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Sepsis in intensive care unit patients with traumatic brain injury: factors associated with higher mortality

Sepse em pacientes com traumatismo craniencefálico em unidade de terapia intensiva: fatores relacionados à maior mortalidade

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ABSTRACT

Objective: Patients with traumatic brain injury are particularly susceptible to sepsis, which may exacerbate the systemic inflammatory response and lead to organ dysfunction. The influence of clinical variables on the mortality of intensive care unit patients with traumatic brain injury and sepsis was investigated.

Methods: The present investigation was a retrospective study involving 175 patients with traumatic brain injury who were treated in a period of 1 year at a reference hospital for trauma and who had sepsis, severe sepsis, or septic shock. Demographic and clinical data were obtained, and the SOFA score was calculated at the time sepsis was found and after 72 hours.

Results: There was a predominance of young men with severe traumatic brain injury, multiple head injuries, sepsis with a pulmonary focus, prolonged hospital stay, and high mortality (37.7%). Circulatory and respiratory failure had a high incidence, but renal and coagulation failure were less frequent, and liver failure was not observed. After logistic regression, the presence of septic shock and respiratory failure 72 hours after the sepsis diagnosis was associated with higher mortality, with an odds ratio of 7.56 (95%CI=2.04-27.31, p=0.0024) and 6.62 (95%CI=1.93-22.78, p=0.0027), respectively. In addition, there was a higher mortality among patients who had no organ failure on D1 but who developed the condition after 72 hours of sepsis and in those patients who already had organ failure at the time sepsis was diagnosed and remained in this condition after 72 hours.

Conclusion: Septic shock and progressive organ (particularly respiratory) dysfunction increases the mortality of patients with traumatic brain injury and sepsis.

Keywords: Sepsis; Craniocerebral trauma; Respiratory distress syndrome, adult; Multiple organ failure; Septic shock; Intensive care units

Conflicts of interest: None.

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INTRODUCTON

Sepsis is defined as a systemic inflammatory reaction caused by an infectious process; this condition is the leading cause of death in intensive care units (ICU) worldwide and thus is a major public health problem.[1-3]

Specific groups of patients are more susceptible to sepsis and its progression to severe forms, such as patients with pulmonary disease, heart disease, liver disease, and immunosuppression.[3] Among these, patients with traumatic brain injury (TBI) due to several changes in their homeostasis are especially prone to acquiring infections and progressing to sepsis, resulting in secondary lesions that

involve considerably increased morbidity and mortality. These conditions are even more common in cases of severe TBI treated in the intensive care environment.[4,5]

Unfortunately, the incidence of TBI and mortality due to the condition in Brazil is still unknown because there are no national studies assessing these parameters. However, data from small studies with local scope suggest that this is a common disease that, in most cases, occurs in the severe form, requiring intensive care.[6,7]

It is noteworthy that the major national studies of sepsis epidemiology have included a small number of trauma patients, including patients with TBI. Thus, the results of these studies may not reflect the behavior of sepsis in patients with neurotrauma due to the peculiarities of this group.[2,3] Consequently, the present investigation was developed to investigate the main factors associated with higher mortality in ICU patients with TBI who developed sepsis.

METHODS

The present investigation was a retrospective cohort study conducted by collecting data recorded in the medical records of TBI patients treated at the *Hospital Metropolitano de Urgência e Emergência*, a reference hospital for trauma in Pará State, Brazil, after approval by the Teaching and Research Division of the hospital and by the Research Ethics Committee of the State of Pará/Center of Biological and Health Sciences (CAAE: 07666012.7.00005174, decision 182.775).

All patients who were discharged or died from June 1, 2011 to May 31, 2012 with a TBI diagnosis as defined by the 10th edition of the International Classification of Diseases (ICD-10) recorded on the discharge summary were identified. Of these, patients who at some point during the hospital stay were treated in an ICU and presented with sepsis, severe sepsis, or septic shock as defined by the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) 1991 Consensus were included.[8] Patients whose medical records were incomplete or contained unreliable data and patients admitted to the pediatric ICU were excluded.

To characterize the sample, the age and gender of the patients were recorded in addition to the time sepsis was diagnosed (at admission or during the ICU stay). All patients were classified as having sepsis, severe sepsis, or septic shock, and the most severe classification was recorded. In addition, the Sequential Organ Failure Assessment (SOFA) score was calculated to evaluate the degree of organ dysfunction in the patients studied, which was measured at the time sepsis was diagnosed (D1) and 72 hours later (D3). In the absence of any of the score parameters, the said parameter received a score of zero. In case of sedation, the score of the Glasgow coma scale item was the last score recorded before the patient was sedated. In cases of death before 72 hours after the onset of sepsis, the SOFA scale score on D3 was obtained with data from the day of death.

A score of 3 or more on a particular item of the SOFA was considered organ failure. This criterion was based on the study by Zygun et al.,[9] who defined organ dysfunction as a score ≥1 in a sector of the Multiple Organ Dysfunction (MOD) score and failure as a score ≥3, but these criteria were adapted to the SOFA score because both scores have similar structures.

The TBI was stratified into mild, moderate, and severe categories using the Glasgow coma scale score at the time of hospital admission as a reference. Values between 14 and 15 were classified as mild TBI; between 9 and 13, as moderate TBI; and between 3 and 8, as severe TBI. The type of brain injury evidenced by cranial computed tomography, the presence of associated trauma, and the type of treatment (clinical or surgical) were also recorded. In addition, the presence of comorbidities, defined as any disease or pathological process that the patient had prior to trauma (for example, hypertension), that were recorded in the medical records, were also identified.

Data of interest for infection included the focus of infection, as well as its source (community or nosocomial, defined according to the criteria of the Centers for Disease Control and Prevention[10] - infections detected less than 48 hours after admission were considered to have a community source) and the culture results. The primary outcome of the present study was the mortality rate. Patients with confirmed brain death who were transferred to other hospitals for organ harvesting were counted as deaths.

For the statistical analysis, categorical data were expressed as percentages, whereas numerical data were expressed as the mean±standard deviation or median±interquartile range, according to each case. Initially, a descriptive analysis of the collected data was performed, followed by an evaluation of the influence of each variable on mortality, and p values <0.05 were defined, *a priori*, as significant. The variables that had a significant influence on mortality were subjected to a multiple logistic regression model to evaluate whether their effect was independent of the other variables, as well as to obtain the value of the odds ratio. To assess the adequacy of the regression model, the Hosmer-Lemeshow and the Nagelkerke R^2 tests were used.

To evaluate the SOFA score, a receiver operating characteristics (ROC) curve was constructed to determine the cutoff point with greater accuracy in predicting the likelihood of the patient dying.

The sample of the present study was a result of the inclusion of patients admitted in a 1-year period, and the sample size was not calculated. Thus, a *post hoc* analysis was performed using the GPower 3.0.10 software to determine

the power of the study in determining an association between septic shock and respiratory failure on D3 with mortality. This analysis exhibited a power greater than 0.90 for both variables (1.00 and 0.99, respectively). For all other statistical analyses, the BioEstat 5.0 software was used.

RESULTS

During the study period, 1,108 medical records of patients diagnosed with TBI were identified, of which 175 met the inclusion criteria. Table 1 lists the general characteristics of the patients.

Table 1 - Distribution of patients according to demographic and clinical variables

General sample data	N (%)
Gender	
Male	161 (92.0)
Female	14 (8.0)
Age (years)	34±14.5
Diagnosis of sepsis	
At ICU admission	21 (12.0)
During the hospital stay	154 (88.0)
Classification of sepsis	
Sepsis	92 (52.6)
Severe sepsis	17 (9.7)
Septic shock	66 (37.7)
TBI severity	
Mild	10 (5.7)
Moderate	42 (24.0)
Severe	123 (70.3)
Type of treatment	
Clinical	93 (53.1)
Surgical	82 (46.9)
Type of injury	
Contusion	65 (37.1)
SDH	58 (33.1)
EPH	41 (23.4)
SAH	39 (22.3)
Simple fracture	33 (18.9)
DAI	24 (13.7)
Other	69 (39.4)
Number of injuries	
Single	65 (37.2)
Multiple	110 (62.9)
Comorbidities	
Yes	13 (7.4)
No	162 (92.6)
Associated trauma	
Musculoskeletal	32 (18.3)
Thoracic	28 (16.0)
Face	24 (13.7)
Other trauma	19 (10.8)
No associated trauma	97 (55.4)
Focus of infection	
Lung	160 (91.4)
Catheter	24 (13.7)
UTI	12 (6.9)
Sinuses	9 (5.1)
Other	26 (14.8)
Source of infection	
Community	37 (21.1)
Nosocomial	138 (78.9)
Cultures	
Negative	149 (85.1)
Positive	26 (14.9)
Isolated bacteria (32 isolates)	
Pseudomonas sp.	8 (25.0)
Klebsiella pneumoniae	5 (15.6)
Enterobacter sp.	5 (15.6)
Staphylococcus aureus	4 (12.5)
Other	10 (31.2)
Length of hospital stay (days)	29.7±27.8
Length of ICU stay (days)	15.4±12.4
Deaths	66 (37.7)

ICU - intensive care unit; TBI - traumatic brain injury; SDH - subdural hematoma; EPH - epidural hematoma; SAH - subarachnoid hemorrhage; DAI - diffuse axonal injury; UTI - urinary tract infection. Results are expressed as the number (%) or the mean±standard deviation.

To analyze the SOFA score, a ROC curve was constructed, which showed that scores ≥7 were the most accurate for predicting the risk of death, with a sensitivity of 63% and specificity of 81% for the SOFA score on D1 (area under the curve [AUC]: 0.72; 95%CI: 0.63-0.80) and sensitivity of 78% and specificity of 86% for the SOFA score on D3 (AUC: 0.82; 95%CI: 0.75-0.88).

The univariate analysis showed that the diagnosis of sepsis on admission, septic shock, non-pulmonary infection, community infection, respiratory failure on D3, neurological failure on D1 and D3, circulatory failure on D1 and D3, renal failure on D3, and SOFA ≥7 on D1 and D3 were factors significantly associated with higher mortality (Tables 2 and 3).

Subsequently, these significant variables were subjected to a multiple logistic regression model, whereby only septic shock and respiratory failure on D3 remained as factors associated with higher mortality (Table 4). In the

Table 2 - Primary analysis of the relationship between demographic and clinical variables and patient mortality

Demographic and clinical variables	Death		p value
	Yes N (%)	No N (%)	
Gender			
Male	59 (36.6)	102 (63.4)	0.48
Female	7 (50.0)	7 (50.0)	
Age			
>50 years	11 (40.7)	16 (59.3)	0.89
<50 years	55 (37.2)	93 (62.8)	
Diagnosis of sepsis			
At ICU admission	13 (61.9)	8 (38.1)	0.02*
During the ICU stay	53 (34.4)	101 (65.6)	
Classification of sepsis			
Septic shock	47 (71.2)	19 (28.8)	<0.0001*
Sepsis/severe sepsis	19 (17.4)	90 (82.6)	
TBI severity			
Grave	50 (40.6)	73 (59.4)	0.28
Mild/moderate	16 (30.8)	36 (69.2)	
Type of treatment			
Clinical	41 (44.1)	52 (55.9)	0.08
Surgical	25 (30.5)	57 (69.5)	
Number of injuries			
Single	21 (32.3)	44 (67.7)	0.33
Multiple	45 (38.9)	65 (59.1)	
Comorbidities			
Yes	3 (23.0)	10 (77.0)	0.37
No	63 (38.8)	99 (61.2)	
Associated trauma			
Yes	24 (30.7)	54 (69.3)	0.12
No	42 (43.2)	55 (56.7)	
Focus of infection			
Lung	56 (35.0)	104 (65.0)	0.02**
Non-pulmonary	10 (66.6)	5 (33.3)	
Source of infection			
Community	20 (54.1)	17 (45.9)	0.03*
Nosocomial	46 (33.3)	92 (66.6)	
Cultures			
Positive	6 (23.0)	20 (77.0)	0.14
Negative	60 (40.3)	89 (59.7)	

ICU - intensive care unit; TBI - traumatic brain injury. Results are expressed as the number (%). * Chi-squared test; ** Fisher's exact test.

Table 3 - Primary analysis of the relationship between the presence of organ failure and mortality

Organ failure	Death		p value
	Yes N (%)	No N (%)	
Respiratory failure			
D1	20 (51.3)	19 (48.7)	0.07
D3	31 (81.6)	7 (18.4)	<0.0001*
Neurological failure			
D1	59 (45.0)	72 (55.0)	0.0011*
D3	59 (48.8)	62 (51.2)	<0.0001*
Circulatory failure			
D1	27 (65.9)	14 (34.1)	<0.0001*
D3	44 (71.0)	18 (29.0)	<0.0001*
Renal failure			
D1	5 (71.4)	2 (28.6)	0.10
D3	10 (90.9)	1 (9.1)	0.0003**
Coagulation failure			
D1	1 (100.0)	0 (0.0)	0.79
D3	2 (100.0)	0 (0.0)	0.27
SOFA			
D1 ≥7	42 (67.7)	20 (32.3)	<0.0001*
D3 ≥7	52 (77.6)	15 (22.4)	<0.0001*

D1 - day of the sepsis diagnosis; D3 - 72 hours after the sepsis diagnosis; SOFA - Sequential Organ Failure Assessment Score. Results are expressed as the number (%). * Chi-squared test; ** Fisher's. exact test.

Table 4 - Analysis after multiple logistic regression of the relationship between the variables significant with respect to the initial analysis and mortality

Variables significantly associated with mortality	OR	95%CI	p value
Diagnosis of sepsis at ICU admission	1.50	0.3-6.55	0.58
Septic shock	7.56	2.04-27.31	0.0024*
Neurological failure on D1	1.42	0.23-8.97	0.70
Circulatory failure on D1	0.87	0.21-3.68	0.86
SOFA on D1 ≥7	2.62	0.82-8.39	0.10
Respiratory failure on D3	6.62	1.93-22.78	0.0027*
Neurological failure on D3	2.34	0.40-13.77	0.34
Circulatory failure on D3	0.51	0.09-3.10	0.46
Renal failure on D3	1.91	0.17-22.01	0.60
SOFA on D3 ≥7	3.72	0.81-17.05	0.08
Pulmonary focus of infection	0.38	0.06-2.69	0.33
Community infection	1.16	0.38-3.55	0.78

OR - odds ratio; 95% CI - 95% confidence interval; ICU - intensive care unit; D1 - day of the sepsis diagnosis; D3 - 72 hours after the sepsis diagnosis; SOFA - Sequential Organ Failure Assessment Score. * Results are significant after logistic regression.

goodness-of-fit assessment, the Hosmer-Lemeshow test yielded p=0.88 (chi-square: 3.665; degrees of freedom: 8), and the Nagelkerke R^2 value was 0.63.

When the temporal evolution of organ failure was observed, there was a significant increase in the risk of death in patients who did not present with organ failure on D1 but who developed the condition after 72 hours of the sepsis diagnosis and in those patients who already had organ failure at the time sepsis was diagnosed and remained in this

condition after 72 hours, compared with patients who did not develop organ failures (Table 5).

DISCUSSION

In the present study, which was performed with TBI ICU patients who developed sepsis, the presence of septic shock and respiratory failure after 72 hours of the sepsis diagnosis were identified as independent factors associated with increased mortality. In addition, there was higher mortality in patients without organ failure on D1 who developed the condition on D3 and in those who already had organ failure on D1 that persisted after 72 hours.

The sample had a marked predominance of young male patients with severe TBI, multiple head injuries, and often associated trauma, resulting in prolonged hospital and ICU stays and high mortality rates. Most infections were diagnosed during the ICU stay, and the main focus of infection was the lung, notably due to nosocomial pneumonia caused by gram-negative bacteria.

Regarding the presence of organ failure, Zygun et al.,[9] in a study of TBI patients, found respiratory failure rates of 23%, cardiovascular failure rates of 18%, coagulation failure rates of 4%, renal failure rates of 1%, and no cases of liver failure, similar to the findings of the present investigation. The high

Table 5 - Relationship between the progression of organ failure between D1 and D3 and the mortality

Organ failure	D1	D3	Number of patients (%)*	Deaths N (%)**	OR (95%CI)	p value
Respiratory failure						
	No	No	116 (66.3)	24 (20.7)	Control	-
	Yes	No	21 (12.0)	5 (23.8)	1.19 (0.39-3.59)	0.97
	No	Yes	20 (11.4)	16 (80.0)	15.33 (4.69-50.11)	<0.0001
	Yes	Yes	18 (10.3)	15 (83.3)	19.16 (5.12-71.64)	<0.0001
Neurological failure						
	No	No	38 (21.7)	6 (15.7)	Control	-
	Yes	No	16 (9.1)	1 (6.2)	0.35 (0.03-3.22)	0.61
	No	Yes	6 (3.4)	1 (16.6)	1.06 (0.10-10.82)	0.58
	Yes	Yes	115 (65.7)	58 (50.4)	5.42 (2.10-13.96)	0.0004
Circulatory failure						
	No	No	108 (61.7)	20 (18.5)	Control	-
	Yes	No	5 (2.9)	2 (40.0)	2.93 (0.45-18.72)	0.54
	No	Yes	26 (14.9)	19 (73.1)	11.94 (4.42-32.24)	<0.0001
	Yes	Yes	36 (20.6)	25 (69.4)	10.00 (4.23-23.61)	<0.0001
Renal failure						
	No	No	162 (92.6)	55 (34.0)	Control	-
	Yes	No	2 (1.1)	1 (50.0)	1.94 (0.11-31.70)	0.78
	No	Yes	6 (3.4)	6 (100.0)	2.95 (2.38-3.65)	0.002
	Yes	Yes	5 (2.9)	4 (80.0)	7.78 (0.84-71.31)	0.09
Coagulation failure						
	No	No	172 (98.3)	63 (36.6)	Control	-
	Yes	No	1 (0.6)	1 (100.0)	2.73 (2.24-3.22)	0.39
	No	Yes	2 (1.1)	2 (100.0)	2.73 (2.24-3.22)	0.13
	Yes	Yes	0 (0.0)	0 (0.0)	-	-
SOFA						
	<7	<7	89 (50.9)	8 (9.0)	Control	-
	≥7	<7	19 (10.9)	6 (31.6)	4.67 (1.39-15.66)	0.0223
	<7	≥7	24 (13.7)	16 (66.7)	20.25 (6.62-61.88)	<0.0001
	≥7	≥7	43 (24.6)	36 (83.7)	52.07 (17.54-154.52)	<0.0001

D1 - day of the sepsis diagnosis; D3 - 72 hours after the sepsis diagnosis; OR - odds ratio; 95% CI: 95% confidence interval; SOFA - Sequential Organ Failure Assessment Score. * The percentage refers to the total number of patients in the sample. ** The percentage refers to the total number of patients in the extract.

rate of patients with circulatory failure is noteworthy, and this was the most affected system in the present study.

In a recent study of ICU patients with severe TBI, high rates of hemodynamic instability were found. In total, 44% of patients had hypotension, and 70% required the use of vasoactive drugs at some point during the ICU stay.[4] Furthermore, respiratory dysfunction was also a common finding, similar to other TBI-patient studies that reported high rates of ventilator-associated pneumonia and acute respiratory distress syndrome (ARDS).[4,11]

Notably, the progression to septic shock has been repeatedly associated with increased mortality in several studies of ICU patients with sepsis. National studies show significant mortality rates of 10.1% to 32.8% for sepsis patients, 22.6% to 49.9% for severe sepsis patients, and 64.8% to 72.7% for septic shock patients.[12,13]

In our study, the logistic regression revealed that patients with septic shock had a 7.5 times higher risk of progressing to death than did patients with sepsis or severe sepsis, and this variable was the most strongly correlated with this outcome. In another study of ICU patients with TBI, a significantly higher mortality in patients with septic shock was also reported.[4]

Conversely, evidence in the literature suggests that the presence of organ dysfunction implies a worse prognosis in TBI patients. Zygun et al.[9] observed a significant increase in the risk of hospital death in patients with high MOD scores and found that the higher the number of failing organs, the worse is the prognosis. In a study of ICU patients with sepsis, the author observed a mortality of 14.6% in cases of failure of up to two organs or systems, whereas in cases of failure of three or more organs or systems, the mortality increased to 59.8% ($p<0.0001$).[12] However, in the present study, the high SOFA score only exhibited a trend toward higher mortality, with no significance. It is possible that in a larger sample, the association between these variables would become significant.

Respiratory failure 72 hours after the sepsis diagnosis was the only failure of a specific system that proved to be an independent predictor of mortality. Corral et al.[4] reported a significant association between the presence of ARDS and death in patients with TBI, with a mortality of 22% in the presence of a PaO_2/FiO_2 ratio between 300 and 200 and a mortality of 47% when this ratio was <200.

Another study reported that the presence of ARDS or acute lung injury (ALI) caused a tenfold increase in mortality. Furthermore, the authors observed that younger individuals were more prone to the occurrence of ARDS or ALI (most likely due to the early death of older patients) and that patients with sepsis had a 7.59 times higher risk of developing these respiratory complications.[14]

The observation of organ failure evolution at the time of sepsis diagnosis and after 72 hours was of special interest. A study performed with patients with severe sepsis and septic shock demonstrated that the longer the duration of an organ dysfunction, the higher was the mortality, and the persistence of dysfunction in one organ or system for more than 48 hours was strongly correlated with the progression to death in a logistic regression model. In the same study, patients who received therapeutic interventions within 48 hours of the onset of organ dysfunction had significantly lower mortality than those who received interventions within an interval greater than 48 hours.[15]

Another study with ICU patients with sepsis found that survivors had lower mean SOFA scores at diagnosis than non-survivors did (4.19 versus 7.99). In survivors, there was a trend toward a decrease in SOFA scores, with a mean score of 2.18 on the last day, whereas in non-survivors, the opposite occurred: this score increased, with a mean of 10.49 on the last day.[12]

The present study has certain limitations. The study design was retrospective, using data recorded in medical records. The sample was relatively small and came from a single medical center. Our logistic regression model had limitations, such as the large number of variables entered (12 variables in a model with only 66 outcomes) and the presence of an interaction between some variables within the model (organ failure and the SOFA score). Consequently, these limitations might have compromised the predictive ability of the regression, leading to bias when interpreting the results, which is why we suggest that further studies be conducted to confirm these findings.

CONCLUSION

The present investigation revealed that patients with septic shock and respiratory failure after 72 hours of the sepsis diagnosis had higher mortality, most likely due to their higher degree of organ dysfunction. We suggest that further studies be conducted to confirm these findings and to evaluate the effect of specific interventions, ultimately aiming to reduce the mortality in traumatic brain injury intensive care units patients who develop sepsis.

RESUMO

Objetivo: Pacientes com traumatismo craniencefálico são particularmente suscetíveis a sepse, a qual pode exacerbar a resposta inflamatória sistêmica e levar à disfunção orgânica. Investigou-se a influência de variáveis clínicas sobre a mortalidade de pacientes com traumatismo craniencefálico e sepse em unidade de terapia intensiva.

Métodos: Trata-se de estudo retrospectivo envolvendo 175 pacientes com traumatismo craniencefálico atendidos durante 1

ano em um hospital de referência em trauma, que apresentaram sepse, sepse grave ou choque séptico. Foram obtidos dados demográficos e clínicos e foi aferida a pontuação no escore SOFA no momento da identificação da sepse e após 72 horas.

Resultados: Observou-se predomínio de homens jovens, com traumatismo cranioencefálico grave, múltiplas lesões cranianas, sepse de foco pulmonar, tempo de internação prolongado e alta mortalidade (37,7%). Falência respiratória e circulatória tiveram alta incidência, já falência renal e da coagulação foram menos frequentes e não se registrou falência hepática. Após a regressão logística, a presença de choque séptico e falência respiratória após 72 horas da identificação da sepse foram associados à maior mortalidade, com *odds ratio* de 7,56 (IC95%=2,04-27,31; p=0,0024) e 6,62 (IC95%=1,93-22,78; p=0,0027), respectivamente. Ainda, houve maior mortalidade nos pacientes que não possuíam falência orgânica em D1, mas que desenvolveram após 72 horas do diagnóstico de sepse e naqueles que já tinham falência orgânica no momento do diagnóstico da sepse e permaneceram assim após 72 horas.

Conclusão: Choque séptico e disfunção orgânica progressiva (particularmente a respiratória) aumentaram a mortalidade de pacientes com traumatismo cranioencefálico e sepse.

Descritores: Sepse; Traumatismos craniocerebrais; Síndrome do desconforto respiratório do adulto; Insuficiência de múltiplos órgãos; Choque séptico; Unidades de terapia intensiva

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