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Original Article

Clinical presentation of secondary infectious complications in COVID-19 patients in intensive care unit treated with tocilizumab or standard of care

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ABSTRACT

Objectives: The hypothesis of this study is that tocilizumab should affect common signs of infection due to its immunosuppressive properties. Primary aim of the study was to investigate whether the administration of tocilizumab to critically ill patients with COVID-19, led to a different clinical presentation of infectious complications compared to patients who did not receive tocilizumab. Secondary aim was investigating differences in laboratory parameters between groups.

Methods: Single-centre retrospective study, enrolling COVID-19 patients who developed a microbiologically confirmed infectious complication [ventilator associated pneumonia or bloodstream infection] after intensive care unit [ICU] admission and either treated with tocilizumab or not [controls].

Results: A total of 58 patients were included, 25 treated with tocilizumab and 33 controls. Median time from tocilizumab administration to infection onset was 10 days [range 2-26]. Patients were 78% male, with median age 65 years [range 45-79]. At first clinical presentation of the infectious event, the frequency of hypotension [11/25, 44% vs. 11/33, 33%], fever [8/25, 32% vs. 10/33, 30%] or hypothermia [0/25,0%, vs. 2/33, 6%], and oxygen desaturation [6/25, 28% vs 4/33, 12%], as well as the frequency of SOFA score increase of $\geq$ 2 points [4/25, 16%,vs. 4/33, 12%] was similar in tocilizumab treated patients and controls [p>0.1 for all comparisons]. Among laboratory parameters, C-Reactive Protein elevation was reduced in tocilizumab treated patients compared to controls [8/25, 32% vs. 22/33, 67%, p=0.009].

Conclusion: The clinical features of infectious complications in critically ill patients with COVID-19 admitted to ICU were not affected by tocilizumab.

1. Background

Tocilizumab is a recombinant humanized monoclonal antibody developed against soluble and membrane-bound isoforms of the interleukin-6 [IL-6] receptor. It prevents the binding of IL-6 to its receptor, thus inhibiting the IL-6 inflammatory cascade [1]. In the first phase of the severe acute respiratory syndrome coronavirus-2 [SARS-CoV-2] pandemic [2,3], tocilizumab has been proposed to counteract the cytokine release syndrome observed in the severe forms of the SARS-CoV-2 disease [COVID-19] [1,4]. Ever since, it has been argued whether such a powerful immune suppressor drug could attenuate or mask the clinical and laboratory manifestations of infectious complications, particularly in critically ill patients admitted to the intensive care unit [ICU] [5].

The definitive diagnosis of an infection is often challenging in the ICU where multiple causes of critical illness can confuse the clinical picture, and the severity of patients' clinical presentation often leads to an overuse of antibiotics, which is reported in up to 70% of ICU patients

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[6]. In patients with COVID-19, the assessment becomes even more complex because the evolution of the viral infection can cause symptoms that overlap with those of a bacterial superinfection, such as fever or respiratory and hemodynamic worsening. The overall picture may be further confused by the use of glucocorticoids, which is suggested in patients with severe COVID-19 [7,8],but masking fever, besides leading to an increase in neutrophils and leukocytes, another sign that overlaps with bacterial infection. The use of tocilizumab in such populations is still under investigation due to conflicting results from several randomized clinical trials [RCTs]. Although the first RCTs showed that tocilizumab did not reduce short-term mortality in COVID-19 patients [9–12], a recent meta-analysis found that it was associated with lower mortality in cohort studies [13], with higher likelihood of providing survival advantage in hyper-inflamed COVID-19 patients when initiated before the establishment of severe respiratory failure [14,15]. Moreover, cumulative moderate certainty evidence exists, derived from both cohort studies and RCTs, which shows that tocilizumab reduces the risk of mechanical ventilation in hospitalized COVID-19 patients [13]. Finally, the preliminary results of RECOVERY and REMAP-CAP trials found a potential benefit in critically ill patients [16,17], while a recent randomized open-label trial found that tocilizumab was associated with more adverse events and worse outcomes [18]. The guidelines for tocilizumab use are continuously being updated, and while tocilizumab was not recommended as a standard of care for COVID-19 until February 2021, the latest version of the Infectious Diseases Society of America Guidelines suggests its use in cases of severe or critical disease with elevated markers of systemic inflammation [7]. However, more information is required about its use in clinical practice and especially in critically ill patients, where the question of whether tocilizumab might affect common signs of infection due to its immunosuppressive properties remains [9,19,20]. Observational studies evaluating tocilizumab use, particularly in cohorts of critically ill patients, have yielded mixed results on mortality [13,21–23], whereas they found no significant differences in the rate of secondary infectious events or death due to non-COVID 19 infections compared with patients who did not receive tocilizumab [21–23]. However, even though patients were closely monitored for signs and symptoms of secondary infections, infection rates ranged from zero to 18%, lower than expected for critically ill patients [21–23]. This might suggest the possibility of underdiagnosis due to atypical presentations of secondary infections. In addition, the clinical and laboratory presentations of secondary infections were not specifically addressed in these studies [21–23] thus leaving a knowledge gap on this issue, which may be very important in the management of the increasing number of patients eligible for tocilizumab. The primary aim of the present study was to investigate whether the administration of tocilizumab to critically ill patients with COVID-19 led to a different clinical presentation of infectious complications compared to patients who did not receive tocilizumab.

2. Methods

2.1. Study setting and population

This was a single-centre retrospective case-series, conducted in two ICUs [27 and 12 beds, respectively] at San Martino Hospital - IRCCS [Genoa, Italy], a 1200-bed teaching hospital in Northern Italy. The primary aim of the study was to investigate the clinical presentation of the infectious episodes occurring in critically ill patients with COVID-19 who received tocilizumab [cases], compared with those who did not receive tocilizumab [controls]. Secondary aims were describing the laboratory parameters at the occurrence of the infectious event and the microbiological etiologies. Criteria for tocilizumab use in our center have been previously described [4]. Briefly, tocilizumab has been introduced for the treatment of COVID-19 in addition to the standard of care since March 11th, 2020, in case of severe pneumonia and systemic inflammation [fever $>$ 38°C, C-reactive protein [CRP] 10 times above the upper limit of normal [ULN] of 5 mg/L, ferritin 2 times above the ULN of 400 μg/L, or IL-6 10 times above the ULN of 3.4 ng/L]. Tocilizumab was administered intravenously at 8mg/kg [maximum 800mg], with the possibility of repeating the dose after 24 hours if no response was obtained. Subcutaneous formulation [162 mg] was also allowed. The use of tocilizumab was thereafter stopped in our center after the June 17th press release by the Agenzia Italiana del Farmaco [AIFA] disseminating the results of the Italian multicenter, open-label, randomized trial of early administration of tocilizumab in patients with COVID-19 pneumonia, in which no benefit on disease progression was observed in patients treated with tocilizumab [12], in accordance with international guidelines [24]. Clinical charts of patients diagnosed with COVID-19 and hospitalized in the participating ICUs between February 29th, 2020 and May 31st, 2020 were reviewed. All patients with a microbiologically documented infection occurring during ICU stay were included. For patients with more than one infectious complication during hospital stay, only the first episode after ICU admission was considered.

2.2. Data collection

Demographical, clinical and laboratory information were retrospectively collected for each patient, at the time of the first infectious complication onset and 24-48 hours earlier including sex, age, total leucocyte and neutrophil counts, procalcitonin [PCT], CRP values, etiology and site of infection.

Upon infection onset, the following clinical parameters were also collected: body temperature, presence of hypotension, oxygen desaturation. Clinical [mean arterial pressure or administration of vasoactive agents required, oxygen flow, urinary output and Glasgow Coma Scale] and laboratory [PaO_2, platelet count, bilirubin and creatinine] parameters were also used to assess sequential organ failure assessment [SOFA] score.

2.3. Methods and definitions

The parameters considered for the primary endpoint, namely for describing the clinical presentation of the infectious complications, were fever or hypothermia, hypotension and oxygen desaturation. Fever was defined as body temperature $>$38°C, hypothermia as body temperature $<$36°C [25,26]; hypotension was defined as a systolic blood pressure $<$90 mmHg in a previously normotensive patient or the increase in amine support in a patient already on treatment; oxygen desaturation as an increase of 3 cmH_2O in the minimum positive end-expiratory pressure during 24-hour period or an increase of 20% in the minimum fraction of inspired oxygen. The laboratory parameters considered for the definition of the secondary endpoint were changes in SOFA score, leucocyte and neutrophil count, CRP, and PCT levels. The SOFA score at infection onset was compared to 24 hours earlier to assess if an increase of $\geq$ 2 points occurred, consistent with sepsis definition [26]. Leucocytes, neutrophils and CRP values are routinely monitored in our clinical practice in critically ill patients admitted to ICU, and were defined as increased, regardless of the amount of change, in case of higher values at infection onset, compared to the previous 24-48 hours. No cut-off values were chosen for CRP increase, but only reference to previous value, as no cut-off has ever been validated in order to make a diagnosis of infection [27–29]. PCT was not monitored routinely, and then systematic comparison with previous values was not feasible. For this reason, we assumed PCT value to be 0-1 ug/L at baseline and considered PCT levels increased if $>$1 ug/L when an infectious complication was diagnosed. The infections considered for the present study were bloodstream infections [BSIs] or ventilator-associated pneumonia [VAP]. BSI was defined by a positive blood culture for fungi or bacteria. For common skin contaminants, like coagulase-negative staphylococci, *Corynebacterium, Peptostreptococcus, Bacillus* and *Propionibacterium* species, at least 2 positive blood cultures were required to define BSI [6,30,31]. VAP was

defined by the detection of new or changing chest X-ray infiltrate in a patient mechanically ventilated for >48 h and concurrent growth of $>10^4$ Colony-Forming Units [CFU]/mL of a possible causative pathogen on a bronchoalveolar lavage [BAL] or $>10^5$ CFU/mL on a bronchial or endotracheal aspirate [BAS] sample [32–35]. For the description of the etiologies underlying the infectious complications in study participants, microbiological isolates on blood or respiratory samples were identified with the Vitek 2 system [bioMérieux, Marcy l'Etoile, France].

2.4. Statistical analysis

Patients were described using frequency [%] for categorical variables and median [interquartile range, IQR, or range] for continuous variables. Our power to detect a significant difference in the frequency of hypotension, body temperature changes and oxygen desaturation between tocilizumab and non-tocilizumab treated patients were 0.13, 0.04 and 0.34. Comparisons of patient demographics and characteristics among cases and controls was performed using the Mann-Whitney test for continue variables and Chi-square test or Fisher's Exact test for categorical variables. The frequencies of the clinical and laboratory characteristics of cases and controls were compared through Chi square or Fisher's Exact test, as appropriate. The association among any clinical or laboratory variable at infection onset and tocilizumab use was further tested by a multivariable logistic regression model, including all variables that were significant on univariate analysis [p-value <0.1] and further adjusted for variables that were different between tocilizumab and non-tocilizumab treated patients at baseline [i.e. steroid use and white blood cell count].

2.5. Ethical considerations

The collection of anonymized data for the present study was approved by the Ethics Committee of the Liguria Region [registry number 163/2020]. Informed consent was waived due to the retrospective nature of the study.

3. Results

During the study period, 117 patients with COVID-19 were admitted to the COVID-19-dedicated ICUs in San Martino University Hospital, of which 50 received tocilizumab treatment. A total of 58 [49.6%] patients subsequently developed a microbiologically documented infection within the same admission, where 25 were treated with tocilizumab [50% of total patients receiving tocilizumab] while 33 patients did not receive tocilizumab [49% of total non-tocilizumab patients, p = 0.9363]. The median time from tocilizumab administration to infection onset was 10 days [range 2–26]. Details of the clinical and laboratory parameters of the study population are outlined in Table 1.

The patients included were mainly male [45/58, 78%], their median age was 65 years [range 45–79] and most of them received steroid treatment [21/25, 84% of patients treated with tocilizumab; 15/33, 45% were non-tocilizumab patients, p = 0.018]. The clinical presentation of the infectious event was similar in the tocilizumab and non-tocilizumab groups, and it was characterised by hypotension in 11/25 [44%] vs. 11/33 [33%] patients, p = 0.407; fever in 8/25 [32%] vs. 10/33 [30%] patients, p = 0.890; hypothermia in 0/25 [0%] vs. 2/33 [6%] patients, p = 0.501; oxygen desaturation in 6/25 [28%] vs. 4/33 [12%] patients, p = 0.127 [Table 2]. In the tocilizumab and non-tocilizumab groups, 6/25 [24%] patients and 12/33 [36%] patients, respectively, did not show any of the above-mentioned signs or symptoms of the infection [p = 0.313].

Among the laboratory parameters, CRP elevation was reduced in tocilizumab-treated patients when compared to the control group [8/25, 32% vs. 22/33, 67%, p=0.009], and it remained persistently below the threshold of detection in six patients who received tocilizumab after a median of 15 days [range 10–34], until hospital discharge [N = 2] or death [N = 4]. In patients who received tocilizumab, compared to those who did not, the frequency of leukocytes [16/25, 64% vs. 17/33, 51%; p = 0.342], neutrophils [11/25, 44% vs. 13/33, 39%; p = 0.724] and PCT increase [2/25, 8% vs. 9/33, 27%; p = 0.093] were comparable [Table 2].

By restricting the PCT assessment to gram-negative BSI, an increase was found in one out of eight episodes among patients on tocilizumab [12.5%] and in two out of four [50%] patients not treated with tocilizumab [p = 0.4795]. The SOFA score at infection onset showed an

Table 1
Characteristics of critically ill COVID-19 patients who developed a microbiologically documented infection during intensive care unit [ICU] stay in the study period.

	TocilizumabN = 25	No TocilizumabN =33	P value
Demographics			
Age in years, median [IQR]	65 [60.5-72.0]	65 [57-69.5]	0.514
Male gender, N [%]	20 [78.8]	26 [80.0]	0.910
Clinical characteristics			
Steroid treatment, N [%]	21 [84.0]	15 [45.4]	0.018
Time between ICU admission and infection, median [IQR]	9 [7-12]	7 [2.5-11]	0.102
Type of infection			
BSI, N [%]	23 [92.0]	27 [81.8]	0.445
VAP, N [%]	9 [36.0]	8 [24.2]	0.330
Laboratory parameters at diagnosis of infection			
WBC in cells/mmc, median [IQR]	15,230 [7,285-19,105]	10,580 [7,355-15,560]	0.044
Neutrophils in cells/mmc, median [IQR]	14,200 [5,850-17,450]	4,500 [6,150-13,750]	0.086
CRP in mg/L, median [IQR]	5.8 [0-37.8]	126 [62-244]	<0.001
PCT in ug/L, median [IQR]	0.04 [0.0-0.4]	0.6 [0.2-1.8]	<0.001
Outcome			
30-day mortality, N [%]	8 [32.0]	15 [45.4]	0.300

BSI: bloodstream infection, CRP: C-reactive protein; IQR: interquartile range; N: number; PCT: procalcitonin; VAP: ventilator associated pneumonia; WBC: white blood cells.

Table 2
Clinical and Laboratory characteristics of critically ill COVID-19 patients at the onset of a microbiologically documented infection.

	TocilizumabN = 25	No TocilizumabN =33	P value
Clinical presentation of infection			
Hypotension, N [%]	11 [44%]	11 [33%]	0.407
Body temperature >38°C, N [%]	8 [32%]	10 [30%]	0.890
Body temperature <36°C, N [%]	0 [0%]	0 [0%]	0.501
Oxygen desaturation	6 [28%]	4 [12%]	0.127
At least one of the above-mentioned clinical features	19 [76%]	21 [64%]	0.236
Laboratory parameters at infection			
Δ SOFA ≥ 2	4 [16%]	4 [12%]	0.715
WBC increase*	16 [64%]	17 [51%]	0.342
Neutrophils increase*	11 [44%]	13 [39%]	0.724
CRP increase*	8 [32%]	22 [67%]	0.009
PCT > 1ug/L	2 [8%]	9 [27%]	0.093
At least one of the above-mentioned laboratory parameters	18 [72%]	28 [85%]	0.329

N: number of patients; %: percentage; SOFA: sequential organ failure assessment score; Δ: delta between SOFA value at infection onset and 24 hours earlier; WBC: white blood cells; CRP: C-reactive protein; PCT: procalcitonin.
* as compared with values measured in the 24-48 hours before infection onset.

increase of ≥ 2 points, in 4/25 [16%] patients in the tocilizumab group and in 4/33 [12%] patients in the non-tocilizumab group, p = 0.715. At multivariable analysis, the reduced frequency of CRP elevation at the infection onset was confirmed to be the only factor significantly associated with tocilizumab use after controlling for possible confounders [odds ratio for CRP elevation 0.18, 95% confidence interval 0.04–0.77, Table 3].

The causative microorganisms of the infectious complications described in this study are outlined in Table 4. After 30 days of observation, 23/57 patients died; 8 [32%] were from the tocilizumab group and 15 [45%] were from the non-tocilizumab group [p = 0.300].

4. Discussion

In critically ill patients with severe COVID-19 admitted to the ICU, we found that 1] the clinical features of infectious complications were not affected by tocilizumab, and 2] among the laboratory parameters, only CRP levels showed a different trend with reduced frequency of CRP elevation in tocilizumab-treated patients compared to non-tocilizumab-treated patients.

The present study addresses an original issue that was not adequately explored by previous studies and RCTs [13]. Tocilizumab use is still under investigation, and the current guidelines suggest using it in severe and critical COVID-19 cases [24]. Thus, more information can be useful in managing and identifying tocilizumab and SARS-CoV-2 complications, especially in ICU patients [13,16]. Despite tocilizumab's immunosuppressive effect, its use did not modify the frequency of common signs of infection such as fever, hypothermia, hypotension and oxygen desaturation. However, in our series, most COVID-19 patients presented few or even no clinical signs of infection regardless of tocilizumab use. Thus, it should be noted how atypical presentations of secondary infections can make the diagnosis challenging, adding to the already high difficulty of differential diagnosis in an ICU patient. At the same time, clinicians should not rely on inflammatory indexes when they suspect infections in tocilizumab-treated patients due to the tocilizumab inhibition of the inflammatory cascade regulated by IL-6, resulting in a lack of production of acute phase reactants such as CRP [36,37]. In fact, when focusing on laboratory parameters at the occurrence of the infectious complication, the CRP levels were different in the tocilizumab and non-tocilizumab treated patients in our study, with a reduced frequency of CRP elevation in those who received tocilizumab. This finding was clearly expected due to the well-known ability of tocilizumab to mechanistically reduce CRP, as above-described [36,37]. On the contrary, tocilizumab should not interfere with PCT production, as its release is driven in vivo, primarily by the proinflammatory cytokines tumour necrosis factor-α and IL-1ß [37], which are not directly regulated by the IL-6 cascade. In our study, the frequency of PCT elevation was comparable in the two groups of patients, and although the levels were slightly higher in the non-tocilizumab patients, the difference in trend was not statistically significant. Similarly, all the other laboratory parameters considered were comparable in tocilizumab- and non-tocilizumab-treated patients. Leucocyte and neutrophil levels seemed higher in the tocilizumab patients, but the frequency of their elevation, when compared to24–48 hours earlier, was similar in the two groups, with the difference in the baseline levels probably owing to the imbalance in steroid administration in the tocilizumab group. Thus, the

Table 3
Clinical and laboratory factors at the onset of a microbiologically documented infection associated with tocilizumab use according to logistic univariate and multivariable analyses.

Variable	OR [95% CI]	p-value	**aOR [95% CI]	p-value
Clinical presentation of infection				
Hypotension	1.57 [0.53-4.59]	0.408		
Body temperature >38°C	1.082 [0.35-3.32]	0.890		
Body temperature <36°C	7.92e-8 [0.00-inf]	0.992		
Oxygen desaturation	2.82 [0.72-11.01]	0.136		
Laboratory parameters at infection				
Δ SOFA ≥ 2	1.38 [0.31-6.16]	0.672		
WBC increase*	1.67 [0.58-4.85]	0.343		
Neutrophils increase*	1.21 [0.42-3.47]	0.724		
CRP increase*	0.23 [0.08-0.71]	0.011	0.18 [0.04-0.77]	0.021
PCT > 1ug/L	0.23 [0.04-1.19]	0.080	0.22 [0.03-1.51]	0.124

Table legend: 95%CI: 95% confidence interval; aOR: adjusted odds ratio; OR: odds ratio, WBC: white blood cell count.
* as compared with values measured in the 24-48 hours before infection onset.
** The multivariable model was further adjusted for WBC count and steroid use.

Table 4
Type of infection and causative microorganisms in 25 patients treated with tocilizumab and 33 patients who did not receive tocilizumab.

		N [%]	Gram -	Gram +	Causative agents [N] *
VAP	Tocilizumab [N= 25]	9 [36%]	8 [32%]	5 [20%]	*S. aureus* [5] *P. aeruginosa* [2] *K. pneumoniae* [2] *S. maltophilia* [2] *P. mirabilis* [1] *H. influenzae* [1]
	No tocilizumab [N=33]	8 [24%]	7 [21%]	2 [6%]	*P. aeruginosa* [2] *Klebsiella* spp[2] *S. maltophilia* [2] *S. marcescens* [1] *E. aerogenes* [1] *S. aureus* [1] *S. pneumoniae* [1]
BSI	Tocilizumab [N= 25]	23 [92%]	7 [28%]	17 [68%]	*E. faecalis* [7] CoNS [6] *S. aureus* [4] *Candida* spp [3] *E. faecium* [2] *P. aeruginosa* [2] *P. mirabilis* [2] *E. aerogenes* [2] *M. morganii* [1] *S. maltophilia* [1] *H. influenzae* [1]
	No tocilizumab [N=33]	27 [82%]	3 [9%]	24 [73%]	CoNS [12] *E. faecalis* [7] *E. faecium* [5] *Streptococcus* spp [3] *P. aeruginosa* [2] *A. baumannii* [1] *Candida* spp [1] *S. aureus* [1] *S. peumoniae* [1] *S. marcescens* [1]

VAP: ventilator associated pneumonia; BSI: bloodstream infection; N: number; CoNS: Coagulase-negative staphylococci
* Four/9 episodes of VAP in cases and 2/8 in controls were polymicrobial; 7/23 BSI in cases and 8/27 in controls were polymicrobial.

results of our study emphasise that inflammatory indexes should not solely be relied on when assessing a possible diagnosis of bacterial/fungal superinfection in ICU patients. This is in accordance with previous studies in which the use of laboratory markers such as CRP or PCT elevation was not recommended to diagnose infection, sepsis or septic shock [27,29,38,39]. This is more true for patients who have received tocilizumab [36,37]. Finally, the microbiological findings were similar in the tocilizumab- and non-tocilizumab-treated patients, and despite the number being low, it reflected the epidemiology of the participating ICU and the etiologies expected in critically ill patients developing common infectious complications such as VAP and BSI during the ICU stay [6,35,40].

Our data suggest that in critically ill patients with severe COVID-19 disease, the immune suppression mediated by tocilizumab use did not significantly alter the clinical presentation and the laboratory parameters other than CRP in case of infectious complications. Furthermore, the common etiologies of VAP and BSI should be considered when starting an empirical treatment in ICU patients treated with tocilizumab as highlighted by the etiologies of these infectious complications described in the present study.

This study has several limitations. The first limitation is the retrospective design and the low power of the study. Moreover, it is possible that some diagnoses of infectious complications were missed because of previous antibiotic administration resulting in negative cultures [41] or because they presented signs and symptoms different from those considered in this study or no symptoms at all. However, this consideration is beyond the scope of the study, as we aimed to describe the clinical presentation of confirmed cases rather than the incidence of infections. The second limitation is that, although microbiologically confirmed, the diagnoses of VAP and coagulase-negative staphylococci bacteraemia might be arbitrary, and their clinical relevance might be questioned [42] even if all the infections recorded have been treated accordingly and are, thus, considered clinically relevant by the caring physicians. Finally, the imbalance in the corticosteroid use in the case and control groups might have contributed to masking the differences in the clinical and laboratory characteristics of the two groups of patients.

In conclusion, the clinical features of infectious complications in ICU patients with COVID-19 were not affected by tocilizumab use. Further, the index of suspicion of an infectious complication should always be high in critically ill patients with severe COVID-19 disease admitted to ICUs and should not only be guided by inflammatory parameters, especially in tocilizumab-treated patients. In fact, even isolated or transient symptoms should drive prompt and complete diagnostic workup to exclude possible infections.

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Conflicts of Interest

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