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ORIGINAL RESEARCH

Effect of Out-Of-Hour Admission on Fluid Treatment of Emergency Department Patients with Suspected Infection; a Multicenter Post-Hoc Analysis

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Abstract: **Introduction:** Sepsis is a life-threatening and common cause of Emergency department (ED) referrals. Out-of-hour staffing is limited in ED, which may potentially affect fluid administration. This study aimed to investigate fluid volume variation in out-of-hour vs. routine-hour admissions. **Methods:** The present study is a post-hoc analysis of a multicentre, prospective, observational study investigating fluid administration in ED patients with suspected infection, from Jan 20th - March 2nd, 2020. Patient groups were "routine-hours" (RH): weekdays 07:00-18:59 or "out-of-hours" (OOH): weekdays 19:00-06:59 or Friday 19:00-Monday 06:59. Primary outcome was 24-hour total fluid volumes (oral + intravenous (IV)). Secondary outcomes were total fluids 0-6 hours, oral fluids 0-6 and 0-24 hours, and IV fluids 0-6 and 0-24 hours. Linear regression adjusted for site and illness severity was used. **Results:** 734 patients had suspected infection; 449 were admitted during RH and 287 during OOH. Mean (95% CI) total 24-hour fluid volumes were equal in simple infection and sepsis regardless of admission time: Simple infection RH: 3640 (3410 - 3871) ml and OOH: 3681 (3451 - 3913) ml. Sepsis RH: 3671 (3443;3898) ml and OOH: 3896 (3542;4250) ml. Oral fluids 0-6h were reduced in simple infection and sepsis among OOH vs. RH. Sepsis patients received more 0-6-hour IV fluid when admitted OOH vs. RH. There were no associations between admission time and 0-24-hour oral or IV volumes in simple infection or sepsis. **Conclusion:** Admission time did not have an association with 24-hour total fluid volumes. Sepsis patients admitted during OOH received more 0-6-hour IV fluids than RH patients, and simple infection and sepsis patients received less oral fluid in 0-6 hours if admitted during OOH vs. RH.

Keywords: Emergency service, hospital; fluid therapy; sepsis; infections; time factors; periodicity

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1. Introduction

Suspected infection and sepsis are very common in emergency department (ED) patients (1-3). Despite the overall decrease in sepsis-related mortality rates along with implementation of guidelines (4-7), rates of deterioration, morbidity and mortality remain significant (8-12). Early targeted treatment to reduce mortality and morbidity, including intravenous (IV) fluid resuscitation, is important (13). For patients with sepsis-induced hypoperfusion, the Surviving Sepsis Campaign (SSC) guideline recommends giving at least 30 ml/kg of IV crystalloid fluid within the first 3 hours. SSC does not give any recommendations on fluid administration in sepsis patients without hypotension or shock. Fluid treatment in sepsis patients not in shock is guided only by weak recommendations and fluid administration practice varies (13-16). Caring for sepsis patients – including administration of IV fluids – is time-consuming and requires close monitoring of disease progression, which might sometimes be challenging in an ED setting.

The organisation and staffing in the ED setting often changes according to time of day and between weekdays and week-

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ends (17). The out-of-hour (OOH) patient intake and referrals (i.e., OOH primary care) affects the admitted population with increased illness severity, other chief complaints and presentations, etc. (18-20). Extensive research has stated a weekend effect, for example, an increased mortality among patients admitted to hospitals in general and in the EDs during weekends (21-26). Also, OOH (sometimes also called "after-hour") admission on weekdays (during evening and night-time) is associated with higher mortality (19, 26). For sepsis patients, the weekend effect and OOH admission seem to affect outcomes such as risk of ICU admission, risk of intubation, and mortality (26-29). The underlying causes of these effects and the OOH phenomenon have never been clearly established, although both severity of illness and staffing levels have been suggested to be causal in ED studies (19, 20).
Whether associations exist between fluid administration practice and patient admission time is unknown. We hypothesized, that patients admitted during "routine-hours" received more total fluid than patients admitted during "out-of-hours". If such differences exist, it may be important knowledge to potentially change or uniform practice. This study aimed to assess the effect of varying admission times on fluid administration practice, volume, and IV versus oral administration in ED patients with simple infection and sepsis in the first 6 and 24 hours following admission.

2. Methods

2.1. Study design and settings

This was a post-hoc analysis of a prospective, observational, multicentre study consecutively enrolling patients with suspected infection admitted to any of three EDs in Central Denmark Region: Regional Hospital Herning, Region Hospital Randers, and Aarhus University Hospital from January 20th, 2020, to March 2nd, 2020 (2).
The three EDs serve a mixed rural–urban population of 0.9 million people and provide 24-hour emergency care to all adult acute patients, except those transferred directly to catheterization laboratories, and stroke units, and women in labor. ED patients are either referred by a general practitioner or brought in by ambulance after an emergency call. In the three EDs, patient contacts vary between 15,000 and 63,000 per year. Emergency health care in Denmark is publicly funded. The original study aimed at describing current 24-hour fluid administration to all ED patients admitted with suspected infection of any severity. The study was approved by the Danish Patient Safety Authority (case no.: 31-1521-188). Approval from an ethics committee was not required according to Danish law.

2.2. Participants

All ED patients at the three sites were screened for eligibility during the study period. We consecutively included all patients who fulfilled all of the following inclusion criteria: age ≥ 18 years, admitted through the ED with suspected infection defined as drawing of a blood culture and/or administration of IV antibiotics within 6 hours of arrival (2). We only included Danish citizens with a personal identification-number to be able to track them in the electronic patient record. Only patients who first presented within the study period and fulfilled all the inclusion criteria were included. We only included patients who were admitted for the entire 24-hour time-period with fluid administration registered. We excluded 1) patients who were admitted due to trauma, 2) patients with serious bleeding defined by the use of more than two units of red blood cells or the need for an invasive intervention for bleeding, and 3) patients, who only received prophylactic antibiotics (e.g., patients scheduled for surgery) who did not have a blood culture drawn. All intravenous fluids ≥ 50 ml were registered.

2.3. Fluid registration

All included patients had oral and IV fluids registered on a paper case report form (CRF) (see original article(2) for the first 24 hours of their hospital stay; including fluids administered in the prehospital setting. All intravenous fluids ≥ 50 ml were registered.
Intravenous fluids included crystalloids, glucose, albumin, parenteral nutrition, and blood products. Oral fluids were registered by the treating nurses and/or by the patient if deemed fully conscious and cooperative. Tube feeding was registered as part of oral fluids. For all fluids – oral and intravenous - the administration start time was noted. The CRF followed the patient for 24 hours or until discharge within 24 hours.
In the analyses, we only included patients who were admitted for the entire 24-hour time-period with fluid administration registered.
Patients were divided into groups of illness severity within 6 hours of ED arrival: simple infection (Sequential Organ Failure Assessment (SOFA)-score < 2), sepsis (increase in SOFA-score ≥ 2 from baseline), and septic shock (mean arterial pressure (MAP) of 65mmHg or greater and serum lactate level > 2 mmol/L (>18mg/dL)) based on the Sepsis-3 guidelines using SOFA-score (30). Descriptive data on vital signs, organ dysfunction, receipt and timing of intravenous antibiotics, comorbidities, mortality, ED length of stay, and in-hospital length of stay were automatically retrieved from the electronic patient record at each hospital.

2.4. Outcomes

The main outcome of both the original and this post-hoc analysis was the total volume of oral and intravenous (combined) fluids administered within the first 24 hours of admission stratified by illness severity (simple infection or sepsis) and admission time. We also report administered fluid in the following categories: total fluid 0-6 hours, oral fluids 0-6 and 0-24 hours, and IV fluids 0-6 and 0-24 hours, stratified by illness severity (simple infection or sepsis).

2.5. Statistical analyses

This post-hoc analysis investigated the effect of out-of-hour admission vs. routine-hour-admission on fluid treatment in patients with suspected infection. All inclusion and exclusion criteria were the same as for the original study. For this sub-study, we only included patients with simple infection or sepsis (i.e. a SOFA-score ≥ 2 (31)), and excluded patients with septic shock (need for vasopressor to maintain MAP > 65 mmHg and lactate > 2 mmol/L), since this group only included eight patients.

The admission time was registered by a secretary at the time of patients' presentation to the ED. We subsequently divided patients into two groups according to the admission time: "routine-hours" and "out-of-hours". "Routine-hours" was considered weekdays working hours and defined as Monday to Friday 07:00-18:59. "Out-of-hours" included both weekday nights defined as Monday to Friday 19:00-06:59 and weekends from Friday 19:00 to Monday 06:59. The intervals were chosen according to staffing levels; "Routine hours" reflected hours with higher staffing levels and "out-of-hours" reflected hours with lower staffing levels in the EDs.

For the original study, we did not calculate a formal sample size a priori, but based on unpublished data from Aarhus University Hospital, we anticipated that approximately 1600 patients with suspected infection would present at the three sites within the study period. This anticipated sample size was deemed adequate for the descriptive goal of the original study and for this post-hoc analysis. Categorical data are reported as counts and proportions (%) and continuous data as means with standard deviations or medians with interquartile range (IQR, first and third quartile), as appropriate. Distributions were assessed for normality using visual inspection of histograms. To assess the association between patient and disease characteristics and fluid administration, we used linear regression models with the amount of fluid within the first 24 hours as the primary outcome; these analyses were adjusted for site and SOFA-score (31) and reported with 95% confidence intervals (CI). The decision to adjust for SOFA-score was based on the assumption that the illness severity of patients admitted during routine-hours and out-of-hours would vary. For all analyses on fluid volumes and differences in these, we included all patients with simple infection or sepsis (n= 726). There was no missing data on neither exposure (admission time), primary or secondary outcomes, nor the adjusting variable for any patients. Data was analyzed using Stata version 17 (StataCorp LP, College Station, TX, USA). $P < 0.05$ was considered as level of significance.

3. Results

3.1. Characteristics of the study population

Of all ED patients (9,992 unique patients during the inclusion period at all three sites), 1924 patients fulfilled all inclusion criteria. 24-hour fluid administration was available for 734 (38%) patients. We excluded the eight septic shock patients from further analyses. Finally, 726 patients with simple infection or sepsis, a minimum of 24-hour hospital admission, and 24-hour fluids available were included in this study. Of these, 443 (61%) were admitted during "routine-hours" and 283 (39%) were admitted during "out-of-hours" (Figure 1).

Baseline characteristics of the included population (n=726) are shown in table 1 based on the admission time. There were no differences in baseline characteristics between patients admitted during "routine-hours" and "out-of-hours". C-reactive protein (CRP) levels were lower in patients admitted during afterhours.

3.2. Primary outcome

24-hour total oral and intravenous fluid administration The mean total, combined, oral and intravenous fluid volume administered during the first 24 hours of admission to patients admitted with simple infection during "routine-hours" was 3640 (95% CI: 3410 - 3871) ml and it was 3681 (95% CI: 3451 - 3913) ml for patients admitted during "out-of-hours", with an adjusted mean difference (for site and SOFA-score) of 50 (95% CI: -29 - 398) ml. For patients with sepsis admitted during "routine-hours", the total volume was 3671 (95% CI: 3443 - 3898) ml and for sepsis patients admitted during "out-of-hours" 3896 (95% CI: 3542 - 4250) ml with an adjusted mean difference of 226 (95% CI: -165 - 616) ml (Table 2).

3.3. Secondary outcomes

6-hour total oral and intravenous fluid administration Total fluid administration of oral and intravenous fluids combined administered during the first 0-6 hours were not statistically significant different between "routine-hours" and "out-of-hours" for patients with simple infection or sepsis patients, with adjusted mean differences of -49 (95% CI: -238 - 139) and 130 (95% CI: -83 - 343), respectively (Table 2).

3.4. Oral and intravenous fluids

We found a difference in oral fluid administration during the first 6 hours of admission. Patients with simple infection re-

Table 1: Baseline characteristics of study participants

Variables	Simple infection (n=387)		P	Sepsis (n=339)		P
	RH (n=241)	OH (n=146)		RH (n=202)	OH (n=137)	
Age (years)						
Median (IQR)	73 (56 - 82)	69 (55 - 81)	0.29	73 (65 - 83)	73 (68 - 83)	0.71
Gender						
Male, n (%)	113 (47%)	73 (50%)	0.55	116 (57%)	80 (58%)	0.86
Anthropometrics						
Height (cm)	170 (163 -177)	171 (164 -179)	0.15	172 (165 -177)	172 (165 -178)	0.91
Weight (Kg)	74 (62 -87)	76 (64 -88)	0.66	76 (63 -87)	75 (61 -90)	0.77
BMI (kg/m2)	25 (22 -29)	25 (22 -29)	0.98	25 (23 -28)	25 (21 -30)	0.50
Do-not-resuscitate/do-not-intubate-orders						
Number (%)	29 (12)	18 (12)	0.93	47 (23)	38 (28)	0.35
Vital signs#						
Respiratory rate (/min)	20 (18 -24)	20 (18 -24)	0.93	22 (20 -26)	24 (20 -28)	0.16
Saturation (%)	96 (94 -97)	95 (94 -97)	0.23	92 (88 -94)	93 (90 -95)	0.001
Heart rate (/min)	92 (80 -103)	94 (85 -110)	0.03	98 (85 -115)	98 (85 -115)	0.93
SBP (mmHg)	130 (113 -144)	136 (118 -148)	0.05	120 (103 -135)	119 (99 -133)	0.47
MAP (mmHg)	91 (81 -101)	94 (84 -104)	0.05	85 (73 -98)	84 (72 -95)	0.41
Temperature (∘C)	38.0(37.5 -38.4)	38.3(37.7 -39.0)	0.04	38.1(37.4 -38.8)	38.4(37.6 -39.1)	0.15
GCS	15 (15 -15)	15 (15 -15)	0.90	15 (15 -15)	15 (13 -15)	0.03
SOFA-score						
Total	0 (0 -1)	0 (0 -1)	0.36	2 (2 -4)	3 (2 -4)	0.27
Respiration	0 (0 -0)	0 (0 -0)		2 (0 -2)	2 (0 -2)	
Coagulation	0 (0 -0)	0 (0 -0)		0 (0 -0)	0 (0 -0)	
Liver	0 (0 -0)	0 (0 -0)		0 (0 -1)	0 (0 -0)	
Cardiovascular	0 (0 -0)	0 (0 -0)		0 (0 -0)	0 (0 -0)	
Central nervous system	0 (0 -0)	0 (0 -0)		0 (0 -0)	0 (0 -1)	
Renal	0 (0 -0)	0 (0 -0)		0 (0 -1)	0 (0 -0)	
Laboratory findings						
Creatinine (µmol/l)	72 (57 -95)	71 (57 -91)	0.64	85 (62 -123)	88 (64 -126)	0.98
Platelets (× 109/l)	267 (215 -37)	253 (193 -16)	0.07	218 (174 -70)	220 (154 -03)	0.72
Bilirubin (µmol/l)	9 (7 -14)	9 (7 -14)	0.93	12 (8 -23)	11 (7 -20)	0.46
Leukocytes (× 10^9/l)	11.3 (8.6 -4.7)	11.0 (8.4 -4.6)	0.59	11.7 (8.6 -5.7)	12.1 (8.6 -7.4)	0.53
CRP (mg/l)	112 (42 -194)	61 (23 -150)	0.002	79 (23 -203)	68 (25 -127)	0.33
Lactate (mmol/l)	1.4 (0.9 -1.9)	1.6 (0.8 -2.9)	0.54	1.6 (1.1 -2.5)	1.5 (1.0 -2.4)	0.53
Time to						
Blood culture (hours)	0.6 (0.4 -0.8)	0.5 (0.3 -0.7)	0.06	0.5 (0.2 -0.7)	0.5 (0.3 -0.8)	0.75
Antibiotics (hours)	2.3 (1.1 -4.7)	1.8 (0.7 -3.4)	0.15	1.5 (0.4 -3.3)	1.6 (0.8 -2.9)	0.88
Infectious source*						
Respiratory	66 (27)	34 (23)		91 (46)	50 (37)	
Urinary	55 (23)	26 (18)		26 (13)	28 (20)	
Skin/soft tissue	34 (14)	14 (10)		11 (5)	3 (2)	
Abdominal	34 (14)	28 (19)		20 (10)	20 (15)	
Bacteriaemia	1 (0.4)	-**		-**	1 (1)	
Viral	5 (2)	11 (8)		6 (3)	7 (5)	
Other	9 (4)	9 (6)		7 (3)	4 (3)	
Unknown	14 (6)	13 (9)		23 (11)	9 (7)	
Length of stay						
ED (hours)	11.5 (6.7 -5.0)	15.6 (7.4 -5.5)	0.47	10.3 (6.0 -5.6)	16.0 (6.7 -1.8)	0.06
In-hospital (hours)	78 (49 -147)	96 (56 -157)	0.53	131 (71 -190)	120 (75 -181)	0.52
Mortality						
In-hospital	5 (2)	4 (3)	0.67	14 (7)	7 (5)	0.50
90-day	23 (10)	17 (12)	0.65	42 (21)	27 (20)	0.81

All data are presented as medians with (interquartile range; IQR) or frequency (%). BMI: Body mass index; ED: emergency department; GCS: Glasgow Coma Scale; MAP: mean arterial pressure; SBP: Systolic blood pressure; SOFA score: Sequential Organ Failure Assessment score (30); CRP: c-reactive protein; RH: Routine-hour admission; OH: Out-of-hour admission.

P-values are based on Wilcoxon rank-sum test and Pearson's X^2.

*Numbers do not sum up to 100%, since it was possible to have more than one infectious source. Therefore, it was not possible to add p-values. **represents no patients in this category

Worst within 6h.

Table 2: Comparing the received fluid volumes between patients admitted to emergency department during the routine hours and out-of-hours

Variables	Fluid volumes (ml)	Mean difference (95% CI)		P value
		Total	SOFA adjusted	
Simple infection				
Oral fluids 0-6 hours				
Routine-hours	653 (584 - 721)	-	-	0.036
Out-of-hours	526 (442 – 611)	-126 (-235 - -17)	-117 (-227 - -8)	
Oral fluids 0-24 hours				
Routine-hours	1897 (1763 – 2031)	-	-	0.27
Out-of-hours	1758 (1597 – 1919)	-139 (-351 – 73)	-117 (-329 – 95)	
IV fluids 0-6 hours				
Routine-hours	925 (819 – 1032)	-	-	0.44
Out-of-hours	1006 (874 – 1138)	80 (-90 – 251)	67 (-104 – 239)	
IV fluids 0-24 hours				
Routine-hours	1744 (1529 – 1958)	-	-	0.30
Out-of-hours	1923 (1716 – 2132)	180 (-139 – 499)	167 (-152 – 487)	
Oral and IV fluids 0-6 hours				
Routine-hours	1577 (1460 – 1695)	-	-	0.60
Out-of-hours	1532 (1388 – 1675)	46 (233 – 142)	-49 (-238 – 139)	
Oral and IV fluids 0-24 hours				
Routine-hours	3640 (3410 – 3871)	-	-	0.78
Out-of-hours	3681 (3451 – 3913)	-41 (305 – 387)	50 (-298 – 398)	
Sepsis				
Oral fluids 0-6 hours				
Routine-hours	428 (370 – 487)	-	-	0.002
Out-of-hours	285 (223 – 346)	-144 (-231 - -56)	-139 (-225 - -54)	
Oral fluids 0-24 hours				
Routine-hours	1366 (1247 - 1485)	-	-	0.23
Out-of-hours	1248 (1098 - 1398)	-118 (-307 - 72)	-113 (-299 - 73)	
IV fluids 0-6 hours				
Routine-hours	1207 (1077 - 1337)	-	-	0.009
Out-of-hours	1468 (1290 - 1647)	261 (46 - 477)	270 (68 - 471)	
IV fluids 0-24 hours				
Routine-hours	2305 (2079 - 2531)	-	-	0.067
Out-of-hours	2648 (2312 - 2983)	343 (-45 - 731)	338 (-23 - 701)	
Oral and IV fluids 0-6 hours				
Routine-hours	1636 (1505 - 1766)	-	-	0.23
Out-of-hours	1754 (1565 - 1942)	-118 (-103 - 338)	-130 (-83 - 343)	
Oral and IV fluids 0-24 hours				
Routine-hours	3671 (3443 - 3898)	-	-	0.26
Out-of-hours	3896 (3542 - 4250)	225 (175 - 626)	226 (-165 - 616)	

Data are presented with 95% confidence interval (CI). P-value for the adjusted analyses are reported. IV: intravenous; SOFA: Sequential Organ Failure Assessment.

ceived a mean of 653 (95%CI: 584 - 721) ml in the first 6 hours of admission if admitted during "routine-hours", whereas patients with simple infection admitted during "out-of-hours" received a mean of 526 (95%CI: 442 - 611) ml, (adjusted mean difference: -117 (95% CI: -227 - -8)) ml. A similar difference was seen in patients with sepsis. For patients with sepsis admitted during "routine-hours" the mean oral fluid in the first 6 hours was 428 (95%CI: 370 - 487) ml and for "out-of-hours" 285 (95%CI: 223 - 346) ml, (adjusted mean difference: -139 (95% CI: -225 - -54)) (Table 2). Looking at 0-24 hours, the variation in oral fluid treatment associated with admission time was no longer present (Table 2).

For IV fluids administered in the initial 6 hours of admission, we found that IV fluid volumes were the same for patients with simple infection admitted during "routine-hours" and "out-of-hours": 925 (95%CI: 819 - 1032) ml for "routine-hours" and 1006 (95% CI: 874 - 1138) ml for "out-of-hours", (adjusted mean difference: 67 (95% CI: 67 (-104 - 239)). Patients with sepsis admitted during "routine-hours" had significantly less IV fluids administered in the first six hours compared to patients admitted during "out-of-hours". They received a mean of 1207 (95% CI: 1077 - 1337) ml if admit-

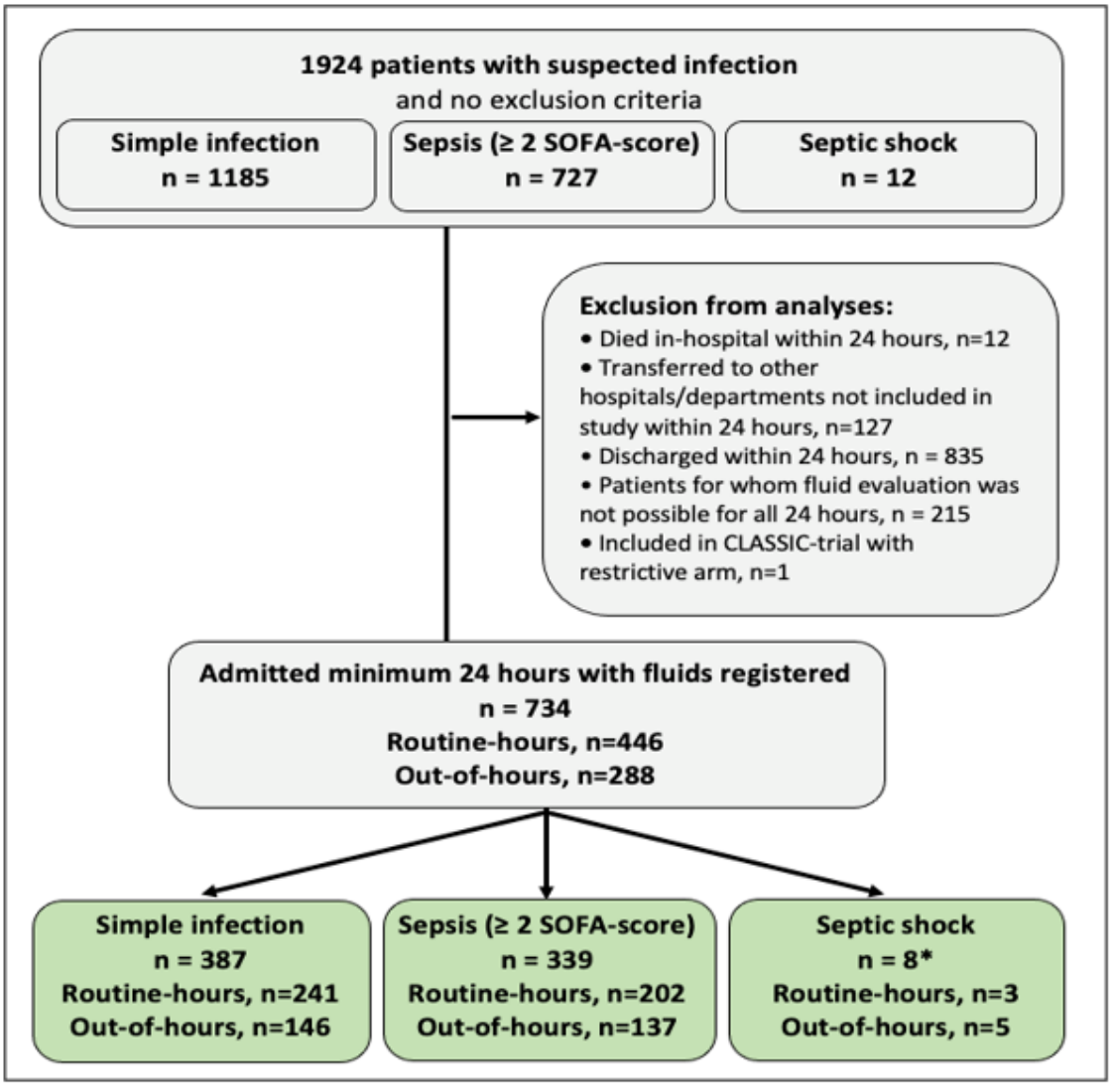

Figure 1: Patient selection flow chart. * Septic shock patients were not included in analyses since only 8 patients had septic shock.

ted during "routine-hours" and 1468 (95% CI: 1290 - 1647) ml if admitted during "out-of-hours" (adjusted mean difference: 270 (95% CI: 68 - 471)). As with oral fluid treatment, the variation found in IV fluid treatment of sepsis patients was limited to the first 6 hours and no differences were found in 24-hour IV fluid volumes according to admission time in simple infection or sepsis (Table 2).

4. Discussion

We found no association between total fluid administration practice and time of admission, neither looking at the first 0-6 hours or 0-24 hours of admission regardless of severity of illness. However, we found that patients with simple infection and sepsis both received less oral fluid and patients with sepsis received more intravenous fluids during the first 6 hours, when admitted during "out-of-hours" compared to "routine-hours". These differences, however, were not present after 24 hours.

Since we hypothesized that patients admitted during "routine-hours" received more total fluid than patients admitted during "out-of-hours", for example due to lower staffing levels during out-of-hours, it was rather surprising that total fluid volumes were the same: Total fluid administration practise does not appear to be affected by organisational changes or staffing in the ED depending on day of week and time of day in the three Danish EDs. A Korean study of ED patients with septic shock, found an even higher sepsis bundle compliance and adherence to fluid resuscitation recommendations for patients admitted during

the night (32), whereas a Brazilian study found lower total bundle adherence, but the same adherence to fluid resuscitation goals in night versus day admissions (33). An Australian study found no association between admission time and receiving fluids at all or time to fluid administration (34). The increased attention towards sepsis patients and the necessity of early therapy and delivering (time-consuming) care to improve clinical outcome for these patients in recent years may have contributed to the uniformity of the total fluid treatment regardless of time of admission, which we found.

The Surviving Sepsis Campaign guideline recommends giving at least 30 ml/kg of IV crystalloid fluid to patients with sepsis induced hypoperfusion or shock within the first 3 hours. This does not apply to patients without hypotension or septic shock (35). We found small differences in the preferred administrative route used in the initial 6 hours and found, that sepsis patients admitted during "out-of-hours" received significantly more intravenous fluids and less oral fluids, than patients admitted during "routine-hours" with sepsis. This could be explained by an intention to spare time or not to awaken and disturb sleeping patients during late hours/night-time to give oral fluids and instead use intravenous fluid treatment during the initial 6 hours of "out-of-hour" admissions. Since intravenous fluids have been suggested to destroy glycocalyx, this strategy may be unfortunate, especially if administered rapidly (15, 36). However, the association was non-existing when exceeding the first 6 hours of admission.

Due to the organisation of the Danish healthcare system, all Danish citizens are assigned a general practitioner (GP). In daytime, the GP refers the patient in need of hospital care; yet, in out-of-hours and weekends referrals go through out-of-hour GPs (who do not know the patient) or emergency service dispatch centres after emergency calls. Because of this, we expected patients admitted during "out-of-hours" to have more severe illness than during "routine-hours" and chose to adjust for illness severity in terms of SOFA-score in our analyses before conducting our analyses. According to the blood test results, vital signs and illness severity scores, this was not the case. No apparent differences in baseline characteristics were found between patients admitted during "routine-hours" and "out-of-hours" except for differences in CRP level (Table 1). When adjusting for illness severity in our analyses to decrease the impact of potential baseline differences, it did not change the mean fluid administration differences, but there may be unmeasured significant differences in the patient groups that we were not able to describe with the collected data and, therefore, also did not adjust for in our analyses.

A substantial part of the study population was excluded from the analyses (Figure 1). We especially suspected the group where fluid registration was not possible or available for the full 24 hours (n=214) to have an overrepresentation of patients admitted during "out-of-hours". One could assume that lower staffing would limit inclusion in a descriptive study of patients fulfilling inclusion criteria, i.e., patients not starting the CRF (timely) due to limited staffing. This could affect a considerable part of the non-included patients, who would have been in the "out-of-hour" category. However, the pattern of patient admission during "routine-hour" and "out-of-hour" for excluded patients was similar to that of the included patients, described in the results section, eliminating this concern.

5. Strengths and limitations

This study was a multicentre study, which made it possible to enrol a large proportion of patients during a relatively short period of time, generating a solid basis for comparison. Patients had 24-hour fluids registered on a paper CRF, so we were also able to include oral fluids, which is a strength. Also, we included all eligible patients regardless of do-not-resuscitate/-intubate orders or limitations in care.

Adjusting for illness severity, using SOFA-score, as a potential confounder of fluid volumes may not be the most appropriate approach in this less sick population, since it may not cover the entire differences in illness severity in for example patients who will never be invasively ventilated or receive vasopressors, although this approach is suggested in SEPSIS-3 (30). Also, we could have considered adjusting for age, since age could decrease fluid volumes to avoid fluid overload in elderly patients with an increased risk of heart failure.

All patients were enrolled during winter season, so no seasonal variations may have influenced the results, however, this limits generalizability to other seasons. Of note, the inclusion period ended before the first COVID-19 patient in Central Denmark Region was admitted on March 6, 2020.

The "time-of-admission" categories were arbitrarily defined but in accordance with staffing at the largest site. Other studies have varying definitions of "out-of-hours" (19, 37, 38). In this study, time of admission categories were limited to "routine-hours" and "out-of-hours", further subdivisions could be of interest, including weekdays vs. weekends.

The study only included patients who were admitted for 24 hours or more and for whom fluid registration was available for the full 24 hours. For patients admitted during late "routine-hours" the administered fluid for the first 6 hours was for the most part administered during "out-of-hours" and for patients admitted during late "out-of-hours" the administered fluid during the first 6 hours happened during "routine-hours", which might level differences between the groups.

Although this post-hoc analysis investigated patients admitted to three relatively large emergency departments in Cen-

tral Denmark Region, we are not able to conclude anything about generalizability to other countries. However, the care given both during routine-hours and out-of-hours must depend on staffing, triage and prioritization of recourses in general. These factors did not seem to affect total fluid volumes in 24 hours, at least in the three included sites.

6. Conclusions

No association was found between total fluid administration practice and time of admission in this post-hoc analysis looking at combined oral and intravenous fluid volumes in 0-6 hours or 0-24 hours of admission, regardless of severity of infection. However, we found differences in distributions between oral and intravenous fluids within the first 6 hours of admission; patients with simple infection and sepsis admitted during "routine-hours" received more oral fluids and patients with sepsis received less intravenous fluids than patients admitted during "out-of-hours". These differences were, however, limited to the initial 6 hours of admission.

7. Declarations

7.1. Acknowledgments

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7.2. Conflict of interest

None of the authors have any conflicts of interest in regard to this manuscript

7.3. Fundings and supports

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7.4. Authors' contribution

MKJ and ADP conducted the study and performed analyses and drafted the manuscript. HK supervised the study. All authors approved the manuscript prior to submission.

7.5. Presentations

The manuscript has been presented as an oral poster presentation at the European Emergency Medicine congress in Lisbon, Portugal, 27th-31st October 2021 and as an oral presentation at Danish Emergency Medicine Conference, Copenhagen, October 15th 2021.

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