Case Series
Volume 11:06, 2021

Clinical Case Reports

ISSN: 2165-7920 Open Access

Septic Shock Complicated with Limb Ischemic Necrosis: Three Case Reports and their Review of Literature

Zhenggong Li*

Sleep Medicine Center, Nanfang Hospital, Southern Medical University, Guangzhou, P. R. China

Abstract

Purpose: Limb ischemic necrosis is a very rare but severe condition that generally leads to amputation in septic shock. Our aim is to review the risk factors for development of limb ischemic necrosis in ICU patients requiring vasopressor support and draw the attention of doctors.

Methods: A retrospective review of clinical information and photographs in 3 septic shock patients, including APACHII scores, dose of norepinephrine, time of ischemic necrosis and final outcome from July 2001 to June 2020 at a single intensive care unit.

Results: All of the three patients had high APACHE II score, obvious coagulation dysfunction and severe hypotension on admission; In order to maintain the target blood pressure, the dose of norepinephrine range from 0.36 to 7.27 μg/kg/min; Case 2 and 3 had a higher average dose and length of NE treatment when comparing to case 1. Finally, case 1 survived but undergone amputation, case 2 and case 3 died.

Conclusion: Septic shock with limb ischemic necrosis is a very serious complication and may indicate a poor prognosis. As an ICU doctor, we should pay attention to the complication in our clinical practice which can greatly affect patient's quality of later life.

Keywords: Septic shock • Refractory septic shock • Limb ischemic necrosis • High dose of norepinephrine • Case report

Introduction

Septic shock complicated with limb ischemic necrosis is a rare manifestation of systemic disease. Critically ill patients with profound shock may experience tissue hypoperfusion, which might result in end-organ ischemic necrosis. Several studies have reported a series of cases with ischemic necrosis of the tongue and limb among patients with cardiogenic shock after norepinephrine use [1-3]. Sepsis is now defined as life-threatening organ dysfunction caused by a dysregulated host response to infection and Norepinephrine (NE) is recommended as the first line therapy in the Surviving Sepsis Guidelines [4]. The pharmacodynamic effects of NE are characterized by a linear increase in effect which is dependent on the logarithmic increase of the concentration [5]. It is known that high-dose (>0.5 μg/kg/min) increases the risk of peripheral vasoconstriction, necrosis and mortality [6-8]. But some studies show that short-term administration of very high doses of NE especially in the first hour, does not only influence outcome but also can be beneficial [7,9]. In this report, we presented clinical information and photographs of 3 patients who were diagnosed with septic shock and review the risk factors for development of limb ischemic necrosis and draw the attention of doctors.

Case Series

Case 1

A comparison of the three cases is presented in Table 1. A 74-year-old woman with type 2 diabetes mellitus was admitted to the geriatrics department with a complaint of fever and altered mentality. The laboratory tests showed the patient had sepsis and dysfunction of coagulation (Table 1) while the hemodynamically was stable. Head Computed Tomography (CT) revealed old multiple lacunar cerebral infarction and chest X-ray moderate pleural effusion (Figure 1). Cefmetazole sodium was administration as soon as possible after admission. The second day morning, she was urgently transferred to the Intensive Care Unit (ICU) after an unprovoked abrupt onset of severe dyspnea in the washing room. Her vital signs were blood pressure 88/43 mmHg, pulse 125/minute, respirations 38/minute, and oxygen saturation 79% while breathing room air. Examination of the lungs demonstrated bilateral breath sound without expiratory wheezing and crackle. Her oxygenation improved significantly after endotracheal intubation and ventilation. Bedside chest radiography demonstrated adequate endotracheal tube position and no pneumothorax or increasing of pleural effusion. CT pulmonary angiography excluded Pulmonary Embolism (PE). We administered broad-spectrum antibiotics, fluid resuscitation, transfusion plasma and pumping noradrenaline at initial dose of 0.42 μg/kg/min to maintenance of blood pressure. After endotracheal intubation and mechanical ventilation, the second day in ICU, the patient began to deteriorate, appearing thrombocytopenia, oliguria, and extremity darkening. We began to transfuse platelet and Continuous Renal Replacement Therapy (CRRT). We noticed the color change in the extremities and tried to reduce the dose of norepinephrine and keep the extremities warm. Bedside vascular ultrasound was performed but did not indicate obvious embolism in the vessels. Blood tests showed IgM and IgG of the antiphospholipid antibody were positive and we administered empirical anticoagulation therapy. The blood culture showed *Acinetobacter baumannii* which was sensitive to the antibiotics. The patient was successfully weaned off the mechanical ventilation and extubation and removed from the ICU two weeks later. But amputation was performed after one month and finally survived.

Case 2

A 48-year-old woman complained of backache, fever, short of breath accompanying skin mottling was admitted to the ICU presenting septic shock. The laboratory tests showed severe coagulation dysfunction, metabolic acidosis and unstable hemodynamic. The whole abdominal CT scan showed there were stones in left upper ureter and right kidney (Figures 2-4). The patient was intubated and ventilated immediately due to shortness of breath. We started high-dose NE because of refractory hypotension. Broad-spectrum antibiotics, fluid resuscitation, and continuous renal replacement therapy were all initialed to rescue the patient. As shown in Table 1, the coagulation profile of patient suggested Disseminated Intravascular Coagulation (DIC). The high dose NE treatment (average dose 1.24 μg/kg/min) was maintained for 69 hours, and the fingers and toes appeared ischemic necrosis (Figures 5 and

***Address for Correspondence:** Li Z, Sleep Medicine Center, Nanfang Hospital, Southern Medical University, Guangzhou, P. R. China, E-mail: 522686296@qq.com*

Received 14 June 2021; **Accepted** 28 June 2021; **Published** 05 July 2021

Table 1. Comparison between the three patients admitted to ICU.

Variables	Patient 1	Patient 2	Patient 3
Age (years)	74	48	47
Gender	Female	Female	Female
Weight (kg)	40	70	55
Comorbidities	Diabetes mellitus	Urinary obstruction	Hyperthyroidism
APACHII	33	26	27
Predicted mortality (%)	78.6	56.9	60.5
Source of infection	Lung	Urinary tract	Lung
Blood culture	*Acinetobacter baumanii*	None	*Klebsiella pneumoniae*
PCT (μg/L)	84.8	≥100	>100
PLT (× 10^9/L)	211	19	11
Coagulation profile			
PT (s)	25.2	36.6	23.5
APTT (s)	56.9	96.9	43.2
FIB (g/L)	6.5	1.3	5.3
D-Dimer (ng/ml)	11420	>20000	17500
Initial dose of NE (μg/kg/min)	0.42	0.36	0.38
Maximum dose of NE (μg/kg/min)	2.50	2.38	7.27
Average dose of NE (μg/kg/min)	1.22	1.24	3.78
Time of NE treatment (h)	44	69	171
Time of skin mottling (day)	2nd	1st	1st
Time of digital necrosis (day)	5th	10th	7th
Possible cause of digital necrosis	APS, DIC	DIC	DIC
Length of CRRT (h)	123	345	150
Length of ventilation (h)	404	740	170
Total cost (RMB)	51,020	101,165	27,147
Final outcome	Survived	Death	Death

PCT: Procalcitonin; PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; FIB: Fibrinogen; CRRT: Continue Renal Replacement Therapy; APS: Antiphospholipid Syndrome; DIC: Disseminated Intravascular Coagulation

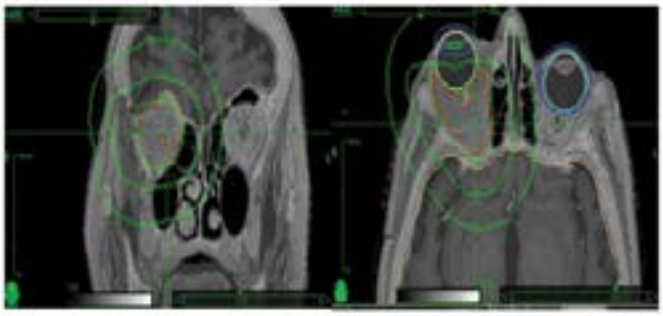

Figure 1. CXR shows left moderate pleural effusion.

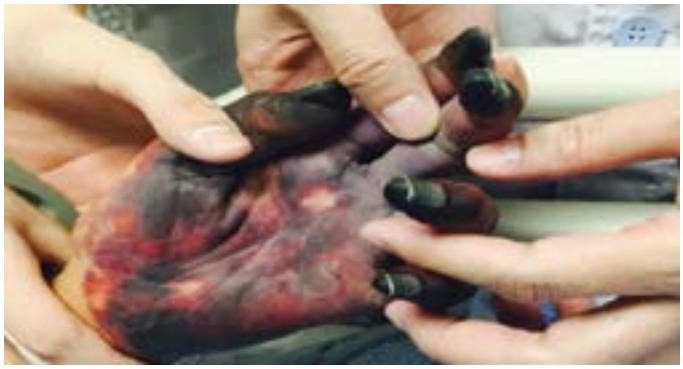

Figure 2. The digital necrosis of the left up limbs.

6) at the tenth day even we decreased the dose of NE. We performed bedside ultrasonography to find the possible causes; however, these examinations did not reveal any diagnostic clues. Unfortunately, we were unable to perform more invasive evaluations (e.g., angiography), due to the patient's poor general condition. We elevated the extremity in attempt to minimize local edema, keeping the extremity warm and applying topical nitroglycerin, but which had very little effect. The patient was successfully weaned off and transferred to the general ward one month later. However, she was readmitted to the ICU again due to repeating infection, and died three weeks later.

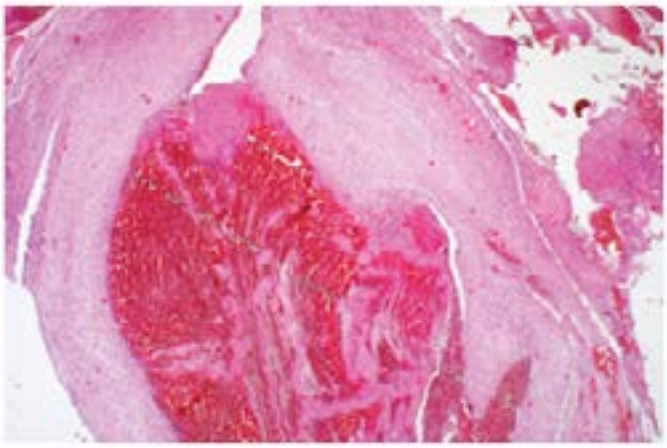

Figure 3. The digital necrosis of the two lower limbs.

Case 3

A 47-year-old woman was admitted to emergency department because of a sore throat, fever for 5 days and confusion for half a day with a history of hyperthyroidism. She took oral anti-thyroidism medication daily as prescription.

She developed granulocytopenia, septic shock, and acute suppurative tonsillitis and was admitted to the hospital after ICU consultation. The laboratory tests showed acute kidney injury, severe metabolic acidosis and the coagulation profile suggested DIC (Table 1). The chest CT scan showed bilateral pneumonia (Figure 7). She was intubed and mechanical ventilation because respiratory and circulatory failed. Sepsis bundles were started and a combination of Meropenem and Vancomycin and Fluconazole were given within one hour. The patient presented four limbs skin mottling and cold on admission and the dose of NE was carefully titrated to avoid aggravating skin ischemia necrosis. We started NE at a dose of 0.38 μg/kg/min to maintain blood pressure, then was increasing to the maximum dose of 7.27 μg/kg/min. Hypervirulent *Klebsiella pneumonia* [10] was isolated from the blood which was sensitive to the antibiotics. Although we work hard, but the patient's condition progressed rapidly, appearing multiple organ dysfunction, limbs necrosis occurred on the 7th day, and died on the 9th day (Figure 8).

Discussion

Ischemic necrosis of tongue and mesenteric in septic shock and cardiogenic shock were well reported [11]. However, there is very rarely report regarding limb ischemic necrosis in patients with septic shock. In Jerrold's review study [12], only three studies reported on peripheral limb and digit ischemia and none of the studies reported on the concurrence of key risk factors for limb and digit ischemia. A review of previous case report and studies, we found that the risk factors for ischemic necrosis of tongue and mesenteric and limbs were mainly vasculitis, DIC and high dose vasopressor therapy [13]. The three patients we reported were critical ill, presenting refractory shock, and we had to upregulated the dosage of noradrenaline after fluid resuscitation. Because

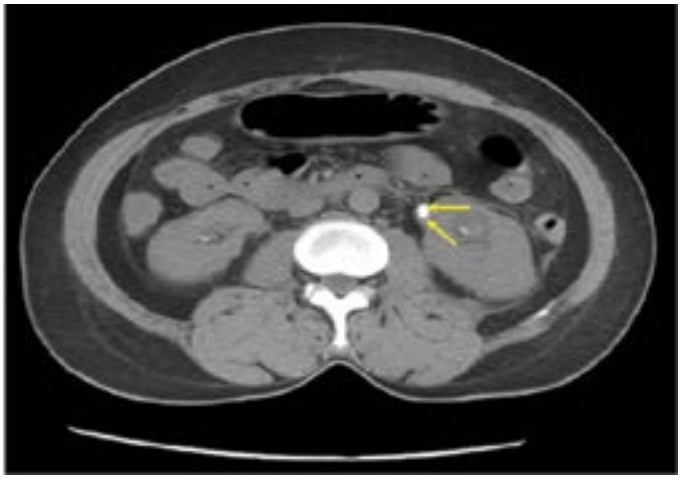

Figure 4. Computed tomography of abdomen shows stones in left upper ureter and right kidney.

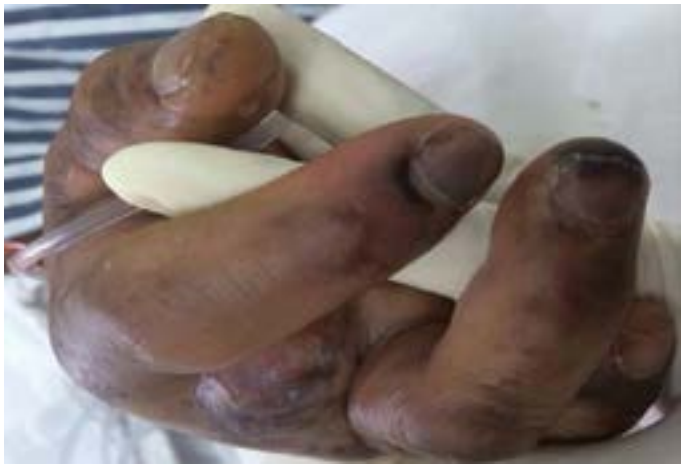

Figure 5. The digital necrosis of the right hand.

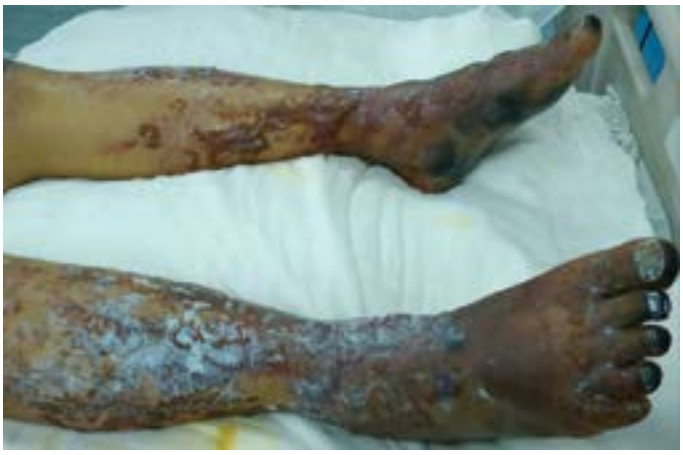

Figure 6. The digital necrosis of the two lower limbs.

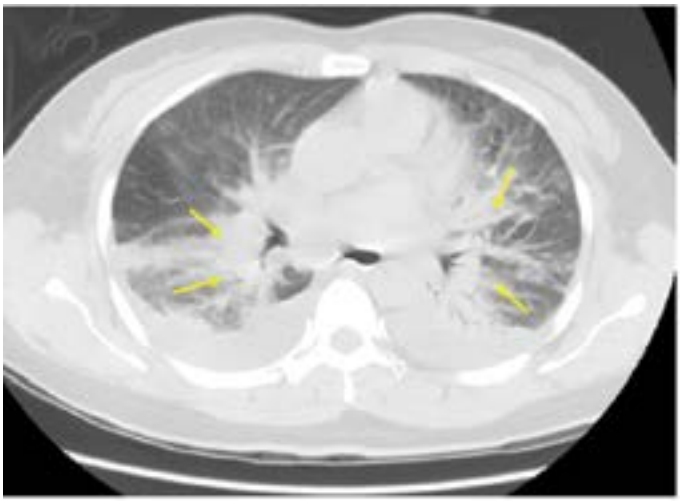

Figure 7. Computed tomography of chest shows bilateral pneumonia.

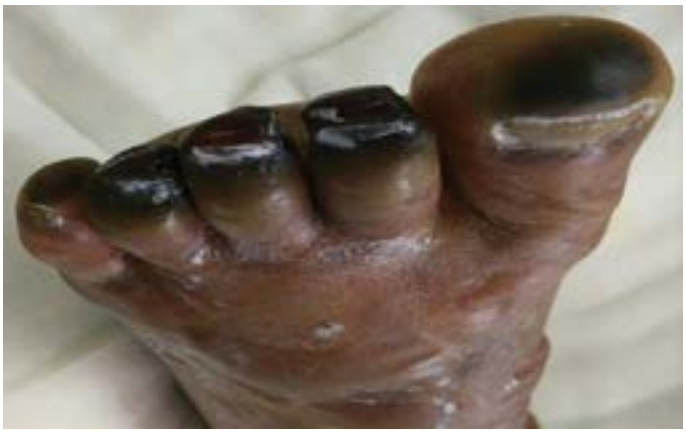

Figure 8. The digital necrosis of the left limb.

of the underlying diseases of each patient were different, the infected sites and pathogens were different, we should not ascribe all the causes of the limbs ischemia necrosis to the high dose vasopressor therapy. Therefore, we performed the analysis on these 3 patients with limb ischemic necrosis after high dose vasopressor therapy as following.

Noradrenaline is the most widely used salvage agent in the ICU due to its pressures-enhancing effects which is dose-dependent and better than Dopamine in treatment of septic shock [14]. Of the biggest side effect is its intense vasoconstriction, resulting in tissue ischemia. Critically ill patients with severe shock may experience hypoperfusion, which might result in end-organ necrosis easily after using high-dose vasoconstrictor. Some studies

reported a rate of 5.7% [15], which might be a predictor of a poor prognosis [11,16]. Norepinephrine, the first choice vasopressor, is titrated with no clear maximum recommended dose in guidelines [17]. High-dose NE was defined as dose ≥ 0.5 μg/kg/min for ≥ 1 h. Brown's study also showed that short-term administration of very high doses of NE especially in the first hour, does not only influence outcome but also can be beneficial in refractory septic shock [18]. Thomas Auchet's study showed that only the weight-based mean dose, with a cut off of 0.75 μg/kg/min, combined with SOFA score >10, was found to be a strong predictor of death, not the weight-based maximum dose and weight-based cumulative dose [19]. In our case, when comparing Case 1 the initial, maximum, and average doses of norepinephrine with Case 2 were approximately the same, but the outcomes were different. The case 3 used the highest dose and longest time of norepinephrine died at last. Therefore, we suggest that the dose and duration of norepinephrine were associated with the occurrence of limb ischemic necrosis and might be a predictor of a poor prognosis.

DIC is also a common risk factor for limbs ischemic necrosis according to the previous reports [20]. As shown in Table 1, three patients presented DIC with septic shock. Two patients had a low platelet count less than 30×10^9/L and very high level of D-Dimer, which suggested the hypercoagulant state and the diagnosis of DIC was established. DIC can be primary or secondary which can cause peripheral limb necrosis. Our patients were likely to be secondary to sepsis, because there was no disease founded associating with thrombocytopenia in the history. The treatment of DIC includes anticoagulation, so we were also concerned about Heparin-Induced Thrombocytopenia (HIT) after anticoagulation with heparin, which can lead to limb necrosis ischemia [21,22]. However, the tests ruled out HIT. Although DIC is one of the risk factors of limb ischemic necrosis, there is no clear study on what severity of DIC leading to finger necrosis; Ultrasound examination did not provide evidence of peripheral vascular embolism in our two patients with DIC.

The other potential causes are peripheral vascular disease, source of infection, types of bacteria and gender. Giant cell arteritis, Wegener's granulomatosis and ANCA associated systemic vasculitis were the most common cause of vascular diseases [1]. In our case, only case 1 was diagnosed with diabetes and Antiphospholipid Syndrome (APS), while the other two patients had no cause of vasculitis. APS is an autoimmune disease, with hypercoagulable state caused by antiphospholipid antibodies. We also found some interesting things that all three patients were refractory septic shock, such as urinary infection and agranulocytosis. Urosepsis and agranulocytosepsis [23,24] are special types of septic shock which presented rapid progress, high mortality and refractory septic shock. Hypervirulent *Klebsiella pneumonia*e infection is a special pathogen. Because of its strong invasion and easy spread, patients sometimes die quickly even if sensitive antibiotics are used. Former reports also found that the limb ischemic necrosis was mainly women and we founded the same in our cases. We speculated that the dosage of NE and the severity of septic shock have sex-specific. Alyson McGregor who studies on women's health told us the truth that there are gender differences in clinical medicine [25,26]. Whether septic shock has sex-specific, such as more severe inflammation or needing fewer dose NE, which will need more deep studies.

Conclusion

Septic shock complicated with limb ischemic necrosis is a very rare event in clinical practice which may increase the cost of treatment and indicate a poor prognosis. Several factors may work together to cause this complication and the most important thing is striving for early detection and early treatment. ICU doctors should pay great attention to this complication and the concentration of norepinephrine must be titrated. At the same time, we also look forward to the development of new drugs.

References

1. Jinbeom Cho, Kiyoung Sung and Dosang Lee. "Ischemic Necrosis of the Tongue in Surgical Patients with Septic Shock: A Case Report." *BMC Surg* 16 (2016): 48.
2. Chuan Han Ang, Oon Thien Koo and Tet Sen Howe. "Howe, Four Limb Amputations Due to Peripheral Gangrene from Inotrope Use: Case Report and Review of the Literature." *Int J Surg Case Rep* 14 (2015): 63-65.
3. Benjamin R. Roman, Sara B. Immerman and Luc G. T. Morris. "Ischemic Necrosis of the Tongue in Patients with Cardiogenic Shock." *Laryngoscope* 120 (2010): 1345-1349.
4. Rhodes, Lamont. "Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016." *Crit Care Med* 45 (2017): 486-552.
5. Breslow J. Michael and Bruno Ligier. "Hyperadrenergic States." *Crit Care Med* 19 (1991): 1566-1579.
6. Estevão Bassi, Marcelo Park and Luciano Cesar Pontes Azevedo. "Therapeutic Strategies for High-Dose Vasopressor-Dependent Shock." *Crit Care Res Pract* 2013 (2013): 654708.
7. Donna Döpp-Zemel and AB Johan Groeneveld. "High-Dose Norepinephrine Treatment: Determinants of Mortality and Futility in Critically Ill Patients." *Am J Crit Care* 22 (2013): 22-32.
8. Jean-Louis Vincent and Daniel De Backer. "Circulatory Shock." *N Engl J Med* 369 (2013): 1726-1734.
9. Katsaragakis, Stilianos. "Refractory Septic Shock: Efficacy and Safety of Very High Doses of Norepinephrine." *Meth Find Exp Clin Pharmacol* 28 (2006): 307-313.
10. Jie Zhu, Tao Wang, Liang Chen and Hong Du. "Virulence Factors in Hypervirulent *Klebsiella Pneumonia*e." *Front Microbiol* 12 (2021): 642484.
11. Rafael Daroca-Pérez and Miguel F. Carrascosa. "Digital Necrosis: A Potential Risk of High-Dose Norepinephrine." *Ther Adv Drug Saf* 8 (2017): 259-261.
12. Jerrold H. Levy, Kamrouz Ghadimi, David Faraoni and Sean Diepen, et al. "Ischemic Limb Necrosis in Septic Shock: What is the Role of High-Dose Vasopressor Therapy." *J Thromb Haemost* 17 (2019): 1973-1978.
13. Donald A. Brand, Patricia A. Patrick, Jeffrey T. Berger and Mediha Ibrahim, et al. "Intensity of Vasopressor Therapy for Septic Shock and the Risk of In-Hospital Death." *J Pain Symptom Manage* 53 (2017): 938-943.
14. Daniel De Backer, Patrick Biston, Jacques Devriendt and Christian Madl, et al. "Comparison of Dopamine and Norepinephrine in the Treatment of Shock." *N Engl J Med* 362 (2010): 779-789.
15. Thomas Auchet, Marie-Alix Regnier, Nicolas Girerd and Bruno Levy, et al. "Outcome of Patients with Septic Shock and High-Dose Vasopressor Therapy." *Ann Intensive Care* 7 (2017): 43.
16. Donna Döpp-Zemel and AB Johan Groeneveld. "High-Dose Norepinephrine Treatment: Determinants of Mortality and Futility in Critically Ill Patients." *Am J Crit Care* 22 (2013): 22-32.
17. Rhodes, Armitage. "Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016." *Intensive Care Med* 43 (2017): 304-377.
18. Samuel M. Brown, Michael J. Lanspa, Jason P. Jones and Kathryn G. Kuttler, et al. "Survival After Shock Requiring High-Dose Vasopressor Therapy." *Chest* 143 (2013): 664-671.
19. Thomas Auchet, Marie-Alix Regnier, Nicolas Girerd and Bruno Levy. "Outcome of Patients with Septic Shock and High-Dose Vasopressor Therapy." *Ann Intensive Care* 7 (2017): 43.
20. Bird, Asherson. "Disseminated Intravascular Coagulation, Antiphospholipid Antibodies, and Ischaemic Necrosis of Extremities." *Ann Rheum Dis* 46 (1987): 251-255.
21. Theodore E. Warkentin, Andreas Greinacher, Andreas Koster and Michael A. Lincoff, et al. "Treatment and Prevention of Heparin-Induced Thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition)." *Chest* 133 (2008): 340-380.
22. Warkentin, Theodore. "The Pathogenesis of Venous Limb Gangrene Associated with Heparin-Induced Thrombocytopenia." *Ann Intern Med* 127 (1997): 804-812.
23. Vaishnavi Divya Nagarajan, Alba Morales, Lawtanya Pleasant and Asha Shenoi. "Sepsis and Thyroid Storm in a Patient with Methimazole-Induced Agranulocytosis." *BMJ Case Rep* 13 (2020): 07.
24. Forsyth, Naomi. "Neutropenic Sepsis." *Nurs Stand* 31 (2017): 64-65.

25. Michael M. Song, Cheryl K. Simonsen, Joanna D. Wilson and Marjorie R. Jenkins. "Development of a PubMed Based Search Tool for Identifying Sex and Gender Specific Health Literature." *J Womens Health* 25 (2016): 181-187.

26. Ronald H. Farkas, Ellis F. Unger and Robert Temple. "Zolpidem and Driving Impairment-Identifying Persons at Risk." *N Engl J Med* 369 (2013): 689-691.

How to cite this article: Zhenggong Li. "Septic Shock Complicated with Limb Ischemic Necrosis: Three Case Reports and their Review of Literature." Clin Case Rep 11 (2021): 1450.