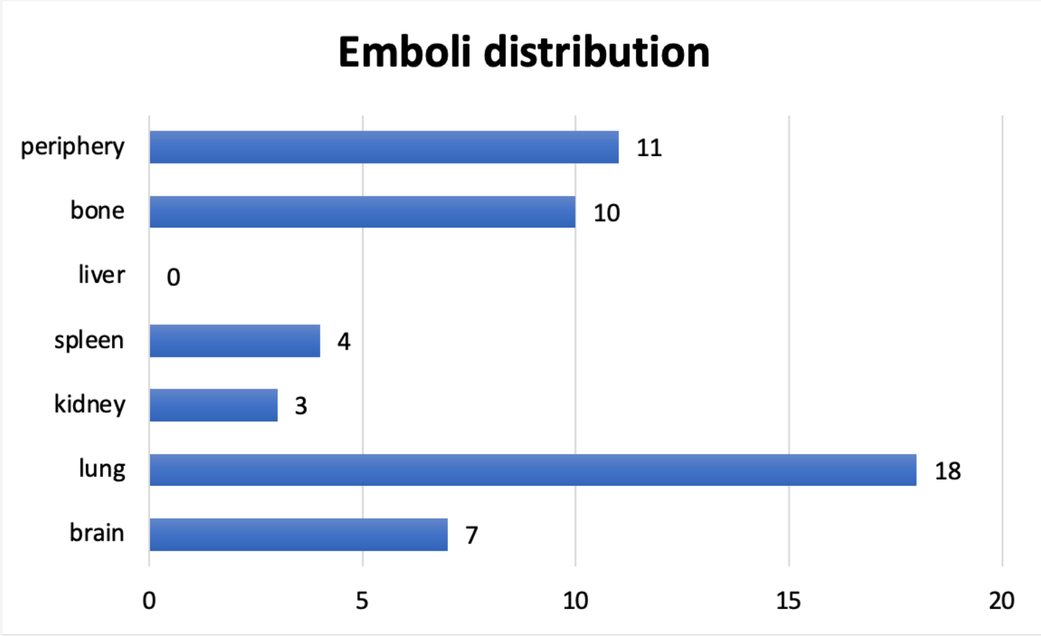
Emboli were investigated in 139 cases **(63%),** performing:

- 115 CT scan (brain, chest, abdomen, others)
- 35 RMN
- 16 PET-CT



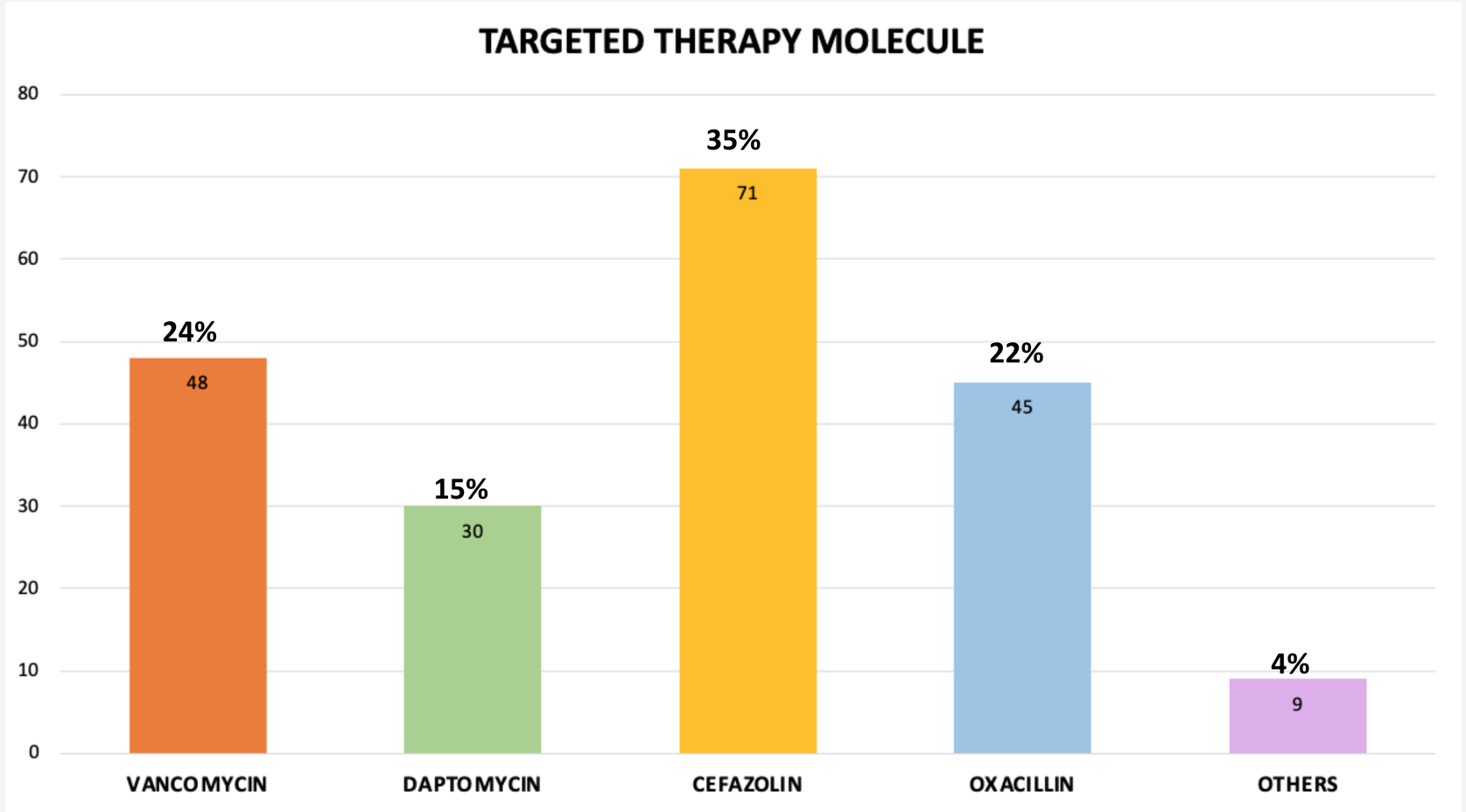
An ecoTT was performed in 166 cases (75%);
An ecoTE was performed in 43 cases (20%). In 10 cases as first exam, in 33 cases was used to confirm doubtful TT:
- in 7 cases the vegetation was confirmed
- in 3 cases the vegetation was excluded
- in 4 cases TE was positive with a negative TT

As a result, endocarditis was diagnosed in 38 cases (28%) of 133 performed TT or TE (60%)



Therapy

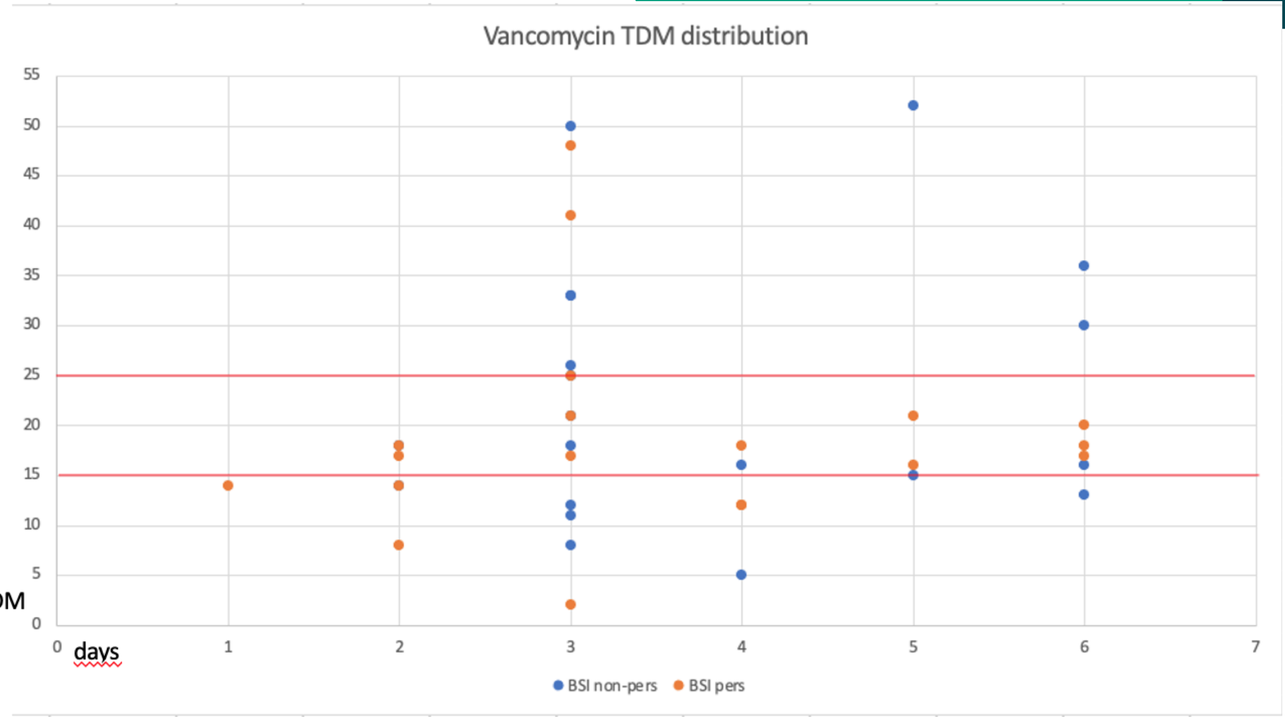
- 143 (79%) patients started an adequate empirical therapy (including an antibiotic effective)
- The median time to anti-Staphylococcus therapy was about 1.5 days (IQR 0-3 days)



Vancomycin Therapeutic Drug Monitoring distribution

In 48 cases vancomycin was used, and in 34 cases a TDM was performed.

26 TDM were checked at 72h;
19 TDM were checked at 6 days.
9 TDM were performed after 7 days from the start of ABT.



	TDM below range	TDM in range	TDM above range
72h	10 (38%)	10 (38%)	6 (23%)
6 days	5 (26%)	10 (52%)	4 (21%)
overall	16 (30%)	25 (47%)	12 (23%)

Risk factors associated with persistent SAB

Control blood coltures were performed in 171 cases.

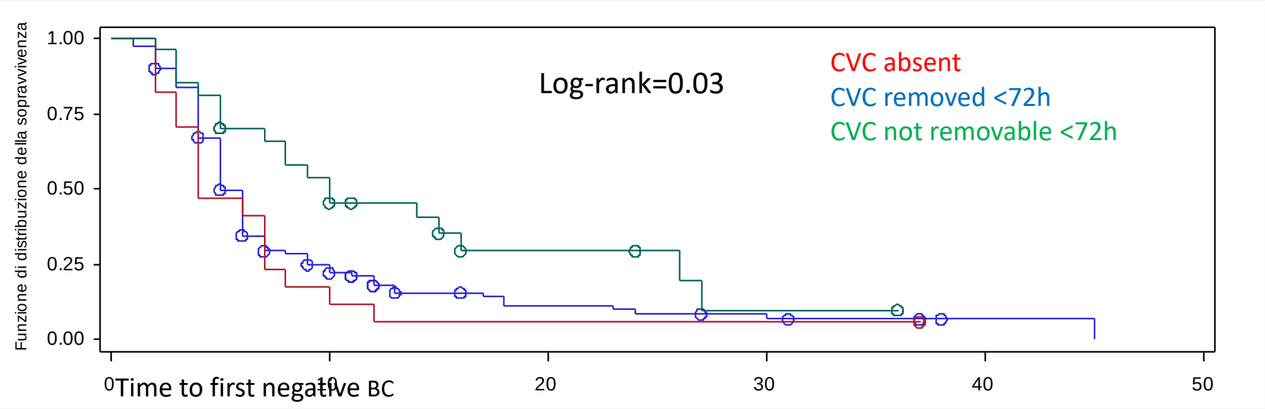
- 64 Persistent bacteremia >= 72h **(38%)**
- 22 Persistent bacteremia > 7 days **(13%)**

	Overall (219)	Non pers BSI (107)	Pers BSI >= 72h (64)	p
Gender M (%)	129 (58.9%)	62 (58%)	42 (66%)	0.31
Age (IQR)	**75 (61-83)**	**77 (66-83)**	**68 (56-80)**	**0.016**
Charlson (IQR)	6 (5-9)	7 (5-9)	6 (4-8)	0.21
PITTs	0 (0-1)	0 (0-1)	0 (0-1)	0.18
Vascular devices (%)	51 (23%)	22 (20%)	17 (27%)	0.36
Dialysis (%)	27 (12%)	11 (13%)	10 (16%)	0.582
Orthopedic prosthesis (%)	17 (8%)	8 (9%)	5 (8%)	0.781
CVC (%)	**64 (30%)**	**28 (26%)**	**25 (39%)**	**0.07**
CVC not removable	**32 (15%)**	**11 (10%)**	**14 (22%)**	**0.03**
MRSA (%)	66 (30%)	31 (28%)	23 (36%)	0.34
Nosocomial BSI (%)	113 (52%)	45 (51%)	29 (45%)	0.478
Cardiac vegetation	33 (18%)	15 (15%)	14 (24%)	0.14
Embolization	**39 (18%)**	**13 (12%)**	**22 (34%)**	**0.006**
Adequate empiric therapy	143 (79%)	75 (79%)	41 (80%)	0.93
Time to antistaphylo-Tp	1.5 (0-3)	2 (1-3)	1 (0-2)	0.10
Therapy				
Cefazolin	71 (32.2%)	**45(42%)**	**17 (26%)**	**0.04**
Oxacillin	45 (20.4%)	23 (21%)	17 (26%)	0.44
Vancomycin	30 (13.6%)	18 (16%)	17 (26%)	0.12
Daptomycin	48 (21.8%)	14 (13%)	12 (18%)	0.31

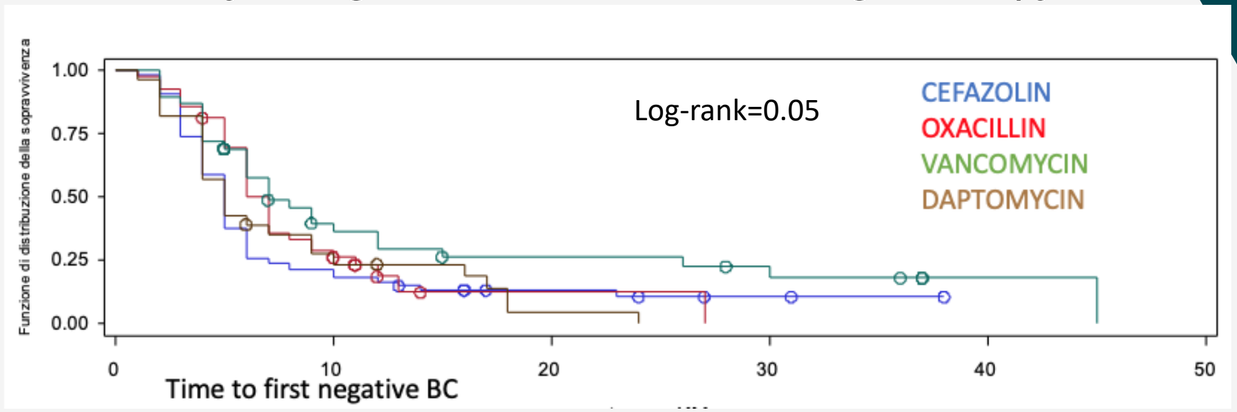
Risk factors associated with persistent bacteremia

The median time from the first positive blood culture to the first negative is 5 days (IQR 4-7 days)

Probability of negative blood culture according to CVC removal



Probability of negative blood culture according to therapy



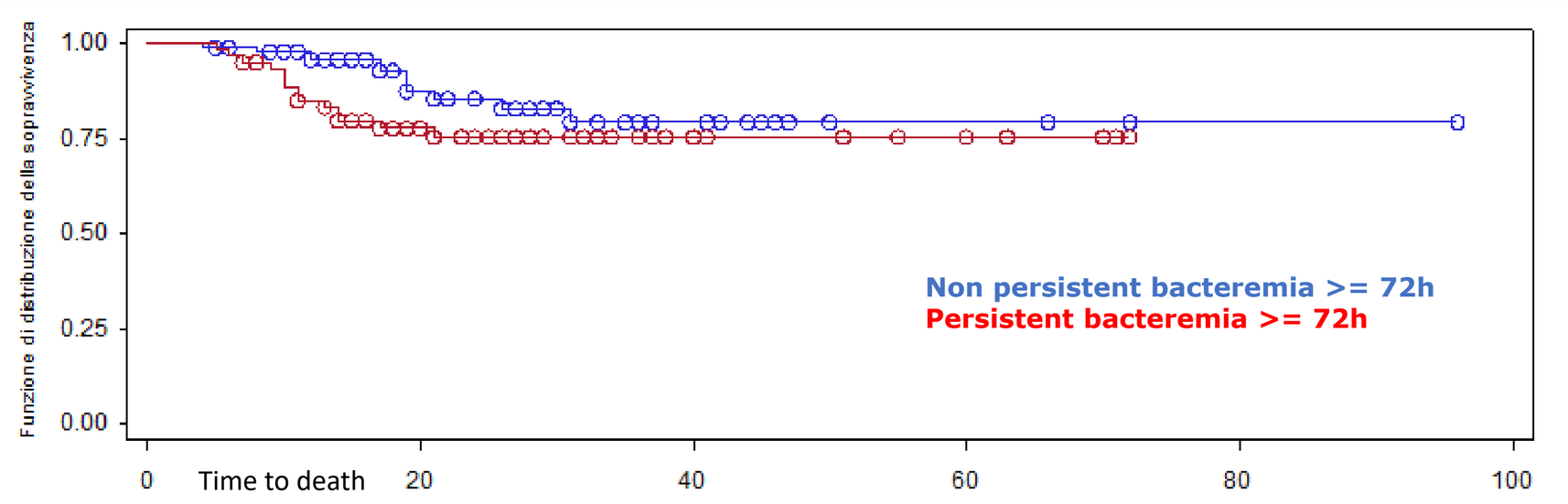
	OR PB>= 72h	p	aOR PB >= 72h	p	aOR PB >7gg	p
Age (year older)	**0.9 (0.95-0.99)**	**0.02**	0.98 (0.96-1.01)	0.3	0.9 (0.9-1.0)	0.05
CVC absent	1		1		1	
CVC removed <72h	1.2 (0.5-2.9)	0.5	1.3 (0.5-3.5)	0.8	0.6 (0.1-3.4)	0.1
CVC not removable <72h	**2.8 (1.16-7.0)**	**0.04**	2.1 (0.8-6.1)	0.2	2.9 (0.7-12.6)	0.09
MRSA	1.5 (0.7-2.9)	0.2				
Adequate empiric tp.	0.8 (0.3-2.16)	0.8	1.1 (0.3-3.4)	0.8	0.3 (0.06-1.5)	0.1
Time to antistafilo-tp	0.8 (0.6-1.0)	0.19				
Cardiac vegetation	1.7 (0.7-4.1)	0.17				
Therapy						
CEFAZOLIN	1		1		1	
OXACILLIN	1.9 (0.8-4.5)	0.11	1.8 (0.7-4.6)	0.7	4.8 (1-22)	0.05
VANCOMYCIN	**2.5 (1.0-5.9)**	**0.03**	3.1 (1.0-9.8)	0.05	3.3 (0.5-20)	0.5
DAPTOMYCIN	2.2 (0.8-5.8)	0.09	2.0 (0.6-6.7)	0.8	1.2 (0.1-10)	0.4

Persistent bacteremia and risk of embolization

	OR emboli	p	aOR	p
Persistent BSI >=72h	3.7 (1.7-8.1)	0.0009	3.7 (1.6-8.6)	0.002
Persistent BSI > 7 days	10.3 (3.8-27.7)	<0.0001		
Cardiac vegetation	3.3 (1.4-7.5)	0.004	2.2 (0.8-5.9)	0.1

30-days in-hospital mortality and risk factors

In-hospital mortality within 30 days from the first positive blood culture: 30% (IC95% 24 – 36)



	HR	p	aHR	p
Age	**1.05 (1.02-1.08)**	**<0.0001**		
Persistent BSI >= 72h	1.6 (0.7-3.4)	0.22	1.5 (0.67-3.38)	0.32
Persistent BSI > 7 days	1.5 (0.5-4.1)	0.44		
MRSA	1.0 (0.6-1.8)	0.85	1.06 (0.3-3.3)	0.9
Adequate antibiotic tp.	0.7 (0.4-1.4)	0.34	0.7 (0.2-2.5)	0.7
PITT (for add unit)	**1.36 (1.13-1.69)**	**0.0008**	1.19 (0.8-1.6)	0.3
Charlson (for add unit)	**1.18 (1.08-1.29)**	**0.002**	**1.16 (1.0-1.33)**	**0.04**

Conclusions

- Prevalence of persistent SAB at San Paolo Hospital is 38%;

- The probability of microbiological clearance differs according to:
  -pathogen and therapy, being lower for MRSA on therapy with vancomycin;
  -the presence of vascular device, in particular CVC not removable within 72h is associated with persistent SAB;

- In-hospital mortality within 30 days from SAB is 30%. The risk increases with persistent SAB, and PITT score, but the main driver remains comorbidity.

Limitations

- Small sample size (only 64 persistent SAB for the moment)
- Retrospective study

Bibliography

1. Chong, Y. P., Park, S. J., Kim, H. S., Kim, E. S., Kim, M. N., Park, K. H., Kim, S. H., Lee, S. O., Choi, S. H., Jeong, J. Y., Woo, J. H., & Kim, Y. S. (2013). Persistent staphylococcus aureus bacteremia: A prospective analysis of risk factors, outcomes, and microbiologic and genotypic characteristics of isolates. Medicine (United States), 92(2), 98–108. https://doi.org/10.1097/MD.0b013e318289ff1e
2. Fowler, V. G., Olsen, M. K., Corey, ; G Ralph, Woods, C. W., Cabell, C. H., Reller, ; L Barth, Cheng, A. C., Dudley, T., & Oddone, E. Z. (n.d.). Clinical Identifiers of Complicated Staphylococcus aureus Bacteremia. https://jamanetwork.com/
3. Fowler, V. G., Sanders, L. L., Sexton, D. J., Kong, L., Marr, K. A., Gopal, A. K., Gottlieb, G., Mcclelland, R. S., & Corey, G. R. (n.d.). Outcome of Staphylococcus aureus Bacteremia According to Compliance with Recommendations of Infectious Diseases Specialists: Experience with 244 Patients. https://academic.oup.com/cid/article/27/3/478/280719
4. Guimaraes, A. O., Cao, Y., Hong, K., Mayba, O., Peck, M. C., Gutierrez, J., Ruffin, F., Carrasco-Triguero, M., Dinoso, J. B., Clemenzi-Allen, A., Koss, C. A., Maskarinec, S. A., Chambers, H. F., Fowler, V. G., Baruch, A., & Rosenberger, C. M. (2019). A prognostic model of persistent bacteremia and mortality in complicated Staphylococcus aureus bloodstream infection. Clinical Infectious Diseases, 68(9), 1502–1511. https://doi.org/10.1093/cid/ciy739
5. Hawkins, C., Huang, J., Jin, N., Noskin, G. A., Zembower, T. R., & Bolon, M. (n.d.). Persistent Staphylococcus aureus Bacteremia An Analysis of Risk Factors and Outcomes. https://jamanetwork.com/
6. Holland, T. L., Bayer, A. S., & Fowler, V. G. (2022). Persistent MRSA Bacteremia: Resetting the Clock for Optimal Management. Clinical Infectious Diseases. https://doi.org/10.1093/cid/ciac364
7. Kathib, R., Johnson, L. B., Fakih, M. G., Riederer, K., Khosrovaneh, A., Tabriz, M. S., Sharma, M., & Saeed, S. (2006). Persistence in staphylococcus aureus bacteremia: Incidence, characteristics of patients and outcome. Scandinavian Journal of Infectious Diseases, 38(1), 7–14. https://doi.org/10.1080/00365540500372846
8. Kathib, R., Johnson, L. B., Sharma, M., Fakih, M. G., Ganga, R., & Riederer, K. (2009). Persistent Staphylococcus aureus bacteremia: Incidence and outcome trends over time. Scandinavian Journal of Infectious Diseases, 41(1), 4–9. https://doi.org/10.1080/00365540802441711
9. Khuel, R., Morata, L., Boeing, C., Subirana, I., Seifert, H., Rieg, S., Kern, W. V., Kim, H. Bin, Kim, E. S., Liao, C. H., Tilley, R., Lopez-Cortés, L. E., Llewelyn, M. J., Fowler, V. G., Thwaites, G., Cisneros, J. M., Scarborough, M., Nsutebu, E., Gurgui Ferrer, M., … Price, J. (2020). Defining persistent Staphylococcus aureus bacteraemia: secondary analysis of a prospective cohort study. The Lancet Infectious Diseases, 20(12), 1409–1417. https://doi.org/10.1016/S1473-3099(20)30447-3
10. Lee, Y. M., Chong, Y. P., Kim, M., Eom, Y., Kim, E. S., Kim, M., Park, K. H., Kim, S. H., Lee, S. O., Choi, S. H., Woo, J. H., & Kim, Y. S. (2020). Long-term methicillin-resistant Staphylococcus aureus bacteremia persisting for more than 2 weeks: risk factors and outcomes. European Journal of Clinical Microbiology and Infectious Diseases, 39(4), 773–781. https://doi.org/10.1007/s10096-019-03795-6
11. Minejima, E., Mai, N., Bui, N., Mert, M., Mack, W. J., She, R. C., Nieberg, P., Spellberg, B., & Wong-Beringer, A. (2020). Defining the Breakpoint Duration of Staphylococcus aureus Bacteremia Predictive of Poor Outcomes. Clinical Infectious Diseases, 70(4), 566–573. https://doi.org/10.1093/cid/ciz257
12. Ok, H. S., Lee, H. S., Park, M. J., Kim, K. H., Kim, B. K., Wi, Y. M., & Kim, J. M. (2013). Predictors and clinical outcomes of persistent methicillin-resistant Staphylococcus aureus bacteremia: A prospective observational study. Korean Journal of Internal Medicine, 28(6), 678–686. https://doi.org/10.3904/kjim.2013.28.6.678
13. Tabah A, Laupland KB. Update on Staphylococcus aureus bacteraemia. Curr Opin Crit Care. 2022 Oct 1;28(5):495-504. doi: 10.1097/MCC.0000000000000974. Epub 2022 Aug 4. PMID: 35942696.
14. Tong SY, Davis JS, Eichenberger E, Holland TL, Fowler VG Jr. Staphylococcus aureus infections: epidemiology, pathophysiology, clinical manifestations, and management. Clin Microbiol Rev. 2015 Jul;28(3):603-61. doi: 10.1128/CMR.00134-14. PMID: 26016486; PMCID: PMC4451395.
15. Tubiana, S., Duval, X., Alla, F., Selton-Suty, C., Tattevin, P., Delahaye, F., Piroth, L., Chirouze, C., Lavigne, J. P., Erpelding, M. L., Hoen, B., Vandenesch, F., Iung, B., & Le Moing, V. (2016). The VIRSTA score, a prediction score to estimate risk of infective endocarditis and determine priority for echocardiography in patients with Staphylococcus aureus bacteremia. Journal of Infection, 72(5), 544–553. https://doi.org/10.1016/j.jinf.2016.02.003
16. Van der Vaart, T. W., Prins, J. M., Soetekouw, R., van Twillert, G., Veenstra, J., Herpers, B. L., Rozemeijer, W., Jansen, R. R., Bonten, M. J. M., & van der Meer, J. T. M. (2022). All-Cause and Infection-Related Mortality in Staphylococcus aureus Bacteremia, a Multicenter Prospective Cohort Study. Open Forum Infectious Diseases, 9(12). https://doi.org/10.1093/ofid/ofac653
17. van Hal SJ, Jensen SO, Vaska VL, Espedido BA, Paterson DL, Gosbell IB. Predictors of mortality in Staphylococcus aureus Bacteremia. Clin Microbiol Rev. 2012 Apr;25(2):362-86. doi: 10.1128/CMR.05022-11. PMID: 22491776; PMCID: PMC3346297.
18. Weis S, Kesselmeier M, Davis JS, Morris AM, Lee S, Scherag A, Hagel S, Pletz MW. Cefazolin versus anti-staphylococcal penicillins for the treatment of patients with Staphylococcus aureus bacteraemia. Clin Microbiol Infect. 2019 Jul;25(7):818-827. doi: 10.1016/j.cmi.2019.03.010. Epub 2019 Mar 27. PMID: 30928559.
19. Wozniak JM, Mills RH, Olson J, Caldera JR, Sepich-Poore GD, Carrillo-Terrazas M, Tsai CM, Vargas F, Knight R, Dorrestein PC, Liu GY, Nizet V, Sakoulas G, Rose W, Gonzalez DJ. Mortality Risk Profiling of Staphylococcus aureus Bacteremia by Multi-omic Serum Analysis Reveals Early Predictive and Pathogenic Signatures. Cell. 2020 Sep 3;182(5):1311-1327.e14. doi: 10.1016/j.cell.2020.07.040. PMID: 32888495; PMCID: PMC7494005.
20. Rose W, Fantl M, Geriak M, Nizet V, Sakoulas G. Current Paradigms of Combination Therapy in Methicillin-Resistant Staphylococcus aureus (MRSA) Bacteremia: Does it Work, Which Combination, and For Which Patients? Clin Infect Dis 2021; 73(12): 2353-60

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