BioSCIENCE Original Article
DOI: https://doi.org/10.55684/2024.82.e00015

Relationship of the Surviving Sepsis Campaign Pediatric protocol with the mortality rate in children hospitalized with sepsis

Relação do protocolo Surviving Sepsis Campaign Pediatric com a taxa de mortalidade em crianças internadas com sepse

Brendha K da Cruz[1], Rafaela S L Correia[1], Talita M Krizonowski[1], Luiza G Rafagnin[1]

ABSTRACT

Introduction: Globally, childhood sepsis is one of the most significant causes of mortality and morbidity. Several guidelines have been published, aiming to provide the medical team with evidence-based conducts to provide safety, standardize care and allow the reduction of sepsis mortality in pediatrics.

Objective: To relate the application of the Surviving Sepsis Campaign Pediatric protocol to the mortality rate in patients diagnosed with sepsis in a tertiary pediatric hospital.

Method: Quantitative, exploratory, descriptive, retrospective and cross-sectional study. A research instrument was used to collect data related to the sociodemographic profile, initial symptoms, conduct and clinical outcomes of patients with sepsis between January 2019 and December 2020.

Results: Of the 225 patients treated, 18 (8%) died. There was no correlation between time of antibiotic initiation and mortality. Hemato-oncological comorbidities and the initial presentation of neurological and perfusion alterations correlated with deaths.

Conclusion: Although the time of initiation of antibiotic administration has not proved to be essential for reducing the mortality rate, some initial symptoms and the presence of hemato-oncological comorbidities are alert for suspicion and early diagnosis of pediatric sepsis.

KEYWORDS: Sepsis. Septic shock. Pediatrics. Clinical protocols. Child mortality.

Central Message

Globally, childhood sepsis is one of the most significant causes of mortality and morbidity. Several guidelines have been published, aiming to provide the medical team with evidence-based conducts to provide safety, standardize care, and allow the reduction of sepsis mortality in pediatrics.

Prospect

In general, the present study demonstrated that the conducts adopted in the hospital guaranteed a mortality rate of 8%. Despite the comparative limitation due to the population discrepancies analyzed in other studies, this value is within the expected for national and international rates.

RESUMO

Introdução: Em termos globais, a sepse na infância é uma das causas mais significativas de mortalidade e morbidade. Diversas diretrizes vêm sendo publicadas, objetivando fornecer à equipe médica condutas baseadas em evidências para prover segurança, uniformizar atendimentos e permitir a redução de mortalidade de sepse na pediatria.

Objetivo: Relacionar a aplicação do protocolo Surviving Sepsis Campaign Pediatric com a taxa de mortalidade em pacientes diagnosticados com sepse em hospital pediátrico terciário.

Método: Estudo quantitativo, exploratório, descritivo, retrospectivo e transversal. Utilizou-se um instrumento de pesquisa para a coleta dos dados relacionados ao perfil sociodemográfico, sintomas iniciais, condutas e desfechos clínicos de pacientes com sepse entre janeiro de 2019 e dezembro de 2020.

Resultados: Dos 225 pacientes atendidos, 18 (8%) faleceram. Não houve correlação entre tempo de início do antibiótico e mortalidade. Comorbidades hemato-oncológicas e a apresentação inicial de alterações neurológicas e de perfusão correlacionaram-se com óbitos.

Conclusão: Apesar do tempo de início da administração do antibiótico não ter se mostrado imprescindível para redução da taxa de mortalidade, alguns sintomas iniciais e a presença de comorbidades hemato-oncológicas são alertas para suspeita e diagnóstico precoce da sepse pediátrica.

PALAVRAS-CHAVE: Sepse. Choque séptico. Pediatria. Protocolos Clínicos. Mortalidade infantil.

[1]Faculdades Pequeno Príncipe, Curitiba, PR, Brasil

Conflict of interest: None | Funding: None | Received: 03/02/2024 | Accepted: 28/03/2024 | Correspondence: brendhakupczyk@hotmail.com | Associate Editor: Thelma Larocca Skare

How to cite:
Da Cruz BK, Correia RSL, Krizonowski TM, Rafagnin LG. Relação do protocolo Surviving Sepsis Campaign Pediatric com a taxa de mortalidade em crianças internadas com sepse. BioSCIENCE. 2024;82:e015

INTRODUCTION

Overall, childhood sepsis is one of the most significant causes of mortality and morbidity, with different forms of clinical presentation, depending on risk factors, disease severity, and geographic location. Annually, about 1.[2] million cases are estimated in the pediatric population worldwide.[1,2] Several guidelines carried out by the Survivng Sepsis Campaign (SSC) have been published since 2004, aiming to provide the medical team with evidence-based approaches to provide safety, standardize care, and reduce sepsis mortality in pediatrics, while providing treatment and early diagnosis schemes.[3,4,5]

The 2005 International Pediatric Sepsis Conseus Conference (IPSCC) was the last consensus on the classification of sepsis in pediatrics. Such concepts are shown in Table 1.

TABLE 1 — Concepts of sepsis according to the 2005 IPSCC

Systemic inflammatory response syndrome (SIRS)	Presence of at least two of the following criteria, one of which must be a change in temperature or number of leukocytes: Change in body temperature – hyperthermia or hypothermia. Leukocyte alteration – leukocytosis or leukopenia not secondary to chemotherapy, or presence of young forms of neutrophils in peripheral blood. Tachycardia – age-inappropriate heart rate (HR) in the absence of external stimuli or bradycardia for children < 1 year. Tachypnea – respiratory rate (RR) inappropriate for age OR need for mechanical ventilation due to infection.
Sepsis	Presence of two or more signs of SIRS, one of which is a change in temperature and/or a change in leukocytes, together with the presence of a confirmed or suspected infection.
Severe Sepsis	Presence of SEPSIS and cardiovascular OR respiratory dysfunction OR two or more organ dysfunctions among the others.
Septic Shock	Severe sepsis with non-volume-responsive hypoperfusion.

Source: Adapted from SOUZA et. al., 20194

The use of the pediatric sepsis protocol created by the Surviving Sepsis Campagin (SSC) makes it easier for health professionals to diagnose sepsis and classify it according to severity. This is aimed at the pediatric age group from the first month of life to 18 years of age, applied internationally and managed in Emergency Rooms (PAs) and pediatric Intensive Care Units (ICUs).[3.5]

The presence of warning signs, such as tachycardia or bradycardia in children over 1 year of age, tachypnea, peripheral perfusion alteration, mental status alteration, decreased peripheral pulse, cold extremities or livedo, decreased diuresis (<1 mL/kg/h), and hypotension, foster the suspicion of sepsis.[4.5]

According to the SSC algorithm, in the first hour of care it is important to: 1) obtain 2 peripheral or intraosseous venous accesses; 2) collection of blood culture and laboratory tests; 3) administration of broad-spectrum antibiotics; and 4) lactate measurement. Up to the first 3 hours after admission, children who develop severe sepsis or septic shock require fluid resuscitation and/or vasoactive drugs.[1] Afterwards, management should be carried out according to the clinical condition, continuously reassessing the determinant parameters of sepsis.[4.5]

Broad-spectrum antimicrobial therapy in the first hour is discussed as the most significant step towards reducing mortality in children with sepsis and that its delay, especially when it exceeds 3 h, increases the probability of additional risk of impairment of the clinical condition.[4,5,6] Lactate measurement appears to be an important factor in the indirect evaluation of tissue hypoperfusion; however, there are no defined values for hyperlactatemia in the pediatric group. The evaluation of this parameter should also be done considering the continuous clinical evaluation of the child.[4]

The identification of clinical signs of sepsis, together with the use of protocols based on the best scientific evidence – even if adjusted according to the availability of local resources – can have an effect on improving the clinical outcome of patients affected by this condition.[3.7]

METHOD

This study was approved by the Human Research Ethics Committee of Faculdade Pequeno Príncipe – CAAE no. 40210920.2.0000.5580. It is exploratory, descriptive, retrospective, and cross-sectional, with a quantitative approach. Patients who received the sepsis kit from a tertiary pediatric hospital in Curitiba, between January 2019 and December 2020, were selected. It was available in all pharmacies in the hospital and was intended to facilitate access to devices and medicines. It consists of antibiotics (oxacillin, ampicillin, gentamicin, amikacin, metronidazole, ceftriaxone, cefotaxime, cefepime, piperacycline-tazobactam, meropenem and vancomycin), saline solution for volume expansion, vials for test collection (blood culture, blood count, C-reactive protein, blood gas, biochemistry, lactate, coagulogram, urinalysis and urine culture) and other necessary materials.

Regarding the selection of medical records, initially 739 medical records were selected in which the kit was taken from January 2019 to December 2020. Medical records that were already hospitalized at the institution, regardless of the sector, were excluded, leaving only those from the emergency room. Next, post-chemotherapy neutropenic patients were also excluded, along with those who had the diagnosis of sepsis ruled out within the first 24 h after opening the kit. Of those that remained, 37 medical records could not be used, as they did not contain medical evolutions with sufficient information to be used in the study, thus leaving the 225 medical records with a diagnosis of sepsis, severe sepsis and septic shock used in this study.

A research instrument created by the authors was used to collect data from the patients' medical records. Information was collected on: age group, gender, associated comorbidities, time and date of admission to the emergency room, initial symptoms presented, time and date of kit administration, oxygen therapy, date and time of prescription of volume resuscitation and vasoactive drug, presence of collection of tests suggested by the SSC, date of hospital discharge or death. The parameters used for age ranges, clinical symptoms assessed at admission, suggested tests, and sepsis classification were taken from the Pediatric Clinical Protocol of the Latin American Sepsis Institute (ILAS) 2019.[8]

Statistical analysis

For data analysis, the Shapiro-Wilk test was performed to assess the normality of the sample, and the results

were reported using the mean (± standard deviation) if the distribution was normal or median (minimum – maximum) if it was non-normal. To verify the statistical significance of our conclusions, the Man-Whitney test, t-test and chi-square test were used. The sample size was selected for convenience. To assess the power of the test that this sample number represented, a posteriori sample calculation was performed – capable of informing the power value of the test.

RESULTS

Sociodemographic characteristics as well as clinical manifestations are shown in Table 2. Most of the medical records belonged to male patients (58.2%) and were in the age group between 1-5 years (34.5%). Patients with neurological comorbidities were mostly (26.9%); however, 27.6% did not have comorbidities in the medical evolution. The most frequent symptom found in presumed sepsis at the first visit was tachycardia (54.7%) and the least frequent was oliguria (13.8%). However, 65% of the medical records analyzed did not present data on diuresis, which interferes with the reliability of this symptom being absent in most patients.

Most of them had a complete blood count (98.2%), blood gas analysis (80.4%) and creatinine (80.4%). Lactate was measured in more than half of the patients (56.9%).

Of the 225 patients analyzed, 13 (5.8%) had SIRS, 56 (29.4%) had sepsis, 102 (45.3%) had severe sepsis, and 54 (24%) had septic shock.

TABLE 2 — Sociodemographic characteristics of the patients

Clinical features	Total (n)	Total (%)	Does not report (N.R.)
Sex			
Female	94	41,8%	
Male	131	58,2%	
Age			
0 to 1 week	2	0,9%	
> week to 30 days	9	4%	
> 1 month to 1 year	43	19,3%	
> 1 year to 5 years	77	34,5%	
> 5 years to 12 years	56	25,1%	
> 12 years to 18 years	36	16,1%	
Comorbidities	36	26,9%	
Neurological	23	10,2%	
Heart	20	8,9%	
Hemato-oncology	15	6,7%	
Respiratory	23	10,2%	
Malformations	53	23,6%	
Other	62	27,6%	
N.R.			
Symptoms	123	54,7%	24 (10,7%)
Tachycardia	67	29,8%	91 (40,4%)
Hypotension	101	44,9%	13 (5,8%)
Neurological changes	112	49,8%	22 (9,8%)
Unsaturation	100	44,4%	17 (7,6%)
Perfusion modification	31	13,8%	147 (65%)
Oliguria	145	64,4%	34 (15,1%)
Fever			
Suggested tests	180	80,4%	
Gas	221	98,2%	
Cbc	181	80,4%	
Creatinine	36	16%	
Bilirubin	57	25,3%	
Coagulogram	128	56,9%	
Lactate Dosage			
Classification of sepsis	13	5,8%	
SIRS	56	24,9%	
Sepsis	102	45,3%	
Severe sepsis	54	24%	
Septic shock			

Regarding the relationship between the time in which the patient was admitted and diagnosed with sepsis in relation to the time of initiation of the administration of the antibiotic contained in the sepsis kit (Table 3), it was observed that among the 225 (100%) patients included, 115 (51.1%) had the medication administered within 60 min of diagnosis and 110 (48.9%) in a time longer than this period. There was little association between symptoms and comorbidities at admission and time to start antibiotic therapy. The only symptom with a statistically significant relationship was oliguria (54.1% - p=0.018) and the only statistically significant comorbidity was cardiac omorbia (10.2% - p=0.021), both received the antibiotic sepsis kit in more than 60 min (p=0.021).

Among the basic tests performed to ascertain the conditions and severities presented, it was not possible to observe differences in relation to the time of admission and the time of administration of the sepsis kit, with a p-value of at least 0.13 (Table 2).

Regarding the outcome, among the 18 (8%) who died, 8 had the first dose of the antibiotic administered in more than 60 min, while 10 did so in less than 60 min after admission.

TABLE 3 — Time of admission and time of antibiotic administration (ATB)

Variables	ATB > 60 minutes	ATB < 60 minutes	p
n total = 225 (100%)	110 (48,9%)	115 (51,1%)	
Death = 18 (8%)	8 (7,3%)	10 (8,7%)	0.694***

***=Chi-Square

Regarding the comparison between the time from admission to the time of administration of the first volume resuscitation, if necessary (Table 4), among the 225 (100%) studied, 176 (69%) required volume resuscitation to improve their clinical condition. Regarding the time of administration of this volume, 133 (74.7%) children had the onset of the infused crystalloids in less than 180 min and 43 (25.3%) in more than 180 min.

All 18 patients who died received volume resuscitation. Among those who received it in less than 180 min, 7.5% died, while 17.8% were infused in more than 180 min also had the same outcome (p=0.048).

Among the 41 patients who used vasoactive drugs (VAD, Table 4), 14 (34.1%) started the infusion in less than 180 min and 27 (65.9%) in more than 180 min. Among the symptoms analyzed, the presence of neurological changes was related to the application of VAD in less than 3 hours (p=0.050). The other symptoms studied were present in more than half of the patients in both temporal scenarios, but they were not related to the p-value.

Although 12 of the 18 total deaths in the study occurred in patients who received VAD, there was no p-correlation between death and drug use, regardless of the time shorter than 180 min.

TABLE 4 — Initiation of volume resuscitation (RV) and initiation of vasoactive drug infusion (VAD) correlated with death

Variables	RV > 180 min	RV < 180 min	p	DVA > 180 min	DVA < 180 min	p
n total=225 (100%)	43 (25,3%)	133 (74,7%)		27 (65,9%)	14 (34,1%)	
Death=18 (8%)	8 (17,8%)	10 (7,5%)	0,048***	6 (22,2%)	6 (42,9%)	0,168***

=Chi-Square

The analysis of the data related to blood culture collection showed that of the 225 children, 198 underwent blood culture; however, the majority (61.6%) started antibiotic therapy before sample collection. Regarding death, it was observed - without p-value correlation - that of the 18 children who died, 17 were collected, and 12 started antibiotic therapy before.

In view of the variables related to death described in Table 5, it was found that only 8% died, demonstrating a survival rate higher than 90%. With the exception of unsaturation (27.8%), all the other symptoms studied were present in more than 60% of the patients. In this scenario, perfusion alterations (p=0.002) and neurological alterations (p=0.007) demonstrated greater susceptibility to death. Among the comorbidities studied, the presence of hemato-oncological conditions was also related to death (p=0.038).

TABLE 5 — Comparison of death with the variables

Variables	He did not die	Death	p
n total=225 (100%)	207 (92%)	18 (8%)	
Symptoms			
Tachycardia	110 (59,8%)	13 (76,5%)	0,177***
Hypotension	56 (47,1%)	11 (73,3%)	0,055***
Neurological changes	87 (44,8%)	14 (77,8%)	0,007***
Unsaturation	85 (44,7%)	15 (83,3%)	0,002***
Perfusion modification	86 (46,5%)	5 (27,8%)	0,128***
Oliguria	26 (37,1%)	5 (71,4%)	0,078***
Fever	134 (64,7%)	11 (61%)	0,953***
Comorbidities			
Neurological	30 (25%)	6 (42,9%)	0,154***
Heart	20 (9,7%)	3 (16,7%)	0,347***
Hemato-oncology	16 (7,7%)	4 (22,2%)	0,038***
Respiratory	15 (7,2%)	-	0,237***
Malformations	21 (10,1%)	2 (11,1%)	0,897***
Other	50 (24,2%)	3 (16,7%)	0,473***

***=Chi-Square

DISCUSSION

In this study, it was possible to verify tachycardia as the most prevalent symptom (54.7%) at hospital admission. The presence of heart rate alterations is important to be detected in the initial evaluation, as it is one of the first warning signs when sepsis is suspected, and can thus be a good indicator for early diagnosis.[4,5] Urinary alterations, according to Weiss et. al. (2020)[1], is one of the main markers of organ dysfunction; however, 65% of the medical records did not contain data on the patients' diuresis.

The initial laboratory tests suggested are intended to evaluate organ dysfunction, evolution, and signs of disease severity.[4,9] Lactate levels were collected in most patients (56.9%). However, it is important to emphasize that lactate levels are more relevant when it comes to sepsis in adults, because although it is a good marker of tissue hypoperfusion, its measurement is not associated with a reduction in mortality in the pediatric population and should be evaluated together with clinical status.[1,4]

The classification of sepsis was made according to the 2005 consensus; although it is not so recent, it is the last one referring to the pediatric population and the same as that used by the SSC 2020 Guideline. The authors classified each patient based on the symptoms described in the medical evolutions. The most frequent classification was severe sepsis (45.3%).

It was possible to verify that 88% of the patients underwent blood culture; however, 61.6% started antibiotic therapy before collecting samples for the test. Such a scenario can produce false-negative results and, thus, impair the administration of specific drugs for the microorganism in question - which also exposes the patient to more aggressive drugs and the possibility of inducing bacterial resistance.[10,11,12]

In the study, it was observed that the start of antimicrobial administration less than 60 minutes after the diagnosis of sepsis was not directly related to the mortality rate (p=0.694). Other publications, such as Sager et. al. (2021)[13] and Bulle et. al. (2020)[14], also analyzed the effects of early antibiotics on mortality and obtained the same results, leading us to question whether waiting to collect samples for blood culture before starting antibiotics would not bring advantages in terms of cost reduction, control of antimicrobial resistance in the hospital, and improvement of patient outcomes.

As recommended by the Surviving Sepsis Campaign Pediatric 2020 protocol, the start of volume infusion in children with signs of hypoperfusion should be performed in less than 180 min, because with this rapid administration the prognosis is better and there is lower mortality.[1,2,13] In this study, it was possible to observe that among those children who died, more than half started the crystalloid infusion in more than 180 min (p=0.048).

A correlation was also observed between antibiotic administration and volume infusion. The same children who had their antibiotic done early also had volume resuscitation done more quickly. These results may indicate both that the professionals are correctly following the steps recommended by the protocol, and that these children with shorter time to start the antibiotic and volume resuscitation are showing signs of greater severity.

The use of vasoactive drugs is related to persistent hypoperfusion refractory to fluid administration.[1,4,8] Although it is recommended that it start in less than 180 minutes, the results obtained in this study showed that there was no difference in mortality in relation to the time of administration. In line with this finding, a study conducted in Canada evaluated the duration of antibiotics, volume, and vasoactive infusions in children hospitalized with sepsis and, likewise, found no association between time of vasoactive drug initiation and unfavorable outcomes.[16] Although we did not find a relationship with mortality, we noticed that the presence of neurological symptoms was associated with the time of vasoactive drug administration that started in less than 180 min (p=0.050).

In general, the present study demonstrated that the conducts adopted in the hospital guaranteed a mortality rate of 8%. Despite the comparative limitation due to the population discrepancies analyzed in other studies, this value is within the expected for national and international

rates. In a study similar to the present one, carried out in Sobral (CE), 11% of deaths were obtained among the 209 pediatric patients analyzed.[17] In Rio de Janeiro, an observational cohort evaluated the prevalence of deaths in the pediatric population before and after the implementation of a sepsis protocol in a children's hospital, demonstrating a mortality rate of 2.9% with the use of the protocol versus 11.9% before its installation, demonstrating the importance of using protocols for sepsis care. In view of the global epidemiology of pediatric sepsis, research has revealed a mortality rate of 25%.[1,18,19]

Our study has some limitations, such as the difficulty of identifying all patients with sepsis in the hospital. The removal of the sepsis kit from the pharmacy is not a reliable way to recognize such patients, since it includes patients without sepsis but who received the kit and excludes those who did not receive it but who had sepsis. It is also necessary to emphasize that this study included children under 30 days of age, although the protocol recommended by the Surviving Sepsis Campaign 2020 analyzes only those older than 1 month.

It is important to emphasize that this study was conducted in a tertiary pediatric referral hospital, with the vast majority of patients with comorbidities already aggravated when compared to those in a general hospital with pediatric care.

CONCLUSION

Early initiation of antibiotic therapy (< 60 min) did not bring significant differences in mortality. Blood culture, in most cases, was performed after the start of antimicrobial therapy, a fact that can interfere with the test result and is not consistent with the SSC recommendation. Volume infusion over 180 min was associated with unfavorable outcomes, while vasoactive drug administration time had no impact on the mortality rate.

Authors' contributions
Conceptualization: All authors
Research: All authors
Methodology: All authors
Writing (original draft):All authors
Writing (proofreading and editing): All authors

REFERENCES

1. Weiss SL, Peters MJ, Alhazzani W, Agus MSD, Flori HR, Inmald DP, et al. Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. Intensive Care Med. 2020;46(Suppl 1):10-67. Doi: 10.1007/s00134-019-05878-6
2. Weiss SL, Fitzgerald JC, Pappachan J, Wheeler D, Bustamante JCJ, Sallo A, et al. Global epidemiology of pediatric severe sepsis: the sepsis prevalence, outcomes, and therapies study. Sepsis Prevalence, Outcomes, and Therapies (SPROUT) Study Investigators and Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network (2015). American journal of respiratory and critical care medicine,191(10), 1147–1157. Doi: 10.1164/rccm.201412-2323OC
3. Balamuth F, Weiss SL, Fitzgerald JC, Hayes K, Centkowski S, Chilutti M, et al. Protocolized Treatment Is Associated With Decreased Organ Dysfunction in Pediatric Severe Sepsis. Pediatr Crit Care Med. 2016;17(9):817-22. Doi: 10.1097/PCC.0000000000000858
4. Souza D, Oliveira CF, Bossa AS, Machado FR. Campanha de Sobrevivência a Sepse - Protocolo Clínico Pediátrico. Instituto Latino-Americano de Sepse. 2019;1(3):1-21.
5. Workman JK, Ames SG, Reeder RW, Korgenski EK, Masotti SM, Bratton SL, et al. Treatment of Pediatric Septic Shock With the Surviving Sepsis Campaign Guidelines and PICU Patient Outcomes. Pediatr Crit Care Med. 2016;17(10):e451-e458. Doi: 10.1097/PCC.0000000000000906.
6. Ray S, Sundaram V, Dutta S, Kumar P. Ensuring administration of first dose of antibiotics within the golden hour of management in neonates with sepsis. BMJ Open Quality 2021;10:e001365. Doi: 10.1136/bmjoq-2021-001365.
7. Garcia PCR, Tonal CT, Piva JP. Septic shock in pediatrics: the state-of-the-art. Jornal de Pediatria, 2020;96(Suppl 1):87-98. Doi:10.1016/j.jpedp.2019.10.007.
8. Instituto Latino-Americano para Estudos da Sepse (ILAS). SEPSE: Um problema de saúde pública. Conselho Federal de Medicina; 2015.
9. Prusakowski MK, Chen AP. Pediatric Sepsis. Emerg Med Clin North Am. 2017;35(1):123-138. Doi: 10.1016/j.emc.2016.08.008.
10. Diament D, Salomão R, Rigatto O, Gomes B, Silva E, Carvalho NB, et al. Diretrizes para tratamento da sepse grave/choque séptico: abordagem do agente infeccioso - diagnóstico. Revista Brasileira de Terapia Intensiva. 2011;23(2):134-144. Doi: 10.1590/S0103-507X2011000200005
11. Pereira RM, Tresoldi AT. Fatores que podem interferir no resultado de hemocultura em unidade de terapia intensiva pediátrica. J Pediatr (Rio J). 1999;75(1):34-8.
12. Hoefel HHK, Lautert L. Administração endovenosa de antibióticos e resistência bacteriana: responsabilidade da enfermagem. Revista Eletrônica de Enfermagem. 2009;8(3). Doi: 10.5216/ree.v8i3.7083
13. Althunayyan SM, Aljanoubi MA, Alghadeer SM, Alharthi MZ, Alotaibi RN, Mubarak AM, et al. The impact of emergency antibiotic administration time on patients with sepsis. Saudi Medical Journal, 2021;42(9):1002-8. Doi: 10.15537/smj.2021.42.9.20210447
14. Bulle EB, Peake SL, Finnis M, Bellomo R, Delaney A. Time to antimicrobial therapy in septic shock patients treated with an early goal-directed resuscitation protocol: A post-hoc analysis of the ARISE trial. Emergency Medicine Australasia, 2021;33:409-17.Doi: 10.1111/1742-6723.13634
15. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021;47:1181-1247. Doi: 10.1007/s00134-021-06506-y
16. Paridon BMV, Sheppard C, Guerra G, Joffe AR, Netword AS. Timing of antibiotics, volume, and vasoactive infusions in children with sepsis admitted to intensive care. Crit Care. 2015;19:293
17. Sales NS. Fatores preditores para mortalidade por sepse em uma unidade de terapia intensiva pediátrica. 2018. 72 f. Dissertação (Mestrado em Ciências da Saúde) - Programa de Pós-Graduação em Ciências da Saúde, Universidade Federal do Ceará, Sobral, 2018.
18. Tan B, Wong JJM, Sultana R, Koh JCJW, Jit M, Mok YH, Lee JH. Global Case-Fatality Rates in Pediatric Severe Sepsis and Septic Shock: A Systematic Review and Meta-analysis. JAMA Pediatr. 2019;173(4):352-362.
19. Santos GR, Barbosa MCM, Raymundo CE, Setta FL, Cunha AJLA, Barbosa AP, et al. Improvement of 1st-hour bundle compliance and sepsis mortality in pediatrics after the implementation of the surviving sepsis campaign guidelines. Jornal de Pediatria. 2021;97(4):459-67 Doi: 10.1016/j.jped.2020.09.005