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RECOMMENDATIONS AND GUIDELINES

Ischemic limb necrosis in septic shock: What is the role of high-dose vasopressor therapy?

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1 | INTRODUCTION

Patients with septic shock have profound vasoplegia and vascular endothelial injury that also causes sepsis-induced coagulopathy, also referred to as disseminated intravascular coagulopathy (DIC).[1,2] The vasodilatory shock requires high-dose vasopressor therapy to maintain blood pressure until volume repletion, antibiotics, and source control can control and eradicate the pathogens responsible.[3] The refractory vasodilation/hypotension in septic shock is due to vascular injury and altered vascular tone, and, in some patients, myocardial depression that requires vasopressor and/or inotropic therapy.[4] Based on current guidelines for septic shock, resuscitation guided by hemodynamic monitoring is titrated to increase mean arterial pressure to at least 65 mm Hg.[5] Norepinephrine, the recommended first-choice vasopressor, is titrated with no clear maximum recommended dose in guidelines to treat vasodilatory shock.[6] Norepinephrine is a potent inotropic and vasopressor agent that is often incorrectly described as a pure vasopressor because of its prominent α-adrenoceptor agonism, but it also provides β1-adrenoceptor agonism to increase myocardial contractility in cardiogenic shock.[7,8] In septic shock, norepinephrine is often the mainstay agent initially used for vasoplegia and is crucial to maintain adequate mean arterial pressure and circulation at times of severe septic shock.[9] Current literature suggests refractory septic shock is based on the need of norepinephrine and/or other vasopressors at doses of ≥0.5–1.0 mcg/kg/min.[9–12]

In septic shock, patients are commonly coagulopathic. DIC occurs in ~35% of patients, a key factor in explaining microthrombosis and ischemic limb injury associated with septic shock, sometimes called symmetrical peripheral gangrene.[13–20] Conceptually, microthrombosis in symmetrical peripheral gangrene reflects profoundly disturbed procoagulant-anticoagulant balance, as can occur when critically ill patients develop concomitant DIC (procoagulant) and shock liver (risk for depletion of the hepatically synthesized natural anticoagulants, proteins C, and antithrombin).[21] These patients can also transiently receive high-dose vasopressor therapy, with the theoretical concern for the risk of peripheral limb or digit ischemia, but the evidence is limited to case reports and anecdotal information. Therefore, we performed a literature search to determine the risk of

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limb ischemia with high-dose vasopressor therapy in septic patients and to evaluate whether such studies considered alternative explanations, such as DIC and shock liver.

2 | METHODS

We conducted a PubMed search using Medline, Cochrane, and EMBASE for publications up to January 2019 as described in Figure 1 using the search terms ischemia (both limb and digit) AND (norepinephrine OR epinephrine OR vasopressin OR phenylephrine OR angiotensin II OR septic shock OR high-dose vasopressors). The search retrieved 514 English-language papers, which were then screened by three reviewers (J. H. L., D. F., K. G.) for reports of high-dose vasopressor administration in septic shock, with or without reports on the incidence of limb and digit ischemia, DIC, or shock liver. We excluded preclinical studies, review articles, and case reports of five or fewer patients. We defined high-dose vasopressor based on prior literature and reports of ≥0.5 mcg/kg/min In total, eight papers were identified and included in this review.

The methodological quality of the studies was assessed independently by two reviewers (D. F., J. H. L.) using the Downs and Black checklist to assess the methodological quality of non- randomized studies of interventions.[22] The checklist consists of 26 items distributed among five subgroups: (a) reporting (10 items) to assess whether the information provided in the paper was sufficient to allow a reader to make an unbiased assessment of the findings of the study, (b) external validity (three items) to address the extent to which the findings from the study could be generalized to the population from which the study subjects were derived, (c) internal validity bias (seven items) to evaluate biases in the measurement of the intervention and the outcome, (d) internal validity confounding (six items) to estimate the bias in the selection of study subjects, and (e) power (one item). Answers were scored 0 or 1, for a total maximum score of 27. The quality of the studies included is categorized on the basis of the score between studies of poor quality (total score < 7), moderate (total score ≥ 7 and <12), and good (total score ≥ 12).[22]

The primary outcome of interest was peripheral limb or digit ischemia based on investigator reporting. Secondary endpoints included doses of vasopressors the study defined as high dose. For studies reporting on digital or limb ischemia/necrosis, we determined whether information on risk factors such as DIC and shock liver was provided. Data analysis was performed using STATA 15 (STATACorp LP). Categorical variables are expressed as number and percentage (%), and continuous variables are expressed as mean and standard deviation.

3 | RESULTS

Among the 514 records identified, 153 studies were screened, with 8 studies identified as reporting high-dose vasopressor use, and 3 of these reporting vasopressor use and limb and digit ischemia endpoints (Figure 1, Table 1). Bowel ischemia and infarction were also reported in several of the studies. Seven retrospective studies and one prospective study were found in our search. Norepinephrine was the primary vasoactive agent used, and high-dose vasopressor therapy was defined as >0.5 mcg/kg/min with a range of 0.58-4 mcg/kg/min for durations of therapy that ranged from 2 to 84 h. The mortality ranged from 51% to 100% in patients receiving high-dose vasopressors at doses defined by the study. Only three studies reported limb and digit ischemia or necrosis, which ranged from 1.6% to 8%. None of these studies provided information on whether DIC or shock liver was present in patients who developed limb and digit ischemia.

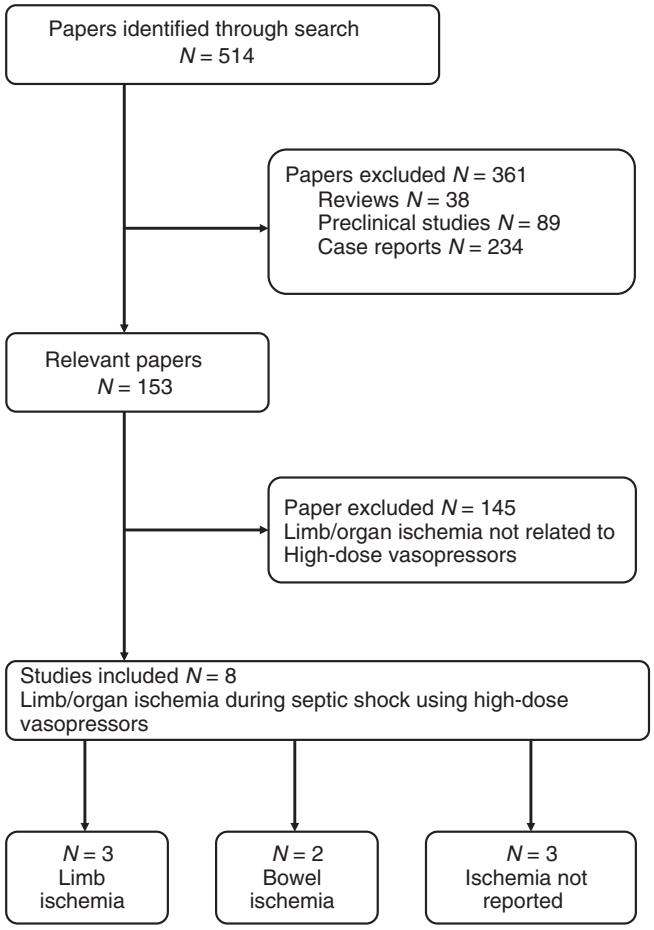

FIGURE 1 Search strategy

3.1 | Study quality

Overall, the quality of the studies included in our analysis was moderate, with a mean Downs and Black Score of 11.1 ± 6.2 (Table 2). Only one study was adjudicated as good quality, six were moderate quality, and one was poor. Across studies, external validity, potential bias and confounding, and power were identified as weaknesses.

TABLE 1 Characteristics of studies included

Author	Design	n	Dose	Drugs	Mortality	Duration of treatment	Limb necrosis or ischemia	Other
Auchet 2017[23]	Retrospective Observational	106	≥1 mcg/kg/min	EPI or NE	60%	84.7 (106) h	5.7% (*n* = 6)	2.8% bowel ischemia (*n* = 3)
Benbenishty 2011[26]	Retrospective Observational	72	>3.8 mcg/kg/min >9.6 mcg/kg/min	NE EPI	100% (*n* = 17) 100% (*n* = 5)	NA	NA	
Brown 2013[10]	Retrospective Observational	76	≥1 mcg/kg/min	EPI or NE	80%	2 h survivors/2.5 h non- survivors	8% survivors	
Jenkins 2009[24]	Retrospective Observational	64	>100 mcg/min	NE	96.7%	NA	NA	
Katsragakis 2006[25]	Retrospective Observational	12	>4 mcg/kg/min	NE	66.6%	NA	NA	
DeBacker 2010[4]	Prospective	821 (502 septic)	0.58 (0.8) mcg/kg/min	NE	56.6%	NA	1.6% leg (*n* = 13)	0.7% bowel (*n* = 6)
Martin 2000[11]	Retrospective Observational	324	>1 mcg/kg/min	NE	51%	24 h	NA	
Dopp-Zenel 2013[27]	Retrospective Observational	113	≥0.9 mcg/kg/min (max 2.91)	NE	65%	48 h	NA	≥2.22 NE dose 100% mortality

Abbreviations: EPI, epinephrine; NA, not assessed; NE, norepinephrine.

4 | DISCUSSION

In our systematic review, we identified eight studies that included information on high-dose vasopressors; only three studies reported on peripheral limb and digit ischemia. Moreover, none of the studies reported on the concurrence of key risk factors for limb and digit ischemia, most notably DIC and shock liver. The doses needed to maintain target blood pressure ranged from 0.5 to 4 mcg/kg/min, titrated up to a mean of 84.7 h.[10,11,23] The incidence of limb and digit ischemia or necrosis in the few studies where high-dose vasopressors were administered ranged from 1.6% to 8%. A summary of the studies is listed in Table 1. Because of the variability of the eight reports, important aspects of the eight studies will be reviewed as follows.

Jenkins evaluated 64 patients who received >100 mcg/min of epinephrine or norepinephrine (~1.33 mcg/kg/min).[24] Hospital survival was 3.3% in 60 patients who received >100 mcg/min norepinephrine, and 3.6% in the 55 patients who received >2 mcg/kg/minnorepinephrine.[24] Katsaragakis reported 12 patients who received norepinephrine (>4 mcg/kg/min) from 1999 to 2002 for septic shock and only 4 patients survived.[25] Benbenishty[26] reviewed 689 patients of whom 72 received vasopressors for septic shock. The 17 patients receiving >3.8 mcg/kg/min of norepinephrine and 5 patients receiving >9.6 mcg/kg/min of epinephrine died. Martin evaluated 324 septic shock patients from 2009 to 2013 and found their mortality rate was 48%, and reached 90% for patients receiving >1 mcg/kg/min of norepinephrine.[11] Döpp-Zemel evaluated circulatory shock outcomes in 113 patients receiving norepinephrine at ≥0.9 mcg/kg/min for at least 1 h with a reported 28-day mortality of 65%.[27] There was no mention of limb or digit ischemia in any of these five studies.

Three studies reported the frequency of limb and digit ischemia/necrosis. Brown evaluated 76 septic shock patients and noted a 28-day mortality of 80% in those requiring ≥1 mcg/kg/min for ~2.5 h.[10] The incidence of either digital or limb necrosis was reported in 6/76 (8%) of survivors and 5/367 (1%) of non-survivors,[10] with no information provided on DIC or shock liver occurrence. Auchet evaluated 106 septic shock patients from 2008 to 2013 of whom 89% received norepinephrine at ≥1 mcg/kg/min for 84.7 ± 106 h.[23] The mortality was 60.4% at 28 days, and limb or digit necrosis occurred in 6 patients (5.7%) of whom 4 required surgical amputation and 3 patients (2.8%) developed bowel ischemia or infarction and died.[23] No additional information, such as DIC or shock liver occurrence, was provided on these patients who developed limb or digit necrosis or bowel infarction. DeBacker reported the only prospective study of patients with shock randomized to dopamine or norepinephrine of whom 821 patients were treated with norepinephrine and 502 had septic shock.[4] The norepinephrine mean doses were 0.6 mcg/kg/min, and hospital mortality was 56.6% in the norepinephrine-treated patients. The incidence of

TABLE 2 Modified Downs and Black scores for included studies

Study	Reporting	External validity	Bias	Confounding	Power	Total	Quality
Auchet[23]	7	0	3	2	0	12	Moderate
Benbenishty[26]	6	0	1	2	0	9	Moderate
Brown[10]	5	0	2	3	1	11	Moderate
Jenkins[24]	1	0	1	2	0	4	Poor
Katsragakis[25]	3	0	2	2	0	7	Moderate
DeBacker[4]	10	3	6	5	1	25	Good
Martin[11]	5	0	3	2	1	11	Moderate
Dopp-Zenel[27]	7	0	1	2	0	10	Moderate
Average score	5.5 (2.7)	0.4 (1.1)	2.4 (1.7)	2.5 (1.1)	0.4 (0.5)	11.1 (6.2)	Moderate

limb ischemia was 1.6% (n = 13), with no information provided on DIC or shock liver occurrence.

Unlike other vasopressors, vasopressin is also administered in septic shock but not titrated to levels usually above 0.4 U/min. One additional study recently published analyzed 20 clinical trials evaluating vasopressin in septic shock.[28] The primary outcome was mortality, and secondary outcomes included the incidence of adverse events. Although they reported reduced mortality, vasopressin receptor agonists significantly increased the risk of digital ischemia (RR 4.85, 95% CI 2.81-8.39, I^2 = 26%), although they did not report whether patients had coagulopathy, DIC, and/or shock liver.[28]

Despite theoretical concerns that vasopressors produce limb or digit ischemia, in the reported studies the incidence was low or not reported, and the studies do not link peripheral ischemia with high-dose vasopressor nor exclude DIC and/or shock liver as an alternative explanation of ischemia. However, DIC is a major complication of septic shock that occurs in approximately 35% of patients and can explain limb ischemia due to thrombotic occlusion of the microvasculature.[14,16,29] Indeed, reviews of published cases of symmetrical peripheral gangrene in critical illness by Molos and Hall[18] and by Knight et al[19] have shown essentially universal occurrence of DIC in such patients. These findings have been extended by more-recent observations that peripheral limb ischemic necrosis in critical illness is characterized not only by circulatory shock for which vasopressor therapy would usually be administered but also by DIC and acute ischemic hepatitis (i.e., shock liver).[29–31] Moreover, there is a characteristic temporal time frame by which onset of shock liver precedes the occurrence of limb ischemic necrosis by a median of 3 days, a period that allows for occurrence of critical depletion of natural anticoagulants including protein C and antithrombin.[32–34] If vasopressors actually caused critical limb ischemia, this complication logically should occur right away, not a median of 3 days later. The view that limb ischemic necrosis can be caused by vasopressor use is held by some clinicians, perhaps because of anecdotal reports of patients so treated who were profoundly septic and coagulopathic and where all relevant pathophysiological factors had not been fully considered.[35]

4.1 | Implications for future research

The lack of consistent definitions and data capture observed in this systematic review has several implications for future research. First, the lack of both a consensus definition of high-dose vasopressor and routine capture does not permit an in-depth evaluation of the association with ancillary outcomes. We suggest that future studies capture peak vasopressor doses and duration in order to evaluate clearly the association between vasopressor dose, vascular complication, and outcome. Second, studies lacked routine monitoring, and data capture for limb and digit ischemia, including the occurrence of pathophysiologically relevant risk factors for explaining microthrombosis in such patients (e.g., DIC, acute ischemic hepatitis, plasma levels of natural anticoagulants). Protocolizing monitoring of pedal pulses and capture of peripheral ischemic events with case report forms could help quantify the association explored in this study.

4.2 | Limitations and strength

Despite our extensive literature search, the majority of the studies were retrospective analyses with multiple potential causes for limb ischemia. As a result, there is an inability to make causal inferences between high-dose vasopressors and limb ischemia, highlighting the need for improved reporting and data capture in future studies. The different trial definitions of high-dose vasopressors and lack of standard diagnostic criteria for limb ischemia influence the observed associations.

5 | CONCLUSIONS

In this systematic review and qualitative meta-analysis of eight studies that included information on high-dose vasopressors, only three studies captured information on limb or digit ischemia, reporting only on the frequency of this complication. We found a lack of consensus definition of peripheral ischemia and assessment for other causes including concurrent DIC and/or acute

ischemic hepatitis (shock liver). The high mortality observed among patients on high-dose vasopressors may be simply due to the severity of the septic shock and potential for multiorgan failure. Despite suggestions that limb and digit ischemic necrosis is a potential complication of high-dose vasopressor therapy, there is insufficient evidence to support that clinical concept or to estimate accurately its incidence in this high-risk population. Our results highlight the need for consensus definitions of high-dose vasopressor therapy and the routine capture of vasopressor doses and peripheral ischemic complications in studies of shock and septic shock management.

CONFLICT OF INTERESTS

Jean M. Connors reports consultancy from Bristol-Myers Squibb, Unum Therapeutics (Data Safety Monitoring Board), Portola (Scientific Advisory Boards); and research funding to the institution CSL Behring. Richard Hotchkiss has received research support from Bristol-Myers Squibb and RevImmune. Bruno Levy reports honoraria from Amomed, Baxter, and Novartis. Jerrold H. Levy has served or serves on research steering committees, data safety monitoring boards, or advisory boards for Boehringer-Ingelheim, CSL Behring, Instrumentation Laboratories, Octapharma, Leading Biosciences, and Merck. Theodore E. Warkentin has received lecture honoraria from Instrumentation Laboratory and royalties from Informa (Taylor & Francis); has provided consulting services to Aspen Global, CSL Behring, Ergomed, Octapharma, and W.L. Gore; has received research funding from Instrumentation Laboratory and W. L. Gore; and has provided expert witness testimony relating to heparin induced thrombocytopenia (HIT) and non-HIT thrombocytopenic and coagulopathic disorders. The other authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

J. H. L., K. G., and D. F. performed searches and with R.S.H. and T. I. wrote first drafts. S. V. R., B. L., and J. M. C. provided editing. T. E. W. subsequently revised and provided additional editing, supporting literature, and guidance.

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REFERENCES

1. Iba T, Levy JH. Inflammation and thrombosis: roles of neutrophils, platelets and endothelial cells and their interactions in thrombus formation during sepsis. J Thromb Haemost. 2018;16:231–41.
2. Iba T, Levy JH. Derangement of the endothelial glycocalyx in sepsis. J Thromb Haemost. 2019;17:283–94.
3. 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.
4. De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, Aldecoa C, et al. Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med. 2010;362:779–89.
5. Asfar P, Meziani F, Hamel JF, Grelon F, Megarbane B, Anguel N, et al. High versus low blood-pressure target in patients with septic shock. N Engl J Med. 2014;370:1583–93.
6. Breslow MJ, Ligier B. Hyperadrenergic states. Crit Care Med. 1991;19:1566–79.
7. Jhanji S, Stirling S, Patel N, Hinds CJ, Pearse RM. The effect of increasing doses of norepinephrine on tissue oxygenation and microvascular flow in patients with septic shock. Crit Care Med. 2009;37:1961–6.
8. Levy B, Clere-Jehl R, Legras A, Morichau-Beauchant T, Leone M, Frederique G, et al. Epinephrine versus norepinephrine for cardiogenic shock after acute myocardial infarction. J Am Coll Cardiol. 2018;72:173–82.
9. Levy B, Collin S, Sennoun N, Ducrocq N, Kimmoun A, Asfar P, et al. Vascular hyporesponsiveness to vasopressors in septic shock: from bench to bedside. Intensive Care Med. 2010;36:2019–29.
10. Brown SM, Lanspa MJ, Jones JP, Kuttler KG, Li Y, Carlson R, et al. Survival after shock requiring high-dose vasopressor therapy. Chest. 2013;143:664–71.
11. Martin C, Medam S, Antonini F, Alingrin J, Haddam M, Hammad E, et al. Norepinephrine: not too much, too long. Shock. 2015;44:305–9.
12. Bassi E, Park M, Azevedo LC. Therapeutic strategies for high-dose vasopressor-dependent shock. Crit Care Res Pract. 2013;2013:654708.
13. Levi M, Toh CH, Thachil J, Watson HG. Guidelines for the diagnosis and management of disseminated intravascular coagulation: British Committee for Standards in Haematology. Br J Haematol. 2009;145:24–33.
14. Hotchkiss RS, Levy JH, Levi M. Sepsis-induced disseminated intravascular coagulation, symmetrical peripheral gangrene, and amputations. Crit Care Med. 2013;41:e290–1.
15. Iba T, Nisio MD, Levy JH, Kitamura N, Thachil J. New criteria for sepsis-induced coagulopathy (SIC) following the revised sepsis definition: a retrospective analysis of a nationwide survey. BMJ Open. 2017;7:e017046.
16. Gando S, Levi M, Toh CH. Disseminated intravascular coagulation. Nat Rev Dis Primers. 2016;2:16037.
17. Okamoto K, Tamura T, Sawatsubashi Y. Sepsis and disseminated intravascular coagulation. J Intensive Care. 2016;4:23.
18. Molos MA, Hall JC. Symmetrical peripheral gangrene and disseminated intravascular coagulation. Arch Dermatol. 1985;121:1057–61.
19. Knight TT Jr, Gordon SV, Canady J, Rush DS, Browder W. Symmetrical peripheral gangrene: a new presentation of an old disease. Am Surg. 2000;66:196–9.
20. Iba T, Levy JH, Wada H, Thachil J, Warkentin TE, Levi M, Subcommittee on Disseminated Intravascular C. Differential diagnoses for sepsis-induced disseminated intravascular coagulation: communication from the SSC of the ISTH. J Thromb Haemost. 2019;17:415–9.
21. Warkentin TE. Ischemic limb gangrene with pulses. N Engl J Med. 2015;373:642–55.
22. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998;52:377–84.
23. Auchet T, Regnier MA, Girerd N, Levy B. Outcome of patients with septic shock and high-dose vasopressor therapy. Ann Intensive Care. 2017;7:43.
24. Jenkins CR, Gomersall CD, Leung P, Joynt GM. Outcome of patients receiving high dose vasopressor therapy: a retrospective cohort study. Anaesth Intensive Care. 2009;37:286–9.

25. Katsaragakis S, Kapralou A, Theodorou D, Markogiannakis H, Larentzakis A, Stamou KM, et al. Refractory septic shock: efficacy and safety of very high doses of norepinephrine. Methods Find Exp Clin Pharmacol. 2006;28:307–13.
26. Benbenishty J, Weissman C, Sprung CL, Brodsky-Israeli M, Weiss Y. Characteristics of patients receiving vasopressors. Heart Lung. 2011;40:247–52.
27. Dopp-Zemel D, Groeneveld AB. High-dose norepinephrine treatment: determinants of mortality and futility in critically ill patients. Am J Crit Care. 2013;22:22–32.
28. Jiang L, Sheng Y, Feng X, Wu J. The effects and safety of vasopressin receptor agonists in patients with septic shock: a meta-analysis and trial sequential analysis. Crit Care. 2019;23:91.
29. Warkentin TE, Pai M. Shock, acute disseminated intravascular coagulation, and microvascular thrombosis: is 'shock liver' the unrecognized provocateur of ischemic limb necrosis? J Thromb Haemost. 2016;14:231–5.
30. Siegal DM, Cook RJ, Warkentin TE. Acute hepatic necrosis and ischemic limb necrosis. N Engl J Med. 2012;367:879–81.
31. Warkentin TE. Heparin-induced thrombocytopenia in critically ill patients. Semin Thromb Hemost. 2015;41:49–60.
32. Tan JH, Mohamad Y, Tan CLH, Kassim M, Warkentin TE. Concurrence of symmetrical peripheral gangrene and venous limb gangrene following polytrauma: a case report. J Med Case Rep. 2018;12:131.
33. Warkentin TE. Microvascular thrombosis and ischaemic limb losses in critically ill patients. Hamostaseologie. 2019;39:6–19.
34. Warkentin TE. Symmetrical peripheral gangrene: mechanisms for limb loss in the ICU in patients with retained pulses. Clin Pulm Med. 2018;25:61–6.
35. Daroca-Perez R, Carrascosa MF. Digital necrosis: a potential risk of high-dose norepinephrine. Ther Adv Drug Saf. 2017;8:259–61.