PROF. GIANCARLO CECCARELLI (Orcid ID : 0000-0001-5921-3180)

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Superinfections in patients treated with Teicoplanin as anti-SARSCoV2 agent

Giancarlo Ceccarelli [1-2], Francesco Alessandri [2-3], Alessandra Oliva [1-2], Serena Dell'Isola [4], Monica Rocco [5], Franco Ruberto [2-3], Francesco Pugliese [2-3], Gabriella d'Ettorre [1-2], Mario Venditti [1-2]

1) Department of Public Health and Infectious Diseases, Sapienza University of Rome, Rome, Italy.

2) Azienda Ospedaliero-Universitaria Policlinico Umberto I, Rome, Italy.

3) Department of Anaesthesiology and Intensive Care, Sapienza University of Rome, Rome, Italy.

4) Belcolle Hospital, Viterbo, Italy.

5) Intensive Care Unit, S. Andrea Hospital, Sapienza University of Rome, Rome, Italy.

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Corresponding author: Giancarlo Ceccarelli, MD PhD MSc. Department of Public Health and Infectious Diseases Sapienza University of Rome, Viale del Policlinico 155, 00161 Rome Italy. Tel 0039-06-49970905, E-mail giancarlo.ceccarelli@uniroma1.it

Dear Editor,

We read with interest the paper by Giacobbe *et al.* estimating a cumulative risk of developing at least one bloodstream infection (BSI) episode (largely due to Gram-positive pathogens) of almost 50% after 30 days at risk in severe COVID-19 patients. (2) Similarly, Somers *et al.* reported an increased risk to develop bacterial superinfections, principally represented by *Staphylococcus aureus* ventilatory associated pneumonia (VAP), in critically ill patients infected with SARS-CoV-2 and treated with Tocilizumab. (1) We previously described a cohort of intubated patients affected by SARS-CoV-2 pneumonia treated with the best available therapy (BAT), including Tocilizumab, and associated with Teicoplanin. (3) This glycopeptide antibiotic was used with a double purpose: as antiviral agent for COVID-19 and as empiric treatment of possible *S. aureus* superinfection since the latter may represent a major complication of respiratory viral infections. (4-5) The study showed that only 19% (4/21 subjects) of patients treated with BAT plus Tocilizumab and Teicoplanin had an isolation of methicillin-resistant/teicoplanin-susceptible *S. aureus* from respiratory secretions and none had Gram-positive superinfections. (5) Here we reported an update of the previous data, analysing bacterial infections in a retrospective multicentric cohort study enrolling 55 mechanically ventilated, SARS-CoV-2 infected patients treated with BAT and Tocilizumab (Tei-COVID Study). Reporting of the study conforms to broad EQUATOR guidelines. (6) For 34 subjects treatment included also a median of 8 days (range 6-12) course of Teicoplanin administration (6 mg/kg every 24h with loading dose every 12 h for three doses, started on ICU admission). Ad interim BAT was compliant with suggestion of the Italian Society of Infectious and Tropical Diseases (SIMIT) and largely based on hydroxychloroquine 200 mg twice/daily plus Azithromycin 500 mg daily. (7) Tocilizumab 8 mg/kg (up to a maximum of 800 mg/dose) twice with an interval of 12h was administered in all patients. As showed in table 1, Gram-positive superinfections were less frequent in Teicoplanin-treated group than in untreated and their incidence in Teicoplanin-treated was lower than that observed in other studies. (1,2) In particular, among 34 patients treated, 35% (12/34) developed a superinfection and only 16% BSIs and 6% bacterial lung superinfections due to Gram-positive pathogens. The 21 Teicoplanin-untreated patients had an incidence of Gram-positive superinfections, comparable to what Somers and Giacobbe previously reported. Interestingly, we observed a higher number of Gram-negative BSI and VAP probably related with the changes in the abundance of aerobic bacteria in the intestinal microbiota associated with administration of

Teicoplanin and SARS-CoV-2 infection. (8-9) Nevertheless the higher number of Gram-negative superinfections observed in Teicoplanin-treated group could be also influenced by a longer follow up time (median 20 days, range 4-39) than that of the other studies.

Based on our data, the use of Teicoplanin could have represented a contributing factor in the reduction of the incidence of Gram-positive superinfections in mechanically ventilated patients with COVID-19. Further investigations are needed to clarify the possible impact of Teicoplanin on host microbiome and on the possible development of glycopeptide resistance in this setting. On the other hand, Teicoplanin role as an antiviral agent for COVID-19 still remains under investigation.

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TABLE 1: Characteristics of patients, including causative agents of superinfection in patients treated or untreated with Teicoplanin: comparison between the results of our data (so called "Tei-COVID Study" and highlighted in grey) and other 2 key studies.

Study	**Tei-COVID Study**				**Somers EC *et al. (1)****				**Giocobbe DR *et al.* (2)**	
Setting	Mechanically ventilated COVID-19 patients				Mechanically ventilated COVID-19 patients				ICU critically ill COVID-19 patients	
Characteristics of patient enrolled	**Number**: 55				154				78	
	Age: 66 y ± 12.1				58 y ± 14.9				66 y (57-70)[§]	
	Sex: 43 M, 12 F				102 M, 54 F				70 M, 12 F	
	CCI: 3 (range 0-6)				Not reported				Not reported	
Pts with a superinfection									only BSI	
○ Overall %	24/55 (43.6%)				62/154 (40.2%)				31/78 (39.7%)	
○ Tocilizumab										
- *treated*	43.6%				54%				-	
- *untreated*	-				26%				-	
○ Teicoplanin										
- *treated*	12/34 (35%)				-				-	
- *untreated*	9/21 (42,8%)				-				-	
Treatment and causative microbiology										
Teicoplanin	Treated 34		Untreated 21		Untreated 154				Untreated 78	
Tocilizumab	Yes 34		Yes 21		Yes 78		No 76		Yes 18	No 60
Superinfection N° isolates/pts	BSI 12/34	VAP 31/34	BSI 12/21	VAP 18/21	BSI 12/78	VAP 41/78	BSI 8/76	VAP 22/76	BSI 23/18	BSI 22/60

Causative microbiology↓									Overall data 45/78
S. aureus (overall)	8%	6%	17%	22%	9%	51%	14%	50%	13%
- MSSA	*0%*	*50%*	*0%*	*0%*	*100%*	*71%*	*0%*	*45%*	-
- MRSA	*100%*	*50%*	*100%*	*100%*	*0%*	*29%*	*100%*	*55%*	-
CONS	-	-	50%	-	33%	-	38%	-	24%
Enterococcus spp.	8%	-	33%	-	25%	-	25%	-	27%
P. aeruginosa	-	26%	-	-	-	12%	-	18%	4%
E. coli	-	-	-	-	-	10%	-	5%	2%
E. aerogenes		6%	-	-	-	10%	-	5%	9%
K. pneumoniae	25%	13%	-	22%	-	7%	-	5%	-
S. marcescens	-	-	-	-	-	7%	-	0%	-
S. maltophilia	-	-	-	22%	-	5%	-	0%	-
A. baumannii	25%	17%	-	33%	-	2%	-	5%	-
Candida spp	17%	-	-	-	25%	-	13%	-	7%
Other	17%	32%	-	-	27%	15%	14%	18%	14%
Overall Gram +	16%	6%	100%	22%	67%	51%	77%	50%	64%

Legend: ICU = intensive care unit, MSSA = Methicillin susceptible *S. aureus*, MRSA = Methicillin resistant *S. aureus*, CONS = Coagulase negative *Staphylococcus*, y = years, Pt = patients, VAP = ventilatory associated pneumonia, BSI = bloodstream infection, CCI = Charlson Comorbidity Index, M = males, F = females. Polymicrobial infections were considered as separate events, one for each causative organism isolated. (§) expressed as median and IQR. (*) Somers *et al.* reported that in their study pathogen numbers can add up to > 100% due to polymicrobial infections.