

INCIDENCE, DEPENDENT AND INDEPENDENT RISK FACTORS ASSOCIATED TO NOSOCOMIAL INFECTIONS AND TO THE MORTALITY AT THE INTENSIVE CARE UNIT OF THE TIMONE UNIVERSITY HOSPITAL

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Abstract

ICU (intensive care unit) patients are highly concerned by a risk of nosocomial infection. This is due to the seriousness of the treated pathologies, and more and more to invasive medical procedures, in short, a day-to-day hazard of health care. The aim of this study is to assess the risk factors of nosocomial infections and mortality in ICU, to estimate the proportion of predominant organisms, and to record the disease resistance profiles. This study was based on a total of 250 patients who were at least 16-year old and who had spent at least 72 hours in ICU.

Among the 46 patients who developed at least one nosocomial episode, 42 (91.3%) had been hospitalized for a minimum of 6 days (this being the average stay for patients without any nosocomial episode). The mortality rate was 23.9%. The most frequently reported infection was pneumonia contracted through mechanical ventilation, with a percentage of 47.8%, followed by lung infections with a rate of 23.9%. Bacteremia and urinary infections represented 17.4% and 10.4%, respectively. 41.3 % of isolated bacteria were Gram-positive. All of the 46 patients received antibiotics during their stay at the intensive care unit. The results of logistic regression and multivariate analysis ($P < 0.05$) conclude that the nosocomial event was significantly related to the length of stay OR: 1.073 [1.009 – 1.149],

neurological disease OR: 3.21 [1.28 – 8.33] and the presence of a CVC (central venous catheter) OR: 15.3 [1.68 – 507.4]. Additionally, age OR: 1.02 [1.002 – 1.054], cancer OR: 3.07 [1.32– 7.21] and SOFA score >4 OR: 7.58 [2.63 - 29.03] are related to the death risk.

In light of this study, we concluded that CVC and neurological disease are high-risk factors for nosocomial infection whereas SOFA score >4 and cancer are identified as high risk factors for mortality.

Keywords: Intensive care, risk factors, nosocomial Infections, ICU-mortality

Introduction

Nosocomial infections are a significant public health problem, because of their frequency, their cost and their severity (Sheng WH, 2005-Mathieu LM, 2001). In the USA, the study on the efficacy of the nosocomial infection control showed that every year almost 2.1 million infections occur out of a total of 37.7 million admissions; with a mortality rate of 77,000 (Haley RW, 1985), (Archibald LK, 2007).

Even if the causes of nosocomial infections are the same, the ICU records an occurrence rate two to five times higher than in other health-care services. Thus, it is reported that the risk of contracting a bacteremia in ICU can reach 31.5% to 82.4% of the patients (Vincent JL, 1995), (Digiovine B, 1999) This high rate may be due to the complexity of the diseases treated and therapeutic actions and / or often invasive diagnoses this implies.

Due to the interaction between pathogenic disease agents, action and care of vulnerable patients (Wenzel r. p. T, 1983), it has been established that the nosocomial event is the consequence of a complex relation involving several factors.

Among these factors, the studies (Sheng WH, 2005), (Vincent JL, 1995), (Wenzel r. p. T, 1983), (Vincent JL, 2003), (Cevik MA, 2005), (Girou E, 1998), (Richards MJ, 2000) quote the use of invasive systems, the reduction of immunosuppression induced or secondary to the acute disease, the relative older age of the population, associated chronic pathologies, antibiotics and resistant bacteria. The studies (Esen S, 2004), (Craven DE, 1988), (Ponce de León-Rosales SP, 2000), (Vincent JL, 2003), (Richards MJ, 1999) established a significant association between nosocomial infection rates and the length of stay, thus leading to elevated costs of treatment. Additionally, though it is difficult to establish a straight-line causal link between nosocomial infection and fatal outcomes in critically ill patients, it has been estimated that they could be responsible for 10 000 to 20 000 deaths per year in France.

For optimized prevention and constant improvement, we absolutely need updated knowledge and data. The aim of the present study is to determine the incidence of the nosocomial infection and its risk factors. It is also to evaluate the death rate in the ICU and the proportion of predominant organisms so as to document the resistance profiles.

Patients and methods

The study took place at the Timone University Hospital's ICU, one of the most important hospitals in Southeast France. It is Europe's third largest hospital, and it is equipped with 1069 beds (793 for adults and 276 for children).

The ICU counts 9 beds. Admissions are done directly by the emergency unit or by the Mobile Emergency Unit.

Patients can be transferred from other hospitals either by internal admission or through a specific request by another service. The approval of the ethics committees was unnecessary as the study was non interventional and done retrospectively.

Every piece of information related to the identity of the patients will stay confidential. Out of a total of 565 patients hospitalized from January 1, 2011 to June 30 2012, 291 patients, aged ≥ 16 and staying at least 3 days were concerned.

Among the 291 selected patients, 41 were excluded due to missing values. Amongst the 250 patients left, 46 developed at least one nosocomial episode.

The accounting of infected cases was done on the basis of bacteriological proofs. It was decided that the day of collection would be referred to as the first day of infection. We only took into account the first nosocomial episode.

The collection of data was done thanks to a standard form. We systematically collected the age, the gender, the ICU admission and discharge date, the number of days spent at the ICU before the start of the first nosocomial infection, the total number of days spent in hospital, the clinical settings (comorbidities, reason of hospitalization), origin of the patient, type of pathology, type of infection and pathogenic causal agents.

We reported every invasive gesture (intubation, tracheotomy, urinary catheter, central catheter, sedation), the duration of antibiotherapy before and after the nosocomial incident. For each patient, the LOD (logistic organ dysfunction) score, the SAPS (Simplified Acute Physiologic) II score and the SOFA (Sequential Organ Failure Assessment) score were calculated retrospectively.

All the reported pejorative values from the last 24 hours were used for calculating each score. The risk factors were divided into two groups: intrinsic and extrinsic. The intrinsic risk factors included the age, the gender,

the reason for admission and the comorbidities. The extrinsic factors were the origin (where the patient comes from), the number of days in hospital before the admission in ICU, endotracheal intubations, the mechanic ventilation, tracheotomy, urinary catheter, peripheral venous catheters, central venous catheter (CVC), arterial catheter, sedation, antibiotics before admission.

We should keep in mind that among the patients, who had not developed any nosocomial episode, some had extrinsic factors considered as present whatever the date of intervention. However they were considered as not present for patients having contracted a nosocomial infection only if they intervened after the first day of infection. The nosocomial occurrence was added to the list of risk factors quoted before (intrinsic and extrinsic) for the mortality analysis. According to the duration of the stay, the gravity scores SAPS II, LOD and SOFA, calculated during the admission, the patients were divided into two groups (Group I and Group II). As all the patients had been under anti-H2 and supporting peripheral venous catheters, we did not introduced these elements in this study.

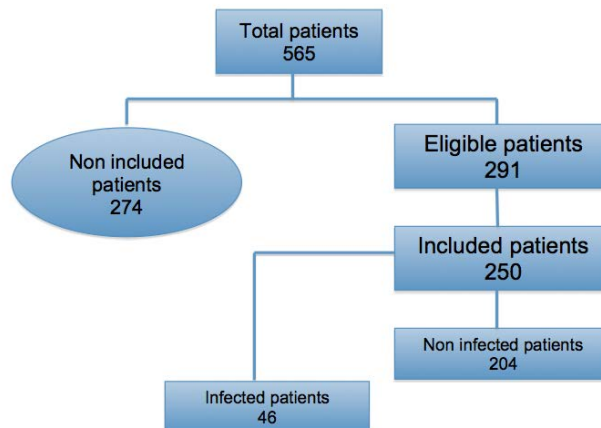


Figure 1: Schematic presentation of study population according to presence or absence of infection.

Statistical analysis

The statistic analysis was done by using the R software.

The qualitative variables are described on the frequency line, while the quantitative variables are described on the waist line [first quartile, third quartile] and/or mean ± standard deviation.

We used the Mann and Withney U-test to compare age and hospitalization duration between the infected group and the non-infected one.

The chi-square test was used to compare categorical variables between the two groups (infected and non- infected): gender, diagnosis,

comorbidities, invasive techniques (intubation, tracheotomy, urinary catheter, central venous catheter, arterial catheter, sedation, antibiotics).

All the potential risk factors studied during this univariate analysis which had p-value < 0.20 were introduced in the multivariate logistic regression model.

The same analysis was done to compare deceased and surviving patients.

Then we tested all the possible interactions between risk factors for each of the following events: nosocomial infection and mortality.

All the interaction terms reaching at least a p-value < 0,20 were introduced in a multi-variate logistic regression model.

We considered a risk $\alpha = 0.05$ to derive confidence intervals of 95 % level.

Results

Out of a total of 250 patients included, 46 (18.4%) developed at least one nosocomial episode. It has been estimated that the average age was 60.23 ± 14.49 years, the gender ratio was 1,72 (36,8 % female and 63,2 % male), the patient type was 12,8% surgical vs 87,2 % medical, the average stay in intensive care before the nosocomial advent diagnostic was $6,63 \pm 4.30$ days [3-27]. 9.6% of the patients had been taking antibiotics during the 15 days preceding their admission to the ICU.

The patients' demographic and clinical characteristics, infected or not, deceased or not are described in Table 1 and Table 2. On the other hand, the global mortality rate is around 23.2 %. More precisely, it is of 23.9% in the infected group versus 23.0% in the non-infected group. The Mc Cabe score was of 1 for 169 patients (67.6%), of 2 for 72 patients (28.8%) and of 3 for 9 patients (3.6%). As far as bacteriologic results are concerned, it has been shown that 58.7 % of the isolated bacteria were Gram-negative vs 41.3% of Gram-positive bacteria. A resistant profile was mentioned for 23.9 % of the bacteria.

In Tables 1 and 2 we present the results of the univariable analysis concerning risk factors of mortality and of infection contracted in the ICU. They show no difference between the two groups (infected and non-infected) as far as intrinsic risk factors are concerned except for acute respiratory illness, neurological disease, the infection at the admission and the SOFA score however, the extrinsic risk factors and antibiotics are significantly associated to the nosocomial infection risk (that is length of stay, tracheotomy, intubation, the existence of a central venous catheter and sedation).

Concerning mortality we noticed that only the following intrinsic factors were significant: age, SAPS II, SOFA and LOD scores, cancer and transplantation. On the contrary, we didn't notice any significant association

for extrinsic risk factors. The results of the multivariate logistic regression analysis (Table 3) show that only the length of stay, a neurological failure and the presence of a central venous catheter could be significantly associated to a nosocomial event. Age, cancer and a SOFA >4 score are associated with the risk of death.

In table 4, we can see the variable interaction terms tested two by two as far as nosocomial risk and mortality with a p-value <0,20 are concerned.

Table 1: Intrinsic factors for ICU-acquired infection and mortality (univariate analyse)

Factors	Infected n= 46(%)	Uninfected n=204(%)	P-value	Survived n=192(%)	Died n=58(%)	P-value
Age (mean / years)	61.09	56.46	0.051	58.8	64.9	0.004
Gender			1			0.758
Male	29 (63.0)	129(63.2)		120 (62.5)	38 (65.5)	
Female	17 (37.0)	75 (36.8)		72 (37.5)	20 (34.5)	
SAPS II			0.634			0.001
≤ 46	25 (54.3)	101(49.5)		107(55.7)	19(32.8)	
> 46	21(45.7)	103 (50.5)		85 (44.3)	39(67.2)	
SOFA			0.018			0.0004
≤ 4	7(15.2)	67(32.8)		70(36.5)	4(6.9)	
> 4	39(84.8)	137(67.2)		122(63.5)	54(93.1)	
LOD			0.624			0.003
≤ 5	18(39.1)	18(8.8)		92(47.9)	16(27.6)	
> 5	28(60.9)	114(60.9)		100(52.1)	42(72.4)	
Underlying disease						
Infection at Admission	2(4.34)	39(19.01)	0.019	32(16.66)	9(15.52)	0.849
Diabetes	7(15.21)	37(18.13)	0.690	30(51.72)	14(7.29)	0.179
Cancer	3(6.52)	27(13.23)	0.228	16(8.33)	14(7.29)	0.0009
IRCR	2(4.34)	6(2.94)	0.651	5(2.60)	3(1.56)	0.385
Hematologic	2(4.34)	4(1.96)	0.592	3(1.56)	3(1.56)	0.143
Transplant	2(4.34)	5(2.45)	0.606	3(1.56)	4(2.08)	0.04
Cause of admission						
ARF	7(15.21)	84(41.17)	0.003	69(35.93)	22 (37.93)	0.867
RDS	8(17.39)	20(9.80)	0.191	20(10.41)	8(13.79)	0.471
CHOC	7(15.21)	43(21.07)	0.433	36(18.75)	14(24.13)	0.467
CRA	4(8.69)	19(9.31)	1	16(8.33)	7(12.06)	0.435
Neurologic Failure	20(43.47)	52(25.49)	0.016	52(27.08)	20(34.48)	0.337

(ARF: acute respiratory failure, RDS: respiratory distress syndrome, CRA: Cardio respiratory arrest)

Table 2: Extrinsic factors for ICU-acquired infection and mortality (univariate analyse)

Factors	Infected n= 46(%)	Uninfected n=204(%)	P-value	Survived n=192(%)	Died n=58(%)	P-value
LOS			0.0004			0.093
≤ 6 j	4(8.7)	111(54.4)		94(49.0)	21(36.2)	
> 6 j	42(91.3)	93(45.6)		98(51.04)	37(63.8)	
Intubation	45(97.82)	154(75.49)	0.003	150(78.12)	49 (84.48)	0.348
Sedation	44(95.65)	155(75.98)	0.004	149(77.60)	50 (86.20)	0.202
Tracheotomy	16(34.78)	18(8.82)	0.000	28(14.58)	6 (10.34)	0.511
Arterial Catheter	45(97.82)	184(90.19)	0.134	179(93.22)	50 (86.20)	0.111
CVC	45(97.82)	141(69.11)	0.000	143(74.49)	43 (74.13)	1
Urinary Catheter	46(100)	193(94.60)	0.144	182(94.79)	57 (98.27)	0.312
Antibiotics usage	46(100)	138(67.64)	0.000	45(75.52)	39 (67.24)	0.229
ICU-AI	-----	-----	-----	47(24.47)	11 (18.96)	0.849

CVC : central venous catheter, ICU-AI : Intensive care unit acquired infection

Table 3: The results of multivariate analysis

Significant risk factors of infection (ICU-AI : intensive care unit-acquired infections)

Factors	Odds ratio	IC à 95%
LOS	1.073	1.009 - 1.149
Neurologic failure	3.211	1.280 - 8.330
CVC	15.37	1.677 - 507.4

LOS: Length of stay, CVC: central venous catheter,

Significant risk factors of mortality

Factors	Odds ratio	IC à 95%
Age	1.027	1.002 - 1.054
Cancer	3.078	1.316 - 7.206
SOFA gII	7.586	2.629 - 29.0

SOFA: Sequential Organ Failure Assessment score, gII: groupe II,

Table 4 : Infectious risk interactions and mortality risk interactions

<i>ICU-AI</i>	<i>p-value</i>	Died	<i>p-value</i>
LOS-SOFA gII	0.047	LOS-Neuro	0.088
ARF - LOS gII	0.061	LOS-Trac	0.089
		LOS -CVC	0.079
		LOS -Ant	0.049
		LOS-Intu	0.031
		ARF-Trac	0.060
		IaA-Trac	0.070
		Trac-Seda	0.012
		Trac-CVC	0.007
		Trac-Intu	0.003
		Antb-Intu	0.074

LOS: Length of stay, **Ant:** antibiotic, **Intu:** Intubation, **Trac :** Tracheotomy, **Neuro :** Neurologic failure, **SOFA :** (Sequential Organ Failure Assessment), **IaA:** Infection at admission, **ARF:** acute respiratory failure, **Seda:** sedation, **CVC :** Central Venous Catheter,

Table 5: The results of multivariate analysis
Significant risk factors of infection (ICU-AI: intensive care unit-acquired infections) considering interaction

Factors	Odds ratio	IC à 95%	
Neuro	2.831	1.050	7.894
Other	29.24	2.536	460.9
LOS gII	6.974	1.228	65.33
LOS-SOFA gII	1.117	0.991	1.273
ARF - LOS gII	0.2953	0.065	1.087

ARF: acute respiratory failure, **LOS:** Length of stay, **Neuro:** neurologic failure, **SOFA:** (Sequential Organ Failure Assessment), **LOS-SOFA gII :** interaction between both LOS and SOFAGII risk factors, **ARF - LOS gII:** interaction between both acute respiratory failure and Length of stay gII

Significant risk factors of mortality considering interaction

Factors	Odds ratio	IC à 95%	
Age	1.025	1.001	1.052
Cancer	2.858	1.206	6.767
Grefe	5.535	0.759	43.948
Sedation	4.448	1.405	16.877
GroupeSOFA.1II	7.666	2.625	29.880*
Antb-Intubation	0.496	0.226	1.095*

SOFA: Sequential Organ Failure Assessment score, **gII:** groupe II, **AC:** arterial catheter, **Antb-Intubation:** interaction between both antibiotic and intubation risk factors.

*: Only when $\alpha = 10\%$.

Discussion

To prevent nosocomial infections we face a constant challenge. It implies a multimodal analysis considering the infection type, the causal agents, the risk factors, increased mortality rates associated (Weinstein RA, 1991), (E.T. Brannigan, 2009), (Holmes A, 2008), (Hugonnet S, 2007). The present study focused onto the epidemiological analysis, the identification of nosocomial infection risk factors and the mortality in the ICU service at the Timone University hospital.

The nosocomial infection diagnosis criteria are those of the CDC (Garner JS, 1988), (Knaus W A, 1985) and of the standard definition from the High Council of Public Hygiene of France (CSHPF, 1999). Given the context of this retrospective study, only a bacteriological proof and a 72-hour minimum stay in ICU signaled the diagnosis of nosocomial infection. Among the 250 patients included in this study 46 (18.4 %) developed at least one nosocomial episode.

The results of the studies by (Legras A, 1998), (Vaque J, 1994), (Jan Muhammad S, 2008), (Shalini S, 2010) and (Oznur Ak, 2010) each one of them show a prevalence rate; respectively 21.6%, 22.8%, 29.13%, 27. 4% and 25.6%.

The disparity of the results could be explained by the difference among the selected criteria, an arbitrary duration of stay (48 to 72 hours) to admit the diagnosis of nosocomial infection, the severity of pathology, of the case-mix, the type of intensive care, the duration of stay, the invasiveness of care, the discharge criteria and the quality of the care (Legras A, 1998), (Erbay. H, 2003).

Additionally, the neurological damage is described in the (Appelgren P, 2001), (Ponce de León-Rosales SP, 2000), (Shinji T, 2003) studies, as being the main reason for admission as well as nosocomial infection and mortality risk factors.

On the contrary, in this study, the main diagnoses of admission for all the patients (infected and non-infected) are the following: respiratory insufficiency 36.4 %, the neurological disease 28.8 %, and the shock (all types of etiology) 20.0 %.

Concerning the proportion of infection types contracted in ICU, most of the studies showed that pneumonia, urinary infections and bacteremia represent 77 % of the total quota;

Thus, thanks to the results of the studies (Vincent JL, 2003), (Richards MJ, 1999), (Erbay H, 2003), (Aly. NY, 2008), (Meriç M, 2005), (Esen S, 2004), lung infections are the most dominant with 47 %, followed by respiratory infections and urinary infections, each corresponding to 18 %. Bacteremia represents 12 %. It should be noted however, the

Markogiannakis and al.'s conflicting results which place bacteremia as the commonest (Markogiannakis H, 2009).

The results of the present studies put at the highest rank pneumonia contracted under mechanical ventilation with a 47.8 % rate followed by lung infections that reach a 21.7 % rate. Bacteremia and urinary infections reach respectively 17.4% and 10.4 %. On the other hand, it is shown thanks to the studies (Vincent JL, 1995), (Richards MJ, 2000), (Ponce de León-Rosales SP, 2000), (INICC, 2010) that half of the infections contracted in reanimation could be due to bacteria that are Gram-negative.

The results of the studies by Vincent et al (Vincent JL, 1995) rank enterobacteriaceae at the highest level with 34 % followed by *Staphylococcus aureus* with 30.1%. *Pseudomonas aeruginosa* reached the third place with 28.7%.

However, the distribution of microbial agents varies from one study to the other. For instance we quote the results of the De Leon-Rosales et al (Ponce de León-Rosales SP, 2000) study. They estimate the proportion of enterobacteriaceae at 25.9%, *P. aeruginosa* at 17.2% and *S. aureus* at 10.9%.

The results of this study show that 58.7 % of isolated bacteria were Gram-negative Vs 41.3% of Gram-positive bacteria. (17.4% *E. coli*, 10.9% *P. aruginosa*, 8.7% *klebsiella*, 8.7% *hemophilus influenzae*) vs (28.2% of *Staphylococcus*, *staphylococcus epidermidis* 4.3%, pneumococcal 2.2%, *Streptococcus pneumoniae* 6.5%).

A resistant profile was mentioned for 23.9% of the bacteria. Furthermore, the global mortality rate fixed on all the patients included in this study reaches 23.2 % including 23.9 % of infected patients and 23.0% of non-infected patients.

The studies (Appelgren P, 2001), (Ponce de León-Rosales SP, 2000) specify the following invasive procedures: central venous catheter and mechanic ventilation. It is said that they are significant risk factors for nosocomial infections and mortality.

This corroborates results of this study (Tables 1 and 2). However we do not agree with the studies (Erbay H, 2003), (Appelgren P, 2001), (Ponce de León-Rosales SP, 2000), (Pekka Y, 2006) as conclusion of this study is that age and gender, are not risk factors for a nosocomial infection. Moreover several studies conclude that comorbidities and underlying medical conditions are associated with the risk of mortality instead of nosocomial risk (Vincent JL, 1995), (Craven DE, 1988), (Appelgren P, 2001), (Pekka Y, 2006). Thanks to the results of the present study, we can conclude that infection at the time of admission is significantly related to the nosocomial risk.

In the multivariate regression analysis, (for infectious risks) only the central venous catheter can still be counted among the other invasive

procedures. No gravity score showed any significant association with nosocomial risk except the SOFA score reaching ($\alpha = 10\%$). Concerning the gravity of ill patients, related to mortality, - measured by general gravity scores usually used in intensive care – it is labeled as one of the most risky factors and one of the main causes of mortality.

It is also considered as a confounding factor between nosocomial infection and mortality. Thus leading to numerous studies (exposed or not) matching or adjusting to general gravity scores measured during the admission like for instance APACHE or SAPS II scores. This matching seems logical at first glance, however, the systematic using of these gravity scores as adjusting markers for intensive care patients could skew the study.

Indeed, the elaboration of these scores was done on patients among whom more than one half had duration of stay shorter than 3 days.

However the different diagnosis criteria of nosocomial infection impose a minimum of 2 days in hospital.

In addition, it has been shown that the discrimination capacity of these scores can be affected as the length of stay at hospital becomes longer. According to Timsit and al (Timsit, 2001), the discrimination capacity of the SAPS II score becomes obsolete on the 14th day. As far as mortality is concerned, we do not get any result -as described in studies (Vincent JL, 1995), (Craven DE, 1988), (Appelgren P, 2001), (Pekka Y, 2006)- showing a link between underlying pathologies and death risk.

Thus, the relatively low number of infected patients studied could explain the lack of significant connection between nosocomial event and mortality. On the flip side, in total adequacy with the studies (Craven DE, 1988), (Legras A, 1998), (Pekka Y, 2006), age and SOFA score (Table 3) keep their status of important risk mortality factors when performing the multivariate regression analysis.

According to the number of risk factors documented – 39 risk factors for nosocomial infections and 40 for death risks in the ICU – this should have been tested.

741 infectious risk interactions and 780 mortality risk interactions.

This step could not be considered as if a number of individuals as high as the number of combinations were required.

The results of this study show that these interaction terms don't improve significantly the additive models built before.

Indeed, as for the nosocomial risk, the AIC (Akaike Information Criterion) of the model integrating the interaction terms is 149,2 though it is 148,8 in the initial additive model.

Concerning the death risk the results are the same.

Indeed, the AIC of the model integrating interaction terms is 245,3 and it is 235,7 in the initial model.

This study has several limits that should be mentioned. The retrospective and mono-centric view limited our range of actions.

Moreover the relatively low number of patients studied prevented us from making more specific comparisons—than those already studied. It would have been interesting to compare surgery patients and medical ones among the infected group, so as to consider other aspects and variations.

Conclusion

After a closer look on this study, one can notice that the main risk factors for ICU-acquired infection are CVC and neurological failure. SOFA score >4, age and cancer are definitely identified as serious mortality risk factors.

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