Original research

Association of sepsis diagnosis at daytime and on weekdays with compliance to the 3-hour sepsis treatment bundles: a multicenter cohort study

Running title: Sepsis treatment bundles on daytime and weekdays

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41

42 **ABSTRACT** (word count: 306)

43 **Rationale:** Compliance with sepsis bundles is associated with better outcomes, but
44 information to support structural actions that might improve compliance is scarce. Few
45 studies have evaluated bundle compliance in different time periods, with conflicting
46 results.

47 **Objective:** To evaluate the association of sepsis identification during the daytime
48 versus during the nighttime and on weekdays versus on weekends with 3-hour sepsis
49 treatment bundles compliance.

50 **Methods:** Observational, multicenter study including septic patients admitted between
51 2010 and 2017 to 10 hospitals in Brazil. Our exposures of interest were Daytime (07:00
52 AM-6:59 PM) versus nighttime (7:00 PM-06:59 AM) and weekdays (Monday 7:00 AM-
53 Friday 06:59 PM) versus weekends (Friday 7:00 PM-Monday 06:59 AM). Our primary
54 outcome was full compliance to the 3-hour sepsis treatment bundles. We adjusted by
55 potential confounding factors with multivariable logistic regression models.

56 **Results:** Of 11,737 patients (8,733 sepsis and 3,004 septic shock), 3-hour bundle
57 compliance was 79.1% and hospital mortality was 24.7%. The adjusted odds ratio (95%
58 CI) for 3-hour full bundle compliance for patients diagnosed during the daytime versus
59 during the nighttime was 1.35 (1.23-1.49, $p<0.001$) and was more pronounced in the
60 emergency department (adjOR 1.55, 1.35-1.77, $p<0.001$) than in non-emergency areas
61 (adjOR 1.19, 1.04-1.37, $p=0.014$). Overall, there was no association between diagnosis
62 on the weekends versus on weekdays and 3-hour full bundle compliance (adjOR 1.08,
63 0.98-1.19, $p=0.115$), although there was an association among those diagnosed in non-
64 emergency areas (adjOR 1.15, 1.00-1.32, $p=0.047$). The lower compliance observed for

65 sepsis diagnosed during the nighttime was more evident two years after

66 implementation of the quality improvement initiative.

67 **Conclusions:** Compliance to sepsis bundles was associated with the moment of sepsis

68 diagnosis. The place of diagnosis and the time from campaign implementation were

69 factors modifying this association. Our results support areas for better design of quality

70 improvement initiatives to mitigate the influence of the period of sepsis diagnosis on

71 treatment compliance.

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73 **Keywords:** nighttime; sepsis; bundles; lactate; weekend.

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INTRODUCTION

Since the publication of the first Surviving Sepsis Campaign (SSC) guidelines (1), a large number of studies have shown that compliance with sepsis treatment bundles could improve outcomes (2, 3). Thus, assessing the factors that impact compliance with SSC guidelines may help in the design of quality improvement initiatives to increase compliance and, consequently, to improve prognosis (4).

The impact of off-hours admission on the diagnosis, treatment and outcomes of several time-sensitive diseases has been studied in the literature (5-14). Part of these associations has been attributed to the heterogeneity in case mix between time periods. Yet, organizational factors likely play a role, such as unfavorable staff/patient ratio at night or on weekends or less-experienced staff working during off-hours compared to daytime and weekdays (14, 15).

Few studies have evaluated the association of diagnosing infectious diseases and sepsis at different periods of the day and the week on compliance with guidelines and outcomes, and the results have been conflicting (16-21). Remarkably, the four studies evaluating compliance with guidelines had several limitations (16, 17, 21, 22), such as limited sample size, single-center design or inclusion of only ICU-admitted patients. Thus, we designed this study to evaluate the association between the period of the day and week of sepsis diagnosis and compliance with 3-hours treatment bundles in a large multicenter cohort of hospital-treated sepsis patients. We hypothesized that the compliance to the 3-hours treatment bundles during the daytime and on weekdays would be higher than during the nighttime and on weekends.

102

103 **METHODS**104 *Study design, setting and data source*

105 This is a multicenter observational study conducted in a network of ten private
106 hospitals in São Paulo, Brazil. One hospital is focused on cardiovascular diseases, and
107 nine are primarily general hospitals. Detailed information about the network and
108 hospital characteristics is published elsewhere (2, 23).

109 The ten hospitals have been on a continuous educational program for early
110 sepsis detection and treatment, supported by the Latin American Sepsis Institute (LASI)
111 (2). All data were prospectively collected using an electronic case report form adapted
112 from the SSC. Each institution had a team of case managers dedicated to the sepsis
113 program who were continuously trained and applying standardized operating
114 procedures for data collection, treatment bundle encouragement and feedback; the
115 aim of this team was to improve sepsis bundle compliance. The network has periodic
116 reviews for data quality and accuracy and regular feedback for performance
117 improvement.

118 The Research and Ethics Committee of Hospital Pró-Cardíaco, which is the
119 reference ethics committee designated by the National Research Ethics Committee to
120 the ten hospitals, approved the retrospective analysis and publication of the data on
121 behalf of the entire network under the number 104.931 and waived the need for
122 informed consent.

123

124 *Definitions*

We retrieved data from the sepsis database from 2010 to 2017. We included the first episode of severe sepsis/septic shock of adult patients. We excluded patients with uncomplicated infection (ie, infection without organ dysfunction) and patients whom a sepsis report case was open but subsequently was deemed not infection/sepsis. We used the Sepsis 1 definitions (24), because of the data collection period and to keep the data harmonized. The definitions for organ failure used in this study followed the definitions used in the SSC quality improvement initiatives. Detailed definitions are reported on e-Methods, online supplement) (25).

Exposures

Our exposures period of day and week were defined based on the date and time of sepsis diagnosis, that is the time and date when the sepsis case report form was started and the “sepsis team” was activated. Daytime was defined as 7:00 AM to 06:59 PM, and nighttime was defined as 07:00 PM to 06:59 AM. Weekdays were defined as the period from Monday 7:00 AM to Friday 06:59 PM. Weekends were defined as the period from Friday 07:00 PM to Monday 06:59 AM and bank holidays. A diagram showing the times defined in our database is shown in e-Figure 1 (e-Methods, online supplement).

Outcome

Our outcome was compliance with the 3-hour sepsis treatment bundle. The bundle comprised 1) lactate measurement, 2) drawing blood cultures before antibiotic administration, 3) prompt administration of broad-spectrum antibiotic and 4) fluid challenge for patients with elevated lactate and/or mean arterial pressure below 65

mmHg. The primary outcome was the full-compliance of the 3-hour sepsis bundle, i.e., achieving compliance with items 1, 2 and 3. Secondary outcomes were adherence to the individual components of the 3-hour bundle.

Data analysis

Categorical variables were described as proportions. Continuous variables were described as the mean $\pm$ standard deviation or median (with 25th and 75th percentiles), as appropriate.

Our analysis plan was defined *a priori* and before any data analysis. We evaluated the association between the period of sepsis diagnosis and compliance with the sepsis bundles using logistic regression models. We estimated crude and adjusted odds ratios (OR) for each exposure, adjusting for potential confounding factors, in separate multivariable logistic regression models (ie, single exposure models). We built a directed acyclic graph (DAG, e-Figure 2, online supplement) to guide the selection of confounding variables, avoiding colliders and mediators (26). We adjusted the model by age, sex, severe sepsis/septic shock, site of diagnosis and type of infection. We accounted for the within-hospital clustering and for the between-hospital confounding by adding hospitals as fixed effects in the model (27). We evaluated a potential interaction between period of the day and period of the week by adding an interaction term in the adjusted model. We ran the models on complete patient data due to the low proportion of missing values (n=11,695, 99.6%). We evaluated for a potential nonlinear association of age using restricted cubic splines. We further evaluated the association between the period of the day and week and sepsis compliance after

stratifying by patients diagnosed in the emergency department (ED) and out of the emergency department (non-ED).

We conducted three post-hoc sensitivity analyses: 1) evaluating the within-hospital clustering effect using a random intercept mixed model and a generalized estimated equation model instead of a fixed-effects model; 2) changing the time zero to define our exposures, using time of ED arrival for those patients diagnosed at the ED; 3) evaluating whether the association between the period of the day and week and compliance changed over time since the beginning of the campaign implementation. To illustrate this effect, we used the marginal predicted probabilities for full-sepsis bundle compliance from the adjusted model plus an interaction term between period of the day and week and the time since campaign implementation (in semesters), using the *margins* command in Stata.

In an exploratory analysis, we performed a mediation analysis to evaluate whether compliance to the full bundle was a mediator between period of day and in-hospital mortality. We used the causal mediation approach as defined by Imai et al (28, 29). We adjusted both the mediator and outcome models for the same set of potential confounders as for the main analysis, and confidence intervals were estimated with a quasi-Bayesian approximation from 1000 simulations.

All analyses were conducted in STATA 13.1 (Statacorp, College Station, TX, USA). The causal mediation analysis was conducted using the package *mediation* and the forest plot was built using the packages *ggplot2* and *ggpubr* with R-3.5.2 (R Core Team, 2019).

196

197 **RESULTS**

198 From June 2010 to June 2017, 14390 patients were enrolled (e-Figure 3,
 199 study flowchart). After exclusion of 1047 patients because of non-first sepsis
 200 episode, 829 patients with uncomplicated infection and 777 patients with a sepsis
 201 case report open but subsequently was deemed not infection/sepsis, 11737
 202 patients with severe sepsis (n=8733) and septic shock (n=3004) were analyzed. The
 203 median recruitment per hospital was 972 [P25–P75, 915 – 1327] patients over 7
 204 years.

205 Table 1 shows the clinical characteristics of the patients with sepsis
 206 diagnosis during the daytime versus the nighttime. The most important differences
 207 were found in age, site of sepsis diagnosis (more diagnosis in the emergency at
 208 nighttime) and sepsis source. E-Table 1 shows the differences between septic
 209 patients diagnosed on weekdays versus on weekends. No important differences
 210 were found between the two groups.

211

212 *Association of period of the day and period of the week with bundle compliance*

213 Table 2 demonstrates the compliance with the items of early sepsis bundles
 214 according to the period of the day of the diagnosis. Patients diagnosed during the
 215 daytime had more frequent lactate measurement and antibiotic administration
 216 than those diagnosed during the nighttime. These differences impacted full bundle
 217 compliance (daytime 80.6% vs nighttime 76.3%, proportion difference 4.3%, 95% CI

2.7-5.9%). The other items of sepsis bundles were not different between the periods of the day of the sepsis diagnosis.

E-Table 2 shows the main differences between compliance with the bundles according to the period of the week of the diagnosis. There were minimal differences for lactate measurement and fluid administration for patients diagnosed on weekdays versus patients diagnosed on weekends.

Table 3 shows the crude and adjusted association between the period of the day and week of the sepsis diagnosis and compliance with the sepsis bundle treatment. Patients diagnosed with sepsis during the daytime had higher odds of compliance with the full 3-hour bundle (adjusted OR 1.35, 95% CI 1.23-1.49, $p < 0.001$) and with all of the bundle items after adjusting for potential confounders compared with those diagnosed at night. Patients diagnosed with sepsis during weekdays had no association with full bundle compliance (adjusted OR 1.08, 95% CI 0.98-1.19, $p = 0.115$) and higher odds of compliance with lactate measurement and adequate fluid administration after adjusting for potential confounders compared with those diagnosed on weekends. There was no interaction between the period of the day and the period of the week for any bundle item (i.e., $p_{\text{interaction}} = 0.162$ for full 3-h bundle compliance). There were small departures from the main results in the sensitivity analysis of different modelling approaches for within-hospital clustering (e-Table 3).

Association of period of the day and period of the week with bundle compliance stratified by the site of diagnosis

The association between the diagnosis of sepsis during the daytime and higher odds of compliance was more pronounced and of higher magnitude for patients diagnosed with sepsis in the ED (3-hour full bundle, adjOR 1.55, 1.35-1.77, $p<0.001$) compared with sepsis in non-ED areas (3-hour full bundle, adjOR 1.19, 1.04-1.37, $p=0.014$) for full compliance and for all bundle items, except for fluid resuscitation. In contrast, the association between the diagnosis of sepsis during the weekdays and higher odds of full compliance (adjOR 1.15, 1.00-1.32, $p=0.047$, non-ED areas), lactate measurement and fluid resuscitation items was more evident for those diagnosed in non-ED areas (Figure 1, e-Table 4).

Association of period of the day and period of the week with bundle compliance using ED arrival as time zero

When defining period of day and week by time of ED arrival contrasted with time of sepsis diagnosis (main analysis) among those patients diagnosed at the ED ($n=7452$), there was great agreement between both exposure definitions: 83% for period of day and 95% for period of week (e-Table 5). The adjusted associations remained comparable with the main analysis, for the 3-hour full bundle (adjusted OR 1.42, 95% CI 1.24-1.62, $p<0.001$, period of day; adjusted OR 1.07, 95% CI 0.93-1.23, $p=0.347$, period of week), and for bundle items (e-Table 6).

Association of period of the day and period of the week with 3-hour full bundle compliance over the time since campaign implementation

The average time since the campaign implementation among the 10 hospitals was 7.2 completed years. The marginal probability of compliance with the 3-hour sepsis bundle according to the period of the day, from the fully adjusted model with an interaction term between daytime and semester, is represented in Figure 2. We observed an increase in the difference between the probability of compliance with the 3-hour bundle for diagnoses made during the daytime compared to diagnoses made during the nighttime with the development of the quality improvement initiative. This pattern was not observed for the period of the week (e-Figure 4).

Mediation analysis between period of day and in-hospital mortality

In-hospital mortality was comparable between period of day and period of the week (Table 1, e-Table 1). The same pattern was observed overtime (e-Figure 5), when there was a great decrease on crude mortality (from 39% in the first year to 18% in the seventh year). The exploratory mediation analysis suggested an “indirect-only mediation”: period of the day had a protective effect on hospital mortality only through its mediated effect by increasing full compliance to the 3h bundle (average causal mediated effect: beta -0.00295, 95% CI -0.00452 to -0.00151, $p < 0.001$); but there was no direct neither total effect of period of the day on mortality (e-Figure 6).

DISCUSSION

In this large retrospective multicenter study comprising 10 private hospitals in Brazil, we observed an association between the time of sepsis diagnosis and compliance with 3-hour sepsis bundles. Patients treated for sepsis during the daytime had more frequent lactate measurement and early antibiotic administration compared to those admitted during the nighttime, resulting in higher full bundle compliance. In contrast, full bundle compliance was similar for sepsis patients diagnosed on weekdays or weekends. These associations seem to behave differently according to the place of diagnosis; daytime association was more pronounced for diagnoses made in ED and weekday association was observed for diagnoses made in non-ED areas. Our study has implications for sepsis quality improvement initiatives aimed at increasing compliance with treatment bundles.

Two studies assessed the impact of different periods of sepsis diagnosis on 3h bundle compliance. In a single-center study of 300 septic patients admitted to the ICU, Almeida et al found that compliance to blood cultures and antibiotic administration were higher at nighttime compared to daytime, defined by hospital entrance period (17). In another study, Matsumura et al evaluated 1148 septic patients admitted to 59 ICUs in Japan (16). They found no difference in compliance with sepsis guidelines according to period of day and period of week, except for the time to antibiotic administration, which was longer during the daytime, defined by sepsis diagnosis time (16). Both studies did not adjust for case-mix. The authors hypothesized that a possible explanation for the higher compliance of some bundle items at night could be related to the reduced number of patients assessed at nighttime compared to daytime, in a scenario where the staff-to-patient ratio was similar during the days and nights (16, 17,

309 30). Two other single-center studies showed no association between period of the
310 week and completion of the previous SSC 6-hour bundle, both analyzing less than 350
311 septic patients from the ED and with low compliance to the bundle (21, 22).

312 Some reasons could explain the differences between our results and previous
313 findings. First, the adjustment for the case-mix, since the characteristics of patients
314 being diagnosed in different periods of day and week are different (15, 31). Second, the
315 larger sample size from a database less prone to measurement error and
316 misclassification, because of several local (by the sepsis case manager) and institutional
317 quality checks (quality improvement performance indicators are used for network
318 benchmarking), and data monitoring from an external institution (LASI)(2, 32-34).
319 Third, differences regarding healthcare system and staff-to-patient ratio. Finally,
320 inclusion of patients from different hospital sites from 10 hospitals under a continuous
321 educational sepsis program, with a successful improvement on overall compliance. It is
322 expected that under low compliance, minor differences between time periods would
323 result in great practice variation; however, under high compliance, we might be able to
324 have a more accurate contrast between time period estimations. Accurate contrast is
325 needed, because previous associations evaluating the exposure time periods suffered
326 from data noise (15) and low magnitude point-estimates (10, 35).

327 We observed higher magnitude of point-estimates for period of the day in ED
328 areas and for period of the week in non-ED areas. Although we have no data regarding
329 the exact number of staff in place during data collection, we hypothesize that the
330 observed difference by location of diagnosis was expected because in Brazil non-ED
331 areas are less staffed during the weekends compared with the weekdays; in contrast,
332 ED areas are similarly staffed during periods of the week, but usually less staffed during

night shifts. Staff number could partially explain the differences between areas (20), but further studies should consider organizational factors (15), workload (4) and healthcare worker's characteristics (e.g., time of experience)(21, 22), to better understand the mechanisms of the observed association.

The gap in the association between daytime and better compliance increased throughout campaign implementation. Even though not backed up by data, we hypothesize that higher turnover of staff during night shifts, including displaced staff from other areas to cover night shifts, could partially explain this association.

Regardless of the potential mechanism, campaign implementations suffer from a lack of motivation and saturation overtime, reinforcing the need for continuous efforts to keep sustained performance (36-40). Our sepsis program aims to train every new healthcare worker and regularly afterwards, which might reflect on the small marginal adjusted difference between periods of the day (4.7% lower during nighttime compared with daytime overall, and 7.6% for the seventh year, Figure 2). Yet, staff turnover is a main challenge for any educational program and further strategies to mitigate this "turnover effect" should be evaluated.

We assumed that compliance to the 3-hour bundle is standard practice for sepsis care and associated with reduction in mortality, as it has been shown in several studies (3, 41, 42), including a study from our group during the initial years of the sepsis campaign in the same 10 hospitals (2). We explored the role of 3-hour full compliance as a causal mediator between period of day and in-hospital mortality (28). We observed a scenario of "indirect-only mediation" as defined by Zhou et al (43), because daytime has a protective effect on hospital mortality only through its mediated effect by 3-hour bundle full compliance. This scenario was expected because

of the strong signal between the mediator (3-hour bundle full compliance) and mortality, compared with the expected small direct effect of period of day (28, 29, 43). This analysis is exploratory because further studies should evaluate the role of other mediators and unmeasured confounding pathways between mediators and mortality.

This study has important strengths, such as its multicenter nature, the large sample size and period of follow-up, the sensitivity analyses and a priori data analysis plan. Additionally, we included patients with sepsis diagnosed in the ED, on the wards and in the ICUs, which increases the generalizability of our findings. However, we must acknowledge important limitations. First, we do not have data to explain the reasons for the difference in the observed bundle compliance, such as actual number of healthcare workers on each time period. Thus, our results should be considered hypothesis generating. In addition, all hospitals participating in this study are involved in sepsis quality improvement programs, and our compliance rates are higher than previously reported in the literature (42, 44). Additionally, our hospitals represent only private institutions in the largest metropolitan area of Brazil. Thus, the external validity of our findings to the entire healthcare system is not straightforward.

CONCLUSION

Compliance with 3-hour sepsis treatment guidelines was associated with the time period of sepsis diagnosis. Diagnosis of sepsis during the daytime is associated with increased lactate measurement, earlier antibiotic administration, and increased full compliance with the 3-hour sepsis bundle. The association with increased full compliance was observed for weekdays compared to weekends only in non-ED areas.

379

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382 responsibility for the integrity of the data and the accuracy of the analysis. All authors
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393 **This manuscript has a visual abstract.**

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FIGURES

Figure 1. Association between period of the day and period of the week with compliance to 3-hour sepsis treatment bundles.

The reference category was nighttime for the period of the day and weekend for the period of the week. The point estimates are represented by circles and their 95% confidence intervals are represented as horizontal lines. The associations were adjusted by age, sex, sepsis severity, source of infection, site of sepsis occurrence and hospital. OR – odds ratio. *Item evaluated for a subgroup of 7395 patients.

Figure 2. Marginal probability of full compliance to the early sepsis treatment bundles by period of the day over time.

The marginal probability was estimated from the fully-adjusted model (i.e., adjusted by age, sex, sepsis severity, source of infection, site of sepsis occurrence and hospital) with an interaction term between the period of the day and the semester of the campaign ($p_{\text{interaction}}=0.001$). The point estimates are represented by circles and their 95% confidence intervals are represented as vertical lines.

Table 1. Clinical characteristics of patients diagnosed with sepsis and septic shock according to the period of day of diagnosis.

Variable	All patients n=11737	Day n=7658	Night n=4079
Age, years - mean (SD)*	61 (21)	62 (21)	60 (21)
Male sex*	5598 (48.0%)	3650 (47.8%)	1948 (48.0%)
Diagnosis			
Severe Sepsis	8733 (74.4%)	5734 (74.9%)	2999 (73.5%)
Septic Shock	3004 (25.6%)	1924 (25.1%)	1080 (26.5%)
Site of sepsis occurrence			
Emergency room	7472 (63.7%)	4704 (61.4%)	2768 (67.9%)
Ward	2869 (24.4%)	1991 (26.0%)	878 (21.5%)
ICU	1396 (11.9%)	963 (12.6%)	433 (10.6%)
Main source of sepsis			
Lungs	5510 (47.0%)	3635 (47.5%)	1875 (46.0%)
Urinary	2027 (17.3%)	1308 (17.1%)	719 (17.6%)
Abdominal	1680 (14.3%)	1042 (13.6%)	638 (15.6%)
Skin/soft tissue	568 (4.8%)	363 (4.7%)	205 (5.0%)
Bloodstream	309 (2.6%)	222 (2.9%)	87 (2.1%)
Other	1643 (14.0%)	1088 (14.2%)	555 (13.6%)
SOFA, points - median [p25-p75]*	4 [2-7]	4 [2-7]	4 [2-7]
Number of organ failures			
1	6372 (54.3%)	4183 (54.6%)	2189 (53.7%)
2	3558 (30.3%)	2324 (30.4%)	1234 (30.3%)
3	1328 (11.3%)	831 (10.9%)	497 (12.2%)
≥4	479 (4.1%)	320 (4.2%)	159 (3.9%)
Time required to diagnose sepsis, hours - median, [p25-p75]			
All patients	0.25 [0-0.98]	0.25 [0-0.93]	0.25 [0-1.00]
Emergency department	0.18 [0-0.72]	0.18 [0-0.67]	0.17 [0-0.81]
Ward	0.33 [0-1.22]	0.33 [0-1.17]	0.33 [0-1.33]
ICU	0.5 [0-2]	0.5 [0-2.5]	0.38 [0-1.5]
ICU admission^a	8713 (74.2%)	5643 (73.7%)	3070 (75.3%)
ICU LOS, days - median [p25-p75]*	4.6 [2.1-9.7]	4.8 [2.1-10.0]	4.1 [2.0-9.0]
Hospital LOS, days - median [p25-p75]*	10.0 [5.1-19.7]	10.0 [5.2-20.2]	9.7 [4.8-18.6]
Hospital mortality	2897 (24.7%)	1930 (25.2%)	967 (23.7%)

Legend: SOFA: Sequential organ failure assessment; ICU: Intensive care unit; LOS: Length of stay.

^a – Include those patients already diagnosed in the ICU

* Missing values: age (4, <0.1%), sex (36, 0.3%), SOFA (54, 0.5%), ICU LOS (221, 2.5%), hospital LOS (5, <0.1%)

610 **Table 2. Compliance to the 3-hour bundle items according to the period of**
 611 **day of sepsis diagnosis.**

Bundle item	All patients n=11737	Day n=7658	Night n=4079	Day minus Night
				Proportion difference (95% CI)
Full 3-hour bundle, n(%)	9278 (79.1%)	6168 (80.6%)	3110 (76.3%)	4.3% (2.7-5.9), p<0.001
Lactate measurement, n(%)	11170 (95.2%)	7321 (95.6%)	3849 (94.4%)	1.2% (0.4-2.1), p=0.003
Blood cultures, n(%)	10670 (90.9%)	6985 (91.2%)	3685 (90.4%)	0.9% (-0.3-2.0), p=0.122
Antibiotic administration, n(%)	10457 (89.1%)	6910 (90.2%)	3547 (87.0%)	3.3% (2.0-4.5), p<0.001
Fluid administration, n(%) (n=7395)	6951 (94.0%)	4502 (94.3%)	2449 (93.4%)	0.9% (-0.2-2.1), p=0.111

612 Missing values: lactate measurement (2, <0.1%), blood cultures (2, <0.1%), antibiotic
 613 administration (2, <0.1%), full 3-hours bundle (2, <0.1%)

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Table 3. Crude and adjusted association between sepsis diagnosis during period of the day and week and compliance to the 3-hour treatment bundle.

Adherence to	Period	Unadjusted OR (95% CI)	Adjusted* OR (95% CI)
Full 3-hours bundle	Day vs Night	1.29 (1.18-1.41), p<0.001	1.35 (1.23-1.49), p<0.001
Lactate measurement	Day vs Night	1.30 (1.09-1.54), p=0.003	1.32 (1.11-1.58), p=0.002
Blood cultures	Day vs Night	1.11 (0.97-1.26), p=0.122	1.18 (1.03-1.35), p=0.019
Antibiotic administration	Day vs Night	1.38 (1.23-1.56), p<0.001	1.41 (1.25-1.6), p<0.001
Fluid administration (n=7395)	Day vs Night	1.17 (0.96-1.43), p=0.111	1.22 (1-1.5), p=0.049
Full 3-hours bundle	Weekday vs Weekend	1.05 (0.96-1.15), p=0.320	1.08 (0.98-1.19), p=0.115
Lactate measurement	Weekday vs Weekend	1.22 (1.02-1.45), p=0.026	1.25 (1.05-1.50), p=0.012
Blood cultures	Weekday vs Weekend	0.99 (0.87-1.13), p=0.915	1.01 (0.88-1.15), p=0.931
Antibiotic administration	Weekday vs Weekend	0.99 (0.88-1.12), p=0.915	1.03 (0.91-1.17), p=0.663
Fluid administration (n=7395)	Weekday vs Weekend	1.24 (1.02-1.51), p=0.033	1.25 (1.02-1.53), p=0.029

* Adjusted for: age, sex, sepsis severity, source of infection, place of sepsis occurrence and hospital. The reference category was Night for period of the day and Weekend for period of week.
OR: odds ratio

A – Day compared to Night

Adjusted OR

B – Weekday compared to Weekend

Adjusted OR

Non Emergency Department Emergency Department

Supplementary appendix:

Association of sepsis diagnosis at daytime and on weekdays with compliance to the 3-hour sepsis treatment bundles: a multicenter cohort study

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e-Methods (Definitions)

Severe sepsis and septic shock: Severe sepsis was defined as two or more signs of systemic inflammatory response syndrome secondary to a known or suspected infection and at least one sepsis-induced organ dysfunction (1, 2).

Sepsis-induced organ dysfunction: Organ dysfunction was considered as one of the following conditions, unrelated to chronic conditions: hypotension (systolic blood pressure (SBP) < 90 mmHg or mean arterial pressure < 65 mmHg or a decrease in SBP > 40 mmHg); bilateral infiltrates and arterial oxygen partial pressure/oxygen inspiratory fraction ($\text{PaO}_2/\text{FiO}_2$) ratio ≤ 300 or a new (or increased) oxygen requirement to maintain $\text{SpO}_2 > 90\%$; lactate level ≥ 2 mmol/L; bilirubin level > 2 mg/dL; urine output ≤ 0.5 ml/kg/hour for > 2 hours or creatinine > 2.0 mg/dL; platelet count $\leq 100,000 \text{ mm}^3$ or INR > 1.5 or aPTT > 60 sec. Septic shock was defined as volume-refractory hypotension with a need for vasopressors (2, 3).

Time of sepsis diagnosis: We defined sepsis diagnosis as the registration of a sepsis hypothesis in the patient's chart, that is the time and date when the sepsis case report form was started and the "sepsis team" was activated.

Time required to diagnose sepsis: This time frame was defined as the number of hours between the onset of the first dysfunction and its recognition by the healthcare provider. To identify the moment of organ dysfunction, the patient's chart was carefully revised to determine the first recording of hypotension, hypoxemia or low urine output as well as the time of the first laboratory test that fulfilled the respiratory, metabolic, coagulation or hepatic criteria for organ dysfunction. For patients admitted from the emergency department who already met the criteria for severe sepsis, we used the time of emergency department arrival (2).

eFigure 1. Sepsis times diagram

For patients diagnosed on wards or ICU, there is no time of arrival and the beginning of organ dysfunction is based on chart review and/or abnormal laboratory results per organ dysfunction definitions. ED: emergency department.

e-Figure 2. Directed acyclic graph used to adjust for potential confounding factors on the association between period of diagnosis and 3-h sepsis treatment compliance

Adapted from <http://dagitty.net/>

1 – Health-seeking behavior: “sequence of remedial actions that individuals undertake to rectify perceived ill-health.”, for example, the time difference between the onset of an illness and getting in contact with a healthcare professional, type of healthcare provider patients sought help from (https://wiki.ubc.ca/Health_Seeking_Behaviour)

2 – SOFA score calculated using the worst values within 24h from sepsis diagnosis.

Salmon nodes are ancestors of both the outcome (3-h treatment bundle) and the exposure (daytime / weekday), representing confounders. Grey nodes are consequence of outcome.

e-Figure 3: Study flowchart.

* Patients excluded:

1 – Duplicates	Patients who presented multiply times with sepsis. We included only the first sepsis episode.
2 – Uncomplicated infection	Patients who had an infection but without criteria for severe sepsis/septic shock.
3 – Not infection	Patients who had a sepsis case report form open, but was deemed not having infection after review. These patients ended not receiving any antibiotic treatment or a single dose and the attended physician and the local sepsis protocol manager (commonly a trained nurse or physician) agreed that clinical condition was not due to infection.

e-Table 1. Clinical characteristics of patients diagnosed with severe sepsis and septic shock according to the period of the week of diagnosis.

Variable	All patients n=11737	Weekday n=7818	Weekend n=3919
Age, years - mean (SD)*	61 (21)	61 (21)	62 (21)
Male sex*	5598 (48.0%)	3726 (47.8%)	1872 (47.9%)
Diagnosis			
Severe Sepsis	8733 (74.4%)	5819 (74.4%)	2914 (74.4%)
Septic Shock	3004 (25.6%)	1999 (25.6%)	1005 (25.6%)
Site of sepsis occurrence			
Emergency room	7472 (63.7%)	4950 (63.3%)	2522 (64.4%)
Ward	2869 (24.4%)	1925 (24.6%)	944 (24.1%)
ICU	1396 (11.9%)	943 (12.1%)	453 (11.6%)
Main source of sepsis			
Lungs	5510 (47.0%)	3641 (46.6%)	1869 (47.7%)
Urinary	2027 (17.3%)	1360 (17.4%)	667 (17.0%)
Abdominal	1680 (14.3%)	1103 (14.1%)	577 (17.7%)
Skin/connective tissue	568 (4.8%)	390 (5.0%)	178 (4.5%)
Bloodstream	309 (2.6%)	219 (2.8%)	90 (2.3%)
Other	1643 (14.0%)	1105 (14.1%)	538 (13.7%)
SOFA, Median [p25-p75]*	4 [2-7]	4 [2-7]	4 [2-6]
Number of organ failures			
1	6372 (54.3%)	4270 (54.6%)	2102 (53.6%)
2	3558 (30.3%)	2325 (29.7%)	1233 (31.5%)
3	1328 (11.3%)	907 (11.6%)	421 (10.7%)
≥4	479 (4.1%)	316 (4.0%)	163 (4.2%)
Time required to diagnose sepsis, [p25-p75]	0.25 [0-0.98]	0.25 [0-1]	0.25 [0-0.88]
All patients	0.25 [0-0.98]	0.25 [0-1]	0.25 [0-0.88]
Emergency department	0.18 [0-0.72]	0.18 [0-0.73]	0.18 [0-0.68]
Ward	0.33 [0-1.22]	0.33 [0-1.25]	0.33 [0-1.17]
ICU	0.5 [0-2]	0.5 [0-2]	0.42 [0-2]
ICU admission^a	8713 (74.2%)	5830 (74.6%)	2883 (73.6%)
ICU LOS, days - Median [p25-p75]*	4.6 [2.1-9.7]	4.7 [2.1-9.3]	4.5 [2.2-10.0]
Hospital LOS, days - Median [p25-p75]*	10.0 [5.1-19.7]	9.9 [5.1-19.7]	10.3 [5.1-19.6]
Hospital mortality	2897 (24.7%)	1929 (24.7%)	968 (24.7%)

Legend: SOFA: Sequential organ failure assessment; ICU: Intensive care unit; LOS: Length of stay.

^a – Include those patients already diagnosed in the ICU

* Missing values: age (4, <0.1%), sex (36, 0.3%), SOFA (54, 0.5%), ICU LOS (221, 2.5%), hospital LOS (5, <0.1%)

e-Table 2. Compliance to the 3h-bundle items according to the period of the week of sepsis diagnosis.

Bundle item	All patients <i>n</i> =11737	Weekday <i>n</i> =7818	Weekend <i>n</i> =3919	Weekday <i>minus</i> Weekend
				Proportion difference (95% CI)
Full 3-hours bundle, n(%)	9278 (79.1%)	6201 (79.3%)	3077 (78.5%)	0.8% (-0.8-2.4), p=0.320
Lactate measurement, n(%)	11170 (95.2%)	7465 (95.5%)	3705 (94.6%)	0.9% (0.1-1.8), p=0.026
Blood cultures, n(%)	10670 (90.9%)	7106 (90.9%)	3564 (91.0%)	-0.1% (-1.2-1.0), p=0.915
Antibiotic administration, n(%)	10457 (89.1%)	6964 (89.1%)	3493 (89.2%)	-0.1% (-1.3-1.1), p=0.915
Fluid administration, n(%) (n=7395)	6951 (94.0%)	4664 (94.4%)	2287 (93.2%)	1.3% (0.1-2.4) , p=0.032
Missing values: lactate measurement (2, <0.1%), blood cultures (2, <0.1%), antibiotic administration (2, <0.1%), full 3-hours bundle (2, <0.1%)				

e-table 3. Different modelling approaches for the hospital clustering effect for the adjusted association between sepsis diagnosis during period of the day and week and full compliance to the 3h treatment bundle.

Outcome: full bundle compliance			
Approach for dealing with clustering at hospital level	Odds ratio	95% confidence interval	P-value
Period of day (daytime/nighttime)			
Without cluster adjustment	1.387	1.260-1.525	0.001
Fixed effect (main analysis)	1.351	1.227-1.487	<0.001
Random intercept	1.353	1.229-1.490	<0.001
Generalized estimating equation	1.348	1.226-1.483	<0.001
Period of week (weekday/weekend)			
Without cluster adjustment	1.067	0.969-1.176	0.186
Fixed effect (main analysis)	1.082	0.981-1.192	0.115
Random intercept	1.081	0.980-1.191	0.119
Generalized estimating equation	1.080	0.981-1.188	0.117

e-Table 4. Adjusted association between sepsis diagnosis during period of the day and week and compliance to the 3h treatment bundle stratified by site of sepsis occurrence.

		Non-ED (n=4243)	ED (n=7452)
Adherence to	Period	Adjusted* OR (95% CI)	Adjusted* OR (95% CI)
Full 3 hours bundle	Day vs Night	1.19 (1.04-1.37), p=0.014	1.55 (1.35-1.77), p<0.001
Lactate measurement	Day vs Night	1.11 (0.85-1.43), p=0.442	1.58 (1.24-2.02), p<0.001
Blood cultures	Day vs Night	1.06 (0.89-1.27), p=0.499	1.36 (1.11-1.67), p=0.004
Antibiotic administration	Day vs Night	1.35 (1.13-1.61), p=0.001	1.53 (1.29-1.83), p<0.001
Fluid administration (n=7395)	Day vs Night	1.35 (0.99-1.83), p=0.057	1.15 (0.88-1.50), p=0.316
Full 3 hours bundle	Weekday vs Weekend	1.15 (1.00-1.32), p=0.047	1.02 (0.89-1.17), p=0.757
Lactate measurement	Weekday vs Weekend	1.51 (1.18-1.94), p=0.001	1.04 (0.80-1.34), p=0.784
Blood cultures	Weekday vs Weekend	0.98 (0.82-1.18), p=0.849	1.06 (0.86-1.32), p=0.585
Antibiotic administration	Weekday vs Weekend	1.17 (0.99-1.39), p=0.074	0.89 (0.73-1.07), p=0.208
Fluid administration (n=7395)	Weekday vs Weekend	1.69 (1.26-2.28), p=0.001	1.00 (0.76-1.31), p=0.979

* Adjusted for: age, sex, sepsis severity, source of infection and hospital. The reference category was Night for period of the day and Weekend for period of week.

ED: Emergency Department; non-ED: non emergency department (ie, ward or intensive care unit); OR: odds ratio.

e-Table 5. Agreement between period of day and week as defined by sepsis diagnosis time (main analysis) versus time of emergency department arrival for patients diagnosed at the emergency department (n=7452)

		Defined by date/time as arrival for ED patients	
		Day	Night
Defined by date/time as sepsis case report from for ED patients	Day	4127	577
	Night	673	2095

Agreement: 83.3%

		Defined by date/time as arrival for ED patients	
		Weekday	Weekend
Defined by date/time as sepsis case report from for ED patients	Weekday	4774	176
	Weekend	178	2344

Agreement: 95.3%

e-Table 6. Association of period of the day and period of the week with bundle compliance using emergency department arrival as time zero among patients diagnosed at the emergency department (sensitivity analysis)

Adherence to	Period	Time zero by sepsis diagnosis (main analysis) (n=7452)	Time zero by ED arrival (sensitivity analysis) (n=7452)
		Adjusted* OR (95% CI)	Adjusted* OR (95% CI)
Full 3 hours bundle	Day vs Night	1.55 (1.35-1.77), p<0.001	1.42 (1.24-1.62), p<0.001
Lactate measurement	Day vs Night	1.58 (1.24-2.02), p<0.001	1.23 (0.96-1.58), p=0.106
Blood cultures	Day vs Night	1.36 (1.11-1.67), p=0.004	1.34 (1.09-1.65), p=0.006
Antibiotic administration	Day vs Night	1.53 (1.29-1.83), p<0.001	1.47 (1.23-1.76), p<0.001
Fluid administration (n=4238)	Day vs Night	1.15 (0.88-1.50), p=0.316	1.13 (0.86-1.47), p=0.385
Full 3 hours bundle	Weekday vs Weekend	1.02 (0.89-1.17), p=0.757	1.07 (0.93-1.23), p=0.347
Lactate measurement	Weekday vs Weekend	1.04 (0.80-1.34), p=0.784	1.11 (0.86-1.42), p=0.442
Blood cultures	Weekday vs Weekend	1.06 (0.86-1.32), p=0.585	1.13 (0.91-1.40), p=0.264
Antibiotic administration	Weekday vs Weekend	0.89 (0.73-1.07), p=0.208	0.95 (0.79-1.14), p=0.586
Fluid administration (n=4238)	Weekday vs Weekend	1.00 (0.76-1.31), p=0.979	1.04 (0.79-1.37), p=0.759

* Adjusted for: age, sex, sepsis severity, source of infection and hospital. The reference category was Night for period of the day and Weekend for period of week.

ED: Emergency Department; CI: confidence interval; OR: odds ratio.

e-Figure 4. Marginal probability of full compliance to the early sepsis treatment bundles by period of week over time. The marginal probability was estimated from the fully adjusted model (ie, adjusted by age, sex, sepsis severity, source of infection, place of sepsis occurrence and hospital) with interaction term between period of week and semester on campaign ($p_{\text{interaction}}=0.775$). The point estimates are represented by circles and their 95% confidence intervals as vertical lines.

e-Figure 5. Crude hospital mortality overtime stratified by period of day and period of week

e-Figure 6. Causal mediation analysis for the effect of period of day and in-hospital mortality

	Estimate	95% CI	p-value
ACME (average)	-0.00295	-0.00452 to -0.00151	<0.001
ADE (average)	0.01075	-0.00351 to 0.02519	0.156
Total Effect	0.00779	-0.00652 to 0.02197	0.312

The model for the mediator and for the outcome was adjusted by age, sex, sepsis severity, source of infection, place of diagnosis and hospital. The reference category was Night for period of the day. Solid lines represent the effect on those diagnosed during the day, dashed lines represent the effect on those diagnosed during the night for ACME and ADE. Confidence intervals estimated with a quasi-Bayesian approximation on 1,000 simulations (4, 5). ACME: average causal mediation effect, ADE: average direct effect.

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