Doi: 10.5152/TJAR.2019.45577

Original Article
Resuscitation
Article in Press

Turkish Journal of Anaesthesiology & Reanimation

Association between Blood Pressure after Haemodynamic Resuscitation in the Prehospital Setting and 28-Day Mortality in Septic Shock

Jouffroy Romain, Anastasia Saade, Pascal Philippe, Milene Buffo, Pierre Carli, Benoit Vivien
Department of Anaesthesia and Intensive Care Unit, SAMU, Paris, France

Cite this article as: Romain J, Saade A, Philippe P, Buffo M, Carli P, Vivien B. Association between Blood Pressure after Haemodynamic Resuscitation in the Prehospital Setting and 28-Day Mortality in Septic Shock. Turk J Anaesthesiol Reanim 2019; DOI: 10.5152/TJAR.2019.45577.

Abstract

Objective: Septic shock results in a decreased blood pressure (BP) leading to organ failure. The haemodynamic resuscitation aims at restoring the BP to allow efficient tissue perfusion. The aim of the present study was to evaluate the association between the mean BP (MBP) reached after haemodynamic resuscitation in patients with septic shock cared for in the prehospital setting by a mobile intensive care unit (MICU) and mortality at 28 days after intensive care unit (ICU) admission.

Methods: Patients with septic shock managed by a mobile intensive care unit (MICU) and admitted in the ICU were retrospectively analysed. The association between mortality and MBP after prehospital resuscitation was studied.

Results: A total of 85 patients with septic shock were included in the study. The origin of sepsis was mainly pulmonary (64%). Mortality reached 35%. Haemodynamic resuscitation was performed using crystalloids (98%) with a mean infused volume indexed on a body weight of 16±11 mL kg^{-1} in the prehospital setting. No patient received catecholamine or antibiotic prior to hospital admission. Final prehospital MBP was 64±8 mm Hg in the overall population and 66±8 mm Hg versus 62±8 mm Hg in alive and deceased patients, respectively (p=0.02). After adjustment, final prehospital MBP [odds ratio adjusted (ORa) (95% confidence interval (CI)]=0.89 (0.80–0.99), MBP <65 mmHg [ORa (95% CI)=14.3 (3.35–77.7)] and MBP >65 mmHg [ORa (95% CI)=0.06 (0.01–0.25)] were associated with mortality.

Conclusion: Persistent low MBP after prehospital initial resuscitation measures in patients with septic shock managed in the prehospital setting is associated with increased mortality. Further studies are needed to evaluate the impact of prehospital haemodynamic management in septic shock to further optimise prehospital care and improve outcome.

Keywords: Haemodynamic, mortality, optimisation, prehospital, septic shock

Introduction

Despite the improvement of our knowledge on the physiopathology of septic shock and improved clinical management with resuscitation measures, sepsis remains a major public health problem. Its incidence is estimated at 300 per 100,000 inhabitants in the United States (1, 2) with mortality rate nearly 30% (1, 3, 4). Recent studies underlined the benefit of early identification and shortened time-lapse to implementation of appropriate treatments on the outcome of patients with sepsis (4, 5). Among effective treatments, antibiotic administration and haemodynamic optimisation, both implemented early, significantly reduced mortality (6, 7).

During sepsis, absolute and relative hypovolemia reflected by a blood pressure (BP) decrease cause hypotension. Currently, septic shock is defined by persistent hypotension despite fluid resuscitation requiring catecholamine and a hyperlactatemia >2 mmol L^{-1} (8). Hypotension leads to hypoperfusion of peripheral organs, which can alter their function. Patients with septic shock generally present with fever, weakness and/or central neurological disorders,

Corresponding Author: Jouffroy Romain E-mail: romain.jouffroy@gmail.com

Received: 13.06.2019 Accepted: 20.07.2019
Available Online Date: 22.10.2019

such as confusion, for which the emergency medical services (EMS) are called.

Haemodynamic resuscitation and optimisation first consist of volume expansion with crystalloid fluid, ideally within the first hour after the identification of sepsis (8-10). Early fluid expansion is significantly associated with decreased mortality (11, 12). Therefore, for patients managed in the prehospital setting, fluid resuscitation has to be initiated in this environment to maintain a mean blood pressure (MBP) >65 mmHg (10). In the prehospital setting, no specific strategy is used to guide fluid resuscitation. Currently, no study has yet assessed the relationship between the modalities of prehospital haemodynamic resuscitation and the outcome of patients with septic shock.

The purpose of the current study was to describe the association between the MBP obtained after prehospital haemodynamic resuscitation and mortality at 28 days in patients initially cared for septic shock in the prehospital setting and admitted in the intensive care unit (ICU).

Methods

Study setting

In France, the management of out-of-hospital emergencies relies on the Service d'Aide Médicale d'Urgence (SAMU), equivalent to the American EMS dispatch centre (13). The SAMU can be reached by dialling the number 15. Each geographical department relies on a SAMU that regulates the population needs and guides each patient to the most appropriate public healthcare facility. The SAMU in Paris is called the SAMU75. The SAMU hospital-based team is composed of switchboard operators and physicians. The SAMU determines the appropriate level of care to dispatch to the scene, based on the patient's symptoms, communicated over the phone. For life-threatening emergencies, a mobile intensive care unit (MICU), the 'Service Mobile d'Urgence et de Réanimation,' composed of a driver, a nurse and an emergency physician, is dispatched (13) and usually gets to the scene within 10 min.

Septic shock is a particular subset of sepsis with profound circulatory, cellular and metabolic abnormalities associated with a high risk of mortality (8). It is considered as a life-threatening emergency requiring the early implementation of appropriate therapeutics, within the first hour (8). When septic shock is suspected based on the phone call, an ambulance is dispatched to the scene to evaluate the patient. If the patient presents physical signs of septic shock or significantly altered vital signs in favour of a septic shock, appropriate care is provided on the scene, and further mobile units are sent, if needed, for medical care or transportation.

Vital signs were collected at first medical contact (initial prehospital vital signs) and before hospital admission (final prehospital vital signs).

Study population

All consecutive patients admitted to the ICU of Necker Academic Hospital for septic shock, between January 2014 and September 2017, initially cared for by a mobile intensive care unit (MICU) in the prehospital setting, were retrospectively included in the study. The ICU department of Necker Academic hospital included eight ICU beds.

Septic shock was defined according to the surviving sepsis campaign criteria (10). Briefly, it is defined as a subset of sepsis in which particularly profound circulatory, cellular and metabolic abnormalities are associated with greater risk of mortality. Patients are usually identified when sepsis is associated with hypotension defined as an MBP <65 mmHg, the need for vasopressor therapy or hyperlactatemia (not yet available in the prehospital setting).

Diagnosis confirmation of septic shock was based on retrospective discharge diagnosis. Identification was based on the clinical criteria of profound circulatory abnormalities in the prehospital setting.

The primary outcome was mortality at 28 days after ICU admission. Patients' outcome was retrieved from ICU medical records. Data were retrieved from wards medical records or correspondence with the family physician for patients discharged before 28 days.

The study protocol was approved by an institutional review board (Comité de Protection des Personnes, Paris, Ile de France 2; no. ID-RCB: 2012-A01289-34).

Data collection

Data were extracted from pre- and in-hospital (ICU) medical reports, wards medical reports and correspondence with the family physician.

Covariates were defined prior to data collection and included patients' demographic characteristics (age, weight, size and gender), immunosuppression status, initial and final prehospital vital signs (MBP, diastolic (DBP) and systolic blood pressure (SBP), heart rate (HR), pulse oximetry (SpO_2), respiratory rate (RR), temperature and Glasgow Coma Scale (GCS)), origin of sepsis, duration of prehospital care, type and volume of prehospital infused fluid, catecholamine infusion (type and dose) and length of stay in the ICU. As previously described, immunosuppression was defined by the presence of one or more of the following elements: diabetes mellitus, chronic renal insufficiency, corticosteroids or another immunosuppressive treatment and infection by human immunodeficiency virus and/or

hepatitis C virus (14). Pulse pressure (15) and shock index (16) were calculated using final prehospital values of BP and HR.

Statistical analysis

Fluid volume expansion and catecholamine administered in the prehospital setting and prehospital and final prehospital vital signs (SBP, DBP, MBP, HR, RR, SpO_2 and temperature) were analysed. Prehospital fluid expansion volume is expressed as absolute value and indexed on body weight.

Multivariate analysis by logistic regression was conducted to evaluate the relationship between all covariates and mortality at day 28. Predictive performance of final prehospital haemodynamic parameters for mortality was assessed using adjusted receiver operating characteristic curve method.

Results are expressed as mean±standard deviation for quantitative parameters with normal distribution, median±interquartile range (25%–75%) for quantitative parameters with non-Gaussian distribution and absolute value and percentage for qualitative parameters.

Results are given as odds ratio with 95% confidence interval (95% CI). All analyses were performed using R 3.4.2 (http://www.R-project.org; the R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 85 patients cared for in the prehospital setting by a MICU and admitted to the ICU for septic shock were included in the present study.

Patients' demographic and clinical characteristics are summarised in Table 1. Of the 85 patients, 51 (60%) were male. The mean age of the patients was 70±15 years. Septic shock

Table 1. Demographic, clinical and biological characteristics of patients with septic shock managed by prehospital mobile intensive care units

	Alive at D28 (n=55)	Deceased at D28 (n=30)	Overall population (n=85)	p
Age (years)	69±15	73±14	70±15	0.2
Weight (kg)	68±15	64±15	66±15	0.3
Size (cm)	170±8	167±10	169±9	0.1
Male gender	36 (65%)	15 (50%)	51 (60%)	0.2
Immunosuppression	30 (54%)	16 (53%)	46 (54%)	0.92
Initial SBP (mmHg)	90±29	94±23	91±27	0.6
Initial DBP (mmHg)	54±22	59±19	56±21	0.7
Initial MBP (mmHg)	65±22	70±19	67±21	0.4
Initial HR (beats min^{-1})	123±27	110±28	118±28	0.05
Initial SpO_2 (%)	89±10	88±10	88±10	0.5
Initial RR (moves min^{-1})	30±8	33±8	31±8	0.11
Initial temperature (°C)	38.4±1.6	37.8±1.9	38.2±1.7	0.07
Duration of prehospital care (min)	103±35	93±35	99±35	0.2
Length of stay in the ICU (days)	5 (3–14)	6 (1–10)	6 (2–13)	0.2
Fluid volume expansion (mL)	1071±612	851±491	993±578	0.1
Fluid volume expansion indexed on body weight (mL kg^{-1})	17±12	14±9	16±11	0.3
Final SBP (mmHg)	96±14	93±16	95±15	0.3
Final DBP (mmHg)	50±8	47±8	49±8	0.01
Final MBP (mmHg)	65±8	62±8	64±8	0.04*
Final HR (beats min^{-1})	110±22	109±24	110±23	0.8
Final SpO_2 (%)	97±4	96±4	97±4	0.2
Final RR (moves min^{-1})	24±9	29±9	26±9	0.02*
Shock index	0.9±0.2	0.9±0.3	0.9±0.2	0.89
Pulse pressure	46±15	46±16	46±15	0.9

D28: day 28; SBP: systolic blood pressure; MBP: mean blood pressure; DBP: diastolic blood pressure; HR: heart rate; SpO_2: pulse oximetry; RR: respiratory rate. Quantitative variables are expressed as mean±standard deviation. Qualitative variables are expressed as absolute value and percentage.
*$p<0.05$

was mainly associated with pulmonary (64%), urinary (18%) and abdominal (5%) infections (Table 2).

On day 28 after ICU admission, mortality reached 35%. The mean duration of prehospital medical care was 99±35 min, with no difference between alive and deceased patients (p=0.2; Table 1). The median length of stay in the ICU was 6 (2–13) days (Table 1) (p=0.08).

Prehospital fluid expansion was performed in 98% of the patients with crystalloids. The mean fluid volume was 993±578 mL (16±11 mL kg^{-1}). A significant difference was observed between alive and deceased patients with a volume expansion of 1071±612 mL (17±11 mL kg^{-1}) and 851±491 mL (14±9 mL kg^{-1}), respectively (p=0.07) (Table 1). No patient received catecholamine prior to hospital admission.

Table 2. Origin of sepsis in patients cared for septic shock by a MICU in the prehospital setting

Site of infection	n (%)
Pulmonary	54 (64)
Urinary	15 (18)
Digestive	7 (8)
Cutaneous	2 (2)
Invasive medical device	2 (2)
Meningeal	1 (1)
Undefined	4 (5)

Data are expressed as absolute value with percentage. MICU: mobile intensive care unit

Table 3. Multivariate analysis of covariates associated with mortality on day 28 after ICU admission in patients cared for septic shock by a MICU in the prehospital setting

Multivariate analysis	
Variables	**ORa (95% CI)**
Final MBP	0.89 (0.80–0.99)*
Fluid volume expansion indexed on body weight	0.96 (0.91–1.02)
Duration of prehospital care	0.98 (0.97–1.01)
Immunosuppression	1.11 (0.40–2.95)
Length of stay in the ICU	0.93 (0.86–1.01)
GCS	0.93 (0.81–1.07)
Final HR	1.03 (0.97–1.11)
Final SpO_2	0.93 (0.79–1.07)
Final prehospital pulse pressure	0.98 (0.92–1.04)
Final prehospital shock index	23 (0.02–199)
Final MBP<65 mmHg	14.3 (3.35–77.7)*
Final MBP>65 mmHg	0.06 (0.01–0.25)*

GCS: Glasgow Coma Scale; MBP: mean blood pressure; HR: heart rate; SpO_2: pulse oximetry; ORa: odds ratio adjusted; 95% CI: 95% confidence interval. Data are presented as odds ratio adjusted with a 95% confidence interval

Initial prehospital SBP was 84±17 mmHg, DBP 51±15 mmHg and MBP 52±15 mmHg in the overall population. A significant difference was found between alive and deceased patients for SBP (p=0.008) and DBP (p=0.01), whereas no difference was found for MBP (p=0.1) (Table 1).

Final prehospital SBP was 95±15 mmHg, DBP 49±8 mmHg and MBP 64±8 mmHg in the overall population. A significant difference was found for SBP (p=0.01), DBP (p=0.02) and MBP (p=0.02) between alive and deceased patients (Table 1).

The area under curve (AUC) for MBP to predict mortality at 28 days was 0.67 (0.56–0.79). Using logistic regression, including final prehospital MBP, GCS, final prehospital HR, final prehospital SpO_2, final prehospital pulse pressure, final prehospital shock index, fluid volume expansion, immunosuppression, duration of prehospital care and length of stay in the ICU, an independent association with mortality remained significant for final prehospital MBP [odds ratio adjusted (ORa) (95% CI)=0.89 (0.80–0.99)], for MBP <65 mmHg [ORa (95% CI)=14.3 (3.35–77.7)] and for MBP >65 mmHg [ORa (95% CI)=0.06 (0.01–0.25)] (Table 3).

Discussion

Among 85 patients with septic shock initially cared for in the prehospital setting by a MICU and admitted to the ICU, initial haemodynamic resuscitation was mainly based on fluid expansion with crystalloids. A significant association between mortality at 28 days and failure to reach efficient haemodynamic state as defined by an MBP >65 mmHg after initial prehospital resuscitation measures was observed.

Sepsis causes relative and absolute hypovolemia through complex and different routes, resulting in decreased BP, leading to tissue hypoperfusion and thus organ failure, which alters the patient's prognosis (17). The prognosis of patients suffering from septic shock is directly related to the early diagnosis and rapid initiation of therapeutics, including antibiotic administration and haemodynamic optimisation (4, 5). Recently, a new concept is evolving with the notion of a bundle of care consisting of a global strategy for the efficient management of patients with sepsis, including both haemodynamic optimisation and antibiotherapy (18). This concept matches the 'survival chain' used in cardiopulmonary resuscitation (19).

The impact of antibiotic administration on mortality in the prehospital setting remains under debate due to the lack of sufficient evidence (20-22). Actually, antibiotherapy is rarely

started in the prehospital setting, especially when the duration of care is short, such as in our setting, excluding specific situations, such as purpura fulminans. A recent study concluded that prehospital advanced life supports, on the contrary to basic life supports only, enabled faster antibiotic initiation (23). Currently, there is a need for randomised controlled trials to evaluate the outcome of patients with septic shock receiving antibiotherapy in the prehospital setting (24). Results of the ongoing French study 'SAMU Save Sepsis,' evaluating the impact of the bundle of care, initiated in the prehospital environment, will probably help answer this question (25).

The two options to optimise haemodynamic resuscitation are fluid expansion and norepinephrine infusion, with an MBP target of at least 65 mmHg (8). Despite controversies regarding the amount of fluid expansion (26-30), guidelines for haemodynamic optimisation recommend a fluid volume expansion of 30 mL kg^{-1} with crystalloids (8). In a previous study performed in the prehospital setting, a relationship between mortality and reduced fluid volume expansion on the one side was observed, and fluid expansion was usually performed to lower volume amount than those recommended (14). The major goal was the improvement of the haemodynamic status, in the case of persistent hypotension despite fluid resuscitation, meaning failure to restore tissue perfusion, catecholamine may be indicated. In this context, early evaluation of haemodynamic parameters in the prehospital setting may be useful to rapidly introduce catecholamine. The optimal timing to start catecholamine remains under debate. The guidelines suggest the use of norepinephrine when initial DBP is <40 mmHg and/or after failure of fluid expansion, e.g. for an MBP <65 mmHg (8). In the present study, the initial DBP was >40 mmHg, and fluid expansion did not reach optimal volumes during prehospital management, which may explain the absence of a vasopressor in this setting.

The present study has a few limitations. First, this is a retrospective, single centre study with a small sample size. Therefore, no causal relationship can be established. Second, the outcome may be influenced by the amount of fluid administered in the prehospital setting, which was reported to be associated with mortality (14). Indeed, patients did not receive optimal fluid expansion in the prehospital setting probably due to the short management time in this environment in our study. Initial fluid resuscitation should be initiated immediately upon recognising a patient with sepsis and hypotension and completed within 3 h of recognition according to the recent guidelines. In addition, vasopressors should be started within the first hour to achieve an MBP ≥65 mmHg. Regardless, in the prehospital setting, fluid expansion remains, unfortunately, not optimal (31). As vasopressors were not initiated in this setting, their benefit in the prehospital environment cannot be evaluated. Third, intrinsic to prehospital studies, data regarding the patient's medical history prior to the first prehospital medical contact and the delay to initiate fluid expansion were lacking. They are very likely many factors, measured and unmeasured, that may have had influenced our results. This probably explains an AUC of 0.67 for an MBP <65 mmHg that is not high enough to discriminate between alive and deceased patients despite a significant difference between alive and deceased patients for this value of MBP.

Conclusion

In the present study, low MBP achieved upon initial fluid resuscitation in the prehospital setting of patients suffering from septic shock is observed to be associated with poor prognosis. To the best of our knowledge, this is the first study evaluating the impact of initial prehospital resuscitation on MBP in patients with septic shock cared for in the prehospital environment. Further studies are needed to evaluate the impact of haemodynamic optimisation on mortality and state on the early use of catecholamine in case of failure to rapidly restore stable haemodynamic.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Comité de Protection des Personnes, Paris-Ile de France 2 (Number ID-RCB: 2012-A01289- 34 on 2012-10-01.

Informed Consent: Due to the retrospective design of the study, informed consent was not taken.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – R.J.; Design – R.J.; Supervision – B.V.; Data Collection and/or Processing – M.B., P.P., R.J.; Analysis and/or Interpretation – R.J., A.S.; Literature Search – R.J., M.B., A.S.; Writing Manuscript – A.S., R.J.; Critical Review – R.J., A.S., P.P., M.B., P.C., B.V.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

References

1. Gaieski DF, Edwards JM, Kallan MJ, Carr BG. Benchmarking the incidence and mortality of severe sepsis in the United States. Crit Care Med 2013; 41: 1167-74. [CrossRef]
2. Jawad I, Luksic I, Rafnsson SB. Assessing available information on the burden of sepsis: global estimates of incidence, prevalence and mortality. J Glob Health 2012; 2: 010404. [CrossRef]
3. Annane D, Aegerter P, Jars-Guincestre MC, Guidet B, Network CU-R. Current epidemiology of septic shock: the CUB-Rea Network. Am J Respir Crit Care Med 2003; 168: 165-72. [CrossRef]

4. Pro CI, Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, et al. A randomized trial of protocol-based care for early septic shock. N Engl J Med 2014; 370: 1683-93. [CrossRef]
5. Delaney AP, Peake SL, Bellomo R, Cameron P, Holdgate A, Howe B, et al. The Australasian Resuscitation in Sepsis Evaluation (ARISE) trial statistical analysis plan. Crit Care Resusc 2013; 15: 162-71. [CrossRef]
6. Leisman DE, Doerfler ME, Ward MF, Masick KD, Wie BJ, Gribben JL, et al. Survival Benefit and Cost Savings From Compliance With a Simplified 3-Hour Sepsis Bundle in a Series of Prospective, Multisite, Observational Cohorts. Crit Care Med 2017; 45: 395-406. [CrossRef]
7. Seymour CW, Gesten F, Prescott HC, Friedrich ME, Iwashyna TJ, Phillips GS, et al. Time to Treatment and Mortality during Mandated Emergency Care for Sepsis. N Engl J Med 2017; 376: 2235-44. [CrossRef]
8. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315: 801-10. [CrossRef]
9. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, Cohen J, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 2004; 32: 858-73. [CrossRef]
10. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013; 41: 580-637. [CrossRef]
11. Band RA, Gaieski DF, Hylton JH, Shofer FS, Goyal M, Meisel ZF. Arriving by emergency medical services improves time to treatment endpoints for patients with severe sepsis or septic shock. Acad Emerg Med 2011; 18: 934-40. [CrossRef]
12. Geeraedts LM, Jr., Pothof LA, Caldwell E, de Lange-de Klerk ES, D'Amours SK. Prehospital fluid resuscitation in hypotensive trauma patients: do we need a tailored approach? Injury 2015; 46: 4-9. [CrossRef]
13. Adnet F, Lapostolle F. International EMS systems: France. Resuscitation 2004; 63: 7-9. [CrossRef]
14. Jouffroy R, Saade A, Muret A, Philippe P, Michaloux M, Carli P, et al. Fluid resuscitation in pre-hospital management of septic shock. Am J Emerg Med 2018; 36: 1754-8. [CrossRef]
15. Dart AM, Kingwell BA. Pulse pressure--a review of mechanisms and clinical relevance. J Am Coll Cardiol 2001; 37: 975-84. [CrossRef]
16. Allgower M, Burri C. Shock index. Dtsch Med Wochenschr 1967; 92: 1947-50. [CrossRef]
17. Brun-Buisson C, Meshaka P, Pinton P, Vallet B, Group ES. EPISEPSIS: a reappraisal of the epidemiology and outcome of severe sepsis in French intensive care units. Intensive Care Med 2004; 30: 580-8. [CrossRef]
18. Jouffroy R, Saade A, Vivien B. Bundle of Care in Pre-Hospital Settings for Septic Shock? Turk J Anaesthesiol Reanim 2018; 46: 406-7. [CrossRef]
19. McCarthy JJ, Carr B, Sasson C, Bobrow BJ, Callaway CW, Neumar RW, et al. Out-of-Hospital Cardiac Arrest Resuscitation Systems of Care: A Scientific Statement From the American Heart Association. Circulation 2018; 137: e645-e60. [CrossRef]
20. Alam N, Oskam E, Stassen PM, Exter PV, van de Ven PM, Haak HR, et al. Prehospital antibiotics in the ambulance for sepsis: a multicentre, open label, randomised trial. Lancet Respir Med 2018; 6: 40-50. [CrossRef]
21. Quinten VM, van Meurs M, Ligtenberg JJ, Ter Maaten JC. Prehospital antibiotics for sepsis: beyond mortality? Lancet Respir Med 2018; 6: e8. [CrossRef]
22. Vincent JL. Antibiotic administration in the ambulance? Lancet Respir Med 2018; 6: 5-6. [CrossRef]
23. Peltan ID, Mitchell KH, Rudd KE, Mann BA, Carlbom DJ, Rea TD, et al. Prehospital Care and Emergency Department Door-to-Antibiotic Time in Sepsis. Ann Am Thorac Soc 2018; 15: 1443-50. [CrossRef]
24. Udy AA, Smith K, Bernard S. Timing of antibiotics in the management of community-acquired sepsis: Can a randomised controlled trial of prehospital therapy provide answers? Emerg Med Australas 2018; 30: 270-2. [CrossRef]
25. Samu Save Sepsis: Early Goal Directed Therapy in Pre Hospital Care of Patients With Severe Sepsis and/or Septic Shock (SSS). ClinicalTrials.gov Identifier:NCT02473263.
26. Byrne L, Van Haren F. Fluid resuscitation in human sepsis: Time to rewrite history? Ann Intensive Care 2017; 7: 4. [CrossRef]
27. Gong YC, Liu JT, Ma PL. Early fluid loading for septic patients: Any safety limit needed? Chin J Traumatol 2018; 21: 1-3. [CrossRef]
28. Jaehne AK, Rivers EP. Early Liberal Fluid Therapy for Sepsis Patients Is Not Harmful: Hydrophobia Is Unwarranted but Drink Responsibly. Crit Care Med 2016; 44: 2263-9. [CrossRef]
29. Malbrain M, Van Regenmortel N, Saugel B, De Tavernier B, Van Gaal PJ, Joannes-Boyau O, et al. Principles of fluid management and stewardship in septic shock: it is time to consider the four D's and the four phases of fluid therapy. Ann Intensive Care 2018; 8: 66. [CrossRef]
30. Self WH, Semler MW, Bellomo R, Brown SM, deBoisblanc BP, Exline MC, et al. Liberal Versus Restrictive Intravenous Fluid Therapy for Early Septic Shock: Rationale for a Randomized Trial. Ann Emerg Med 2018; 72: 457-66. [CrossRef]
31. Seymour CW, Cooke CR, Heckbert SR, Spertus JA, Callaway CW, Martin-Gill C, et al. Prehospital intravenous access and fluid resuscitation in severe sepsis: an observational cohort study. Crit Care 2014; 18: 533. [CrossRef]