Journal of Critical Care 54 (2019) 175–179

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Hemodynamic profiles following digoxin use in patients with sepsis in the ICU

Svetlana Herasevich, MD [a,*], Courtney E. Bennett, DO [b], Alex R. Schwegman, MD [c], Yosuf W. Subat, MD [c], Ognjen Gajic, MD [a], Namita Jayaprakash, MB Bch BAO, MRCEM [d]

[a] Department of Medicine, Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, United States of America
[b] Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, United States of America
[c] Department of Internal Medicine, Mayo Clinic, Rochester, MN, United States of America
[d] Department of Emergency Medicine, Division of Pulmonary Critical Care Medicine, Henry Ford Hospital, Detroit, MI, United States of America

ARTICLE INFO

Keywords:
Digoxin
Sepsis
Hemodynamics
Cardiotonic agents
Myocardial depression
Shock index

ABSTRACT

Purpose: To explore the impact of digoxin on hemodynamic parameters in patients with sepsis and tachycardia admitted to the intensive care unit.
Materials and methods: Retrospective review of adult patients admitted to the medical and mixed ICU at Mayo Clinic Rochester, Minnesota from March 2008 to February 2018, initiated on digoxin within 24 h of ICU stay. Hemodynamic parameters were reviewed before digoxin administration and at 6, 12 and 24 h after. Adverse events including new onset conduction abnormalities or arrhythmias during the first 48 h after digoxin administration were reviewed by a critical care cardiologist.
Results: Study included 180 patients. We observed significant decrease in heart rate from 124 (115–138) beats/min 1 h before digoxin to 101 (87–117) 6 h after digoxin and 94 (84–112) 12 h after ($p < .01$). Median systolic blood pressure increased from 100 (91–112) mm Hg 1 h before to 110 (100−122) ($p < .01$) and 111 (103–124) at 6 and 12 h respectively after digoxin.
Conclusions: Early digoxin administration in patients with sepsis and tachycardia is uncommon but associated with improvements of hemodynamic parameters. These preliminary results will help formulate future hypotheses for focused trials on utility, efficacy and safety of digoxin in sepsis.

1. Introduction

Sepsis-induced myocardial dysfunction, with depressed systolic function, is a common complication occurring in approximately 30–60% of patients with sepsis and is associated with increased mortality [1-3]. The hyperdynamic phase of sepsis impacts the circulatory system by resulting in a state of increased cardiac output and decreased systemic vascular resistance. Tachycardia during this phase is a compensatory effect responding to both an intramyocardial inflammatory response and adrenergic stimulation from cardiac under filling, fever, anemia, agitation and drug effects [3-5]. The modified shock index (MSI) can be applied to measure the effects of this hyperdynamic phase in sepsis as it is a measurement of the ratio of the heart rate (HR) to the mean arterial blood pressure (MAP). In sepsis, especially in the early course, an increase in the MSI is associated with an increased mortality [6,7].

Excessive tachycardia during the hyperdynamic phase of sepsis can impede the diastolic filling phase of the cardiac cycle and subsequently cardiac output. The use of esmolol in this hyperdynamic phase improves tachycardia and mortality. However, the widespread use of esmolol has been limited because of concerns surrounding the negative inotropic effects of beta-blockers and the potential for worsening sepsis associated cardiovascular decompensation [8,9].

In contrast to beta-blockers, the cardiac glycoside digoxin possesses a negative chronotropic effect along with a positive inotropic effect. Thus, it is an appealing drug for improving heart rate without inducing or enhancing hypotension [5]. Concerns about the narrow therapeutic index of digoxin however may limit its use, especially in those with renal insufficiency and in the elderly [10]. The objective of this study was to conduct a preliminary exploration of the hemodynamic effects of early digoxin administration in patients admitted to the intensive care unit (ICU) with sepsis and tachycardia.

* Corresponding author at: Division of Pulmonary and Critical Care Medicine, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, United States of America.
E-mail address: Herasevich.Svetlana@mayo.edu (S. Herasevich).

https://doi.org/10.1016/j.jcrc.2019.08.026
0883-9441/

2. Materials and methods

2.1. Study design and setting

This is a single-center retrospective review of adult patients (≥18 years old) with sepsis and tachycardia or tachyarrhythmia, admitted to the medical and mixed (medical and surgical) ICUs at Mayo Clinic Rochester, Minnesota from March 2008 to February 2018, whom were initiated on digoxin within the first 24 h of their ICU stay. This research study was reviewed and approved by the Mayo Clinic Institutional Review Board (IRB 18-002424).

2.2. Study patients

2.2.1. Inclusion

Adult patients (≥18 years of age) in whom digoxin was newly initiated within 24 h of ICU admission and had a diagnosis of sepsis and tachycardia or tachyarrhythmia (HR ≥ 100 bpm).

2.2.2. Exclusion

Patients without research authorization, <18 years of age, pregnant or those who received digoxin at home before hospital admission.

2.3. Definitions

Digoxin use was defined as initiation of intravenous digoxin as documented in the electronic medical record (EMR). Digoxin total loading dose was defined as total load of digoxin within 24 h of initiation.

We defined sepsis by applying the Sepsis-3 criteria: increase in a SOFA score at day 1 of ≥2 and suspicion for infection. Suspicion for infection was identified by whether cultures were obtained (regardless of the result) and antimicrobial therapy was administered [11,12].

Tachycardia was defined as a heart rate (HR) ≥100 beats per minute within 1 h before digoxin administration.

Tachyarrhythmia was defined atrial fibrillation (paroxysmal, new onset or persistent) and/or atrial flutter within 1 h prior to digoxin administration.

2.4. Data sources

Data retrieval was performed by the anesthesia clinical research unit (ACRU) and a research fellow using our institutional databases and query tools. The ICU DataMart is an integrated institutional database that collects a near-real-time copy of clinical and administrative data from the EMR [13] and Advanced Cohort Explorer (ACE) is a query tool that allows access to data stored in the Enterprise Data Trust (EDT). Further manual data abstraction from the EMR was performed by a research fellow and two internal medicine residents. The manual abstractors identified sepsis by application of the Sepsis-3 criteria. SOFA scores were available from the institutional databases and abstractors reviewed the EMR to identify suspicion of infection (cultures obtained, antimicrobial therapy administered). JMP Pro software (SAS Institute, Cary, NC) was used for data collection and analysis.

2.5. Outcome variables

The primary endpoint of interest was impact of digoxin administration on hemodynamic profiles including MSI, HR, systolic blood pressure (SBP) and diastolic blood pressure (DBP). The MAP at 1 h before digoxin administration and at 6, 12 and 24 h after digoxin administration were also reviewed. Secondary outcomes included vasoactive medication use; development of clinically significant bradycardia (defined by concurrent hypotension requiring use of vasopressors); new onset cardiac arrhythmias or conduction abnormalities within 48 h of initiation of digoxin or during the hospital stay if digoxin was continued after ICU discharge.

Digoxin administration details including doses and continuation after ICU and hospital discharge were extracted from the EMR. Additional variables including patient demographics and clinical data (age, sex, weight at ICU admission, comorbidities (Charlson comorbidity index), Acute Physiology and Chronic Health Evaluation (APACHE) III score, and Sequential Organ Failure Assessment (SOFA) score, and ejection fraction within 1 year before ICU admission and during ICU stay were collected. The following variables were also of interest for secondary outcomes: ICU length of stay (LOS) and hospital LOS in days; ICU mortality and hospital mortality; vasopressor administration data at the time of digoxin administration and at 24 h; use of beta-blockers, calcium channel blockers, and amiodarone within 24 h of ICU admission. Vasopressor doses were converted to NE equivalents using the following rules: 1 μg epinephrine = 1 μg norepinephrine, 1 μg phenylephrine = 0.45 μg norepinephrine, 1 unit vasopressin = 5 μg norepinephrine, 100 μg dopamine = 1 μg norepinephrine [14-16].

Laboratory parameters extracted include creatinine and potassium levels prior to digoxin administration, and lactate level – the first measurement in ICU and the highest level during the ICU stay.

2.6. Statistical analysis

Descriptive statistics of baseline comorbidities, severity of illness, dose and timing of digoxin and other vasoactive medications administered, vital signs, organ failure (SOFA) and ICU and hospital outcomes (length of stay, mortality) was performed. Paired analysis was used to compare heart rate, blood pressure and vasoactive medication use and dosage before and after initiation of Digoxin (1 h before and 6, 12 and 24 h after).

Continuous variables are expressed as median (IQR) and differences in median before and after digoxin administration were tested with Wilcoxon signed rank test. Categorical variables are presented as count and percentage and compared using McNemar's test.

A subgroup analysis of outcomes was performed on two groups of patients, those who had baseline atrial tachyarrhythmias (atrial fibrillation or atrial flutter) and those who had sinus tachycardia.

3. Results

Of the adult patients who were admitted to the medical and mixed ICU during the study period, 483 patients were initiated on Digoxin within the first 24 h of their ICU stay. We excluded 33 patients without research authorization and 51 patients who had a SOFA score day 1 < 2. The EMR of the remaining 399 patients were reviewed by the two trained internal medicine residents and the research fellow to verify sepsis as per Sepsis-3 criteria (Fig. 1).

The final cohort included 180 patients of which one hundred fifty-four patients (85.5%) had atrial fibrillation or atrial flutter, 23 patients (12.8%) had sinus tachycardia, and 3 patients (1.7%) had other arrhythmias (two had supraventricular tachycardia and one had a multifocal atrial tachycardia). Of these 180 study patients, 59% were admitted to the medical ICU and 41% were admitted to the mixed ICU. Table 1 demonstrates the baseline characteristics of the cohort.

Baseline characteristics of the subgroup of patients with atrial fibrillation or atrial flutter and sinus tachycardia are outlined in Table E1, E-data supplement.

Table 2 shows the primary endpoints which include changes from baseline modified shock index, heart rate and blood pressure at 6, 12 and 24 h following digoxin administration.

The hemodynamic profiles of patients with atrial tachyarrhythmia and sinus tachycardia are outlined in Table E2 and E3 of the electronic supplementary data. Seventy-five (42%) of patients required vasopressor support. 60 patients (33%) received vasopressors before digoxin use and 71 (39%) – during the first 24 h of digoxin use. Median dose of vasopressors was similar before and 24 h after Digoxin

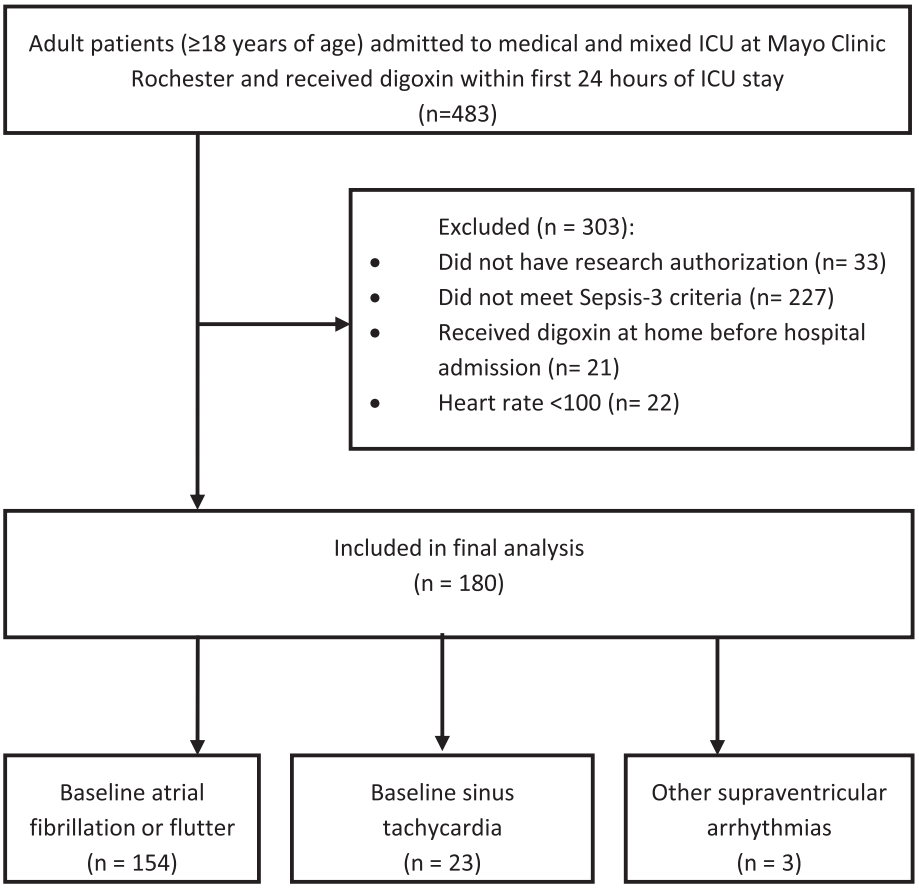

Fig. 1. Study flow diagram.

administration, 0.053 (0.024, 0.133) μg/kg/min vs 0.048 (0.015, 0.124) μg/kg/min in norepinephrine equivalent units, $p = .65$. Similarly, there was no difference in the median vasopressor doses in subgroups of atrial fibrillation or atrial flutter and sinus tachycardia (Table E4, *E*-data supplement). The concomitant use of antiarrhythmic drugs (beta-blockers, calcium channel blockers, amiodarone) in the first 24 h of ICU stay was common (Table E5). Median SOFA score decreased from 6 (4–10) in day 1 to 4 (3–8) in day 2, $p < .01$. The median ICU length of stay for the sample was 2.1 days (1.3–4.2), median hospital length of stay 10.4 days (5.9–18.3), ICU mortality was 15.6% and hospital mortality 27.8%.

Of note, in a subset of 40 patients, an echocardiogram with documented ejection fraction (EF) was available within the preceding year from ICU admission. The median (IQR) EF in this group was 57 (34.8–64.3). Following administration of digoxin, the median EF measured by echocardiogram during ICU stay was 55 (34.8–64.3), $p = .45$.

Adverse events: All potential digoxin side effects were reviewed by a critical care cardiologist. For patients continued on digoxin beyond the initial dose and beyond ICU stay, the EMR was reviewed for any new onset arrhythmias or conduction abnormality over the course of the entire hospitalization. In total, we identified 2 episodes of new atrial flutter with variable block, 6 cases of sinus bradycardia, 1 case of atrial fibrillation with bradycardia, and no ventricular arrhythmias within 48 h of digoxin administration. No interventions were required for the identified dysrhythmias.

4. Discussion

This retrospective review of a cohort of patients who received digoxin within 24 h of ICU admission and had sepsis with tachycardia or tachyarrhythmia, found improvement in the hemodynamic parameters including MSI after administration of digoxin. Digoxin use in sepsis is uncommon at our center. In >30,000 ICU admissions at only 483 received digoxin within the first 24 h and only 180 of these patients met Sepsis-3 criteria and had tachycardia. The majority of these patients (85.5%) had an atrial tachyarrhythmia (atrial fibrillation or atrial flutter).

The use of digoxin in sepsis has been previously studied in a limited fashion in small trials. Worthley et al. and Nasraway et al. have shown improvements in HR and MAP along with stroke volume index and left ventricular stroke work index with use of digoxin [5,17]. Our study supports these findings related to HR and MAP calculated as in improvements of MSI.

Digoxin is a cardiac glycoside that binds selectively to the α-subunit of Na-K-ATPase resulting in increased intra-cellular calcium. The increase in the intra-cellular calcium is the primary driver of the positive inotropy with digoxin. Other effects include a negative chronotropic effect, increased vagal tone, vasoconstriction within the coronary arteries, reduced sympathetic tone, indirect vasodilation in patients with heart failure, reduced oxidation of fats and a related reduced basal metabolic rate, and immunomodulatory effects including suppression of the production of IL-6 and TNF-α in endotoxemia [5].

The most common sepsis-associated arrhythmia is atrial fibrillation (AF) with up to half of all patients with septic shock developing new-onset AF [18,19]. New-onset AF makes up more than 70% of all the supraventricular arrhythmias that present in septic shock [18-21]. In our study of patients with sepsis admitted to the ICU, 85.5% of patients who received digoxin in the first 24 h of their ICU stay were noted to have atrial fibrillation or atrial flutter. Current FDA recommendations state that digoxin can be safely administered at a dose of 500 μg as a single initial dose, followed by 250 μg 6 h latera and a further 250 μg 6 h after that for a total loading dose of 1000 μg [22]. The FDA listed indications and usage are specific to heart failure and atrial fibrillation.

Table 1
Baseline characteristics.

Characteristic	Median (IQR) or N (%)
All patients ($n = 180$)	
Atrial fibrillation or atrial flutter	154 (85.5%)
Atrial fibrillation	134 (74.4%)
Atrial flutter	20 (11.1%)
Sinus tachycardia	23 (12.8%)
Other supraventricular tachycardias	3 (1.7%)
Age	72 (62–78)
Male sex	114 (63%)
Weight (kg)	84 (70–99)
Comorbidities (Charlson comorbidity index)	3 (1–5)
APACHE III	90 (75–101)
SOFA day 1	6 (4–10)
Creatinine[a]	1.2 (0.9–1.9)
Potassium[a]	4.1 (3.7–4.5)
Vasopressor use[b]	60 (33%)
Lactate at admission[c] ($N = 147$)	1.9 (1.3–3.1)
Time of first lactate measurement after ICU admission, hours	1.2 (0.7–2.4)
Maximum lactate during the ICU stay ($N = 147$)	2.3 (1.3–4.0)
Time of maximum lactate measurement after ICU admission, hours	3.2 (1.2–18.4)
Invasive ventilation use	49 (27%)
Digoxin start dose (1st bolus)	
250 μg	51 (28%)
500 μg	129 (72%)
Digoxin total loading dose	750 (500–1000)
Digoxin time of administration after ICU admission, hours	5.8 (2.2–12.8)
Digoxin continued during the hospital stay after ICU discharge	42 (23%)
Digoxin continued after hospital discharge	26 (14%)

[a] Prior to digoxin administration, the most recent.
[b] Prior to digoxin administration.
[c] The first measurement during ICU stay.

Previous studies of digoxin use in critically ill patients have used doses of 10–12 μg/kg intravenously without reported adverse effects [5,23].

Adverse effects of digoxin have not been evaluated in a randomized controlled manner and largely come from sub-group analyses or meta-analyses of observational trials. These trials are mainly related to rate control in atrial fibrillation or chronic outpatient therapy of mild to moderate systolic heart failure [24]. In our study like in previously described sepsis trials that have looked at digoxin in sepsis, we found that the majority of use was limited to the ICU at initial doses of either 250 μg or 500 μg. The median (IQR) total loading dose was 750 (500–1000) μg. Only 23% of our sample had digoxin continued throughout the hospitalization with only 14% being discharged on digoxin. The majority of these were patients with atrial fibrillation or atrial flutter. Three out of the 23 patients with sinus tachycardia had digoxin continued after the ICU but none were discharged on digoxin. Additionally, while this study identified 9 dysrhythmias following the administration of digoxin, none of these events had specific interventions. Thus, in this study we found that in sepsis associated tachycardia a loading dose of digoxin provided hemodynamic benefits without ventricular dysrhythmias but some rhythm changes for which interventions were not required. This is of interest when considering the opportunity of using digoxin as an alternative to agents such as esmolol. The opportunity may be present to avoid the concerns of beta blocker induced hypotension or depressed stroke volume given the negative chronotropic and positive ionotropic impact of digoxin. This study, of course, serves only as a very preliminary pilot investigation for the potential of digoxin use in patients with early sepsis. Further investigation is warranted.

4.1. Limitations

This study has several limitations. It is a single center retrospective study with limited generalizability. We defined the study population and used cases as their own controls to reduce random error and confounding. As the study has a retrospective design it is difficult to determine the exact circumstances that influenced the clinical decision of administering digoxin. While the majority of patients had atrial fibrillation or atrial flutter, it is unclear why some clinicians used digoxin in patients with sinus tachycardia. Moreover, while we report changes in the hemodynamic profiles following digoxin administration we cannot exclude that this may be part of the natural evolution of the disease process or the result of other interventions related to early resuscitation. We also note that a large majority of the patients were on other rate moderating medications such as beta-blockers, calcium channel blockers and amiodarone. Thus, it is difficult in this type of study to identify the impact of other these agents on the hemodynamic parameters of interest. Another limitation arising from the retrospective nature of this study, was that accurate data related to fluid administration was not readily available. Absence of control groups limits our ability to compare the effects of digoxin in patients with sepsis to patients receiving placebo or other medications. This data however, serves as interesting preliminary pilot data that will help formulate hypotheses for future trials that specifically test for efficacy and safety of digoxin in the hyperdynamic phase of sepsis.

5. Conclusions

Patients with sepsis and tachycardia who receive digoxin within the first 24 h after ICU admission have improvements in their hemodynamic parameters. Digoxin may serve as an alternative agent to esmolol in hyperdynamic phases of early sepsis, in particular septic shock. This preliminary pilot data will help formulate hypotheses for future prospective and larger studies to investigate the impact on clinical outcomes, safety and efficacy of digoxin in sepsis.

Table 2
Changes in the hemodynamic parameters.

Time	N	Heart rate	Systolic blood pressure	Diastolic blood pressure	Mean arterial blood pressure	Modified shock index (HR/MAP)
Changes in the hemodynamic parameters in 6 h after digoxin compared to 1 h prior to digoxin						
1 h before digoxin	180	124 (115–138)	100 (91–112)	57 (50–67)	69 (62–78)	1.88 (1.58–2.08)
6 h after digoxin	180	101 (87–117)	110 (100–122)	57 (50–65)	71 (64–79)	1.37 (1.16–1.68)
p-value*		<0.001	<0.001	0.08	0.16	<0.001
Changes in the hemodynamic parameters in 12 h after digoxin compared to 1 h prior to digoxin						
1 h before digoxin	175	124 (115–138)	100 (92–113)	57 (50–67)	69 (62–78)	1.87 (1.58–2.08)
12 h after digoxin	175	94 (84–112)	111 (103–124)	56 (49–66)	72 (66–80)	1.30 (1.14–1.58)
p-value*		<0.001	<0.001	0.11	0.02	<0.001
Changes in the hemodynamic parameters in 24 h after digoxin compared to 1 h prior to digoxin						
1 h before digoxin	174	124 (115–138)	100 (92–113)	57 (50–67)	69 (62–78)	1.87 (1.58–2.08)
24 h after digoxin	174	95 (82–107)	112 (101–129)	57 (51–67)	72 (65–82)	1.33 (1.08–1.53)
p-value*		<0.001	<0.001	0.85	0.048	<0.001

* Wilcoxon signed rank test for paired data.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2019.08.026.

References

[1] Landesberg G, Gilon D, Meroz Y, Georgieva M, Levin PD, Goodman S, et al. Diastolic dysfunction and mortality in severe sepsis and septic shock. Eur Heart J 2012;33(7):895–903.
[2] Lv X, Wang H. Pathophysiology of sepsis-induced myocardial dysfunction. Mil Med Res 2016;3:30.
[3] Jayaprakash N, Gajic O, Frank RD, Smischney N. Elevated modified shock index in early sepsis is associated with myocardial dysfunction and mortality. J Crit Care 2018;43:30–5.
[4] Walley KR. Sepsis-induced myocardial dysfunction. Curr Opin Crit Care 2018;24(4):292–9.
[5] Worthley LI, Holt AW. Digoxin in the critically ill patient. Crit Care Resusc 1999;1(3):252–64.
[6] Liu YC, Liu JH, Fang ZA, Shan GL, Xu J, Qi ZW, et al. Modified shock index and mortality rate of emergency patients. World J Emerg Med 2012;3(2):114–7.
[7] Smischney NJ, Seisa MO, Heise KJ, Schroeder DR, Weister TJ, Diedrich DA. Elevated modified shock index within 24 hours of ICU admission is an early Indicator of mortality in the critically ill. J Intensive Care Med 2018;33(10):582–8.
[8] Antonucci E, Fiaccadori E, Donadello K, Taccone FS, Franchi F, Scolletta S. Myocardial depression in sepsis: from pathogenesis to clinical manifestations and treatment. J Crit Care 2014;29(4):500–11.
[9] Morelli A, Ertmer C, Westphal M, Rehberg S, Kampmeier T, Ligges S, et al. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. JAMA 2013;310(16):1683–91.
[10] Walkey AJ, Evans SR, Winter MR, Benjamin EJ. Practice patterns and outcomes of treatments for atrial fibrillation during Sepsis: a propensity-matched cohort study. Chest 2016;149(1):74–83.
[11] Rhee C, Dantes R, Epstein L, Murphy DJ, Seymour CW, Iwashyna TJ, et al. Incidence and trends of Sepsis in US hospitals using clinical vs claims data, 2009-2014. Jama 2017;318(13):1241–9.
[12] 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(8):801–10.
[13] Herasevich V, Pickering BW, Dong Y, Peters SG, Gajic O. Informatics infrastructure for syndrome surveillance, decision support, reporting, and modeling of critical illness. Mayo Clin Proc 2010;85(3):247–54.
[14] Brown SM, Lanspa MJ, Jones JP, Kuttler KG, Li Y, Carlson R, et al. Survival after shock requiring high-dose vasopressor therapy. Chest 2013;143(3):664–71.
[15] Jentzer JC, Coons JC, Link CB, Schmidhofer M. Pharmacotherapy update on the use of vasopressors and inotropes in the intensive care unit. J Cardiovasc Pharmacol Ther 2015;20(3):249–60.
[16] Vallabhajosyula S, Jentzer JC, Khanna AK. Vasodilatory shock in the ICU: perils, pitfalls and therapeutic options. In: Vincent J-L, editor. Annual update in intensive care and emergency medicine 2018. Cham: Springer International Publishing; 2018. p. 99–111.
[17] Nasraway SA, Rackow EC, Astiz ME, Karras G, Weil MH. Inotropic response to digoxin and dopamine in patients with severe sepsis, cardiac failure, and systemic hypoperfusion. Chest 1989;95(3):612–5.
[18] Meierhenrich R, Steinhilber E, Eggermann C, Weiss M, Voglic S, Bogelein D, et al. Incidence and prognostic impact of new-onset atrial fibrillation in patients with septic shock: a prospective observational study. Crit Care 2010;14(3):R108.
[19] Seguin P, Signouret T, Laviolle B, Branger B, Malledant Y. Incidence and risk factors of atrial fibrillation in a surgical intensive care unit. Crit Care Med 2004;32(3):722–6.
[20] Balik M, Kolnikova I, Maly M, Waldauf P, Tavazzi G, Kristof J. Propafenone for supraventricular arrhythmias in septic shock-comparison to amiodarone and metoprolol. J Crit Care 2017;41:16–23.
[21] Balik M, Matousek V, Maly M, Brozek T. Management of arrhythmia in sepsis and septic shock. Anaesthesiol Intensive Ther 2017;49(5):419–29.
[22] FDA. Highlights of prescribing information: Lanoxin (digoxin) injection, for intravenous or intramuscular use; 1954 [accessed December 20th,.2017].
[23] Nasraway SA, Rackow EC, Astiz ME, Karras G, Weil MH. Inotropic response to digoxin and dopamine in patients with severe sepsis, cardiac failure, and sysptemic hypoperfusion. Chest 1989;95(3):612–5.
[24] Biteker M, Basran O, Dogan V, Beton O, Tekinalp M, Cagri AA, et al. Real-life use of digoxin in patients with non-valvular atrial fibrillation: data from the RAMSES study. J Clin Pharm Ther 2016;41(6):711–7.