

Original Article

## Factors associated with mortality in severely malnourished hospitalized children who developed septic shock

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### Abstract

**Introduction:** Septic shock can often lead to death, even in resourceful settings, if not handled carefully. Therefore, we sought to evaluate the factors associated with deaths in the context of severe malnutrition and also the effects of early, i.e., within 3 hours of diagnosing septic shock vs. late blood transfusion.

**Methodology:** Here, all under-five severely malnourished septic shock children were admitted to ICU during 2013-2017. Children who died constituted cases (n = 54), and the survived (n = 39) represented controls. We excluded children who received the blood transfusion for other causes and who left against medical advice.

**Results:** In both descriptive and multivariate analysis, we found that death was significantly associated with the use of fourth-line antibiotics, corticosteroids, and the addition of vasopressors on top of dopamine (all  $p < 0.05$ ). However, the decrease of serum calcium level was found significantly associated with death only after adjusting ( $p < 0.05$ ). Even though the cases more often received early blood transfusion than the controls, the difference was insignificant ( $p = 0.134$ ).

**Conclusions:** When a severely malnourished under-five child develops septic shock, requiring vasopressors, fourth-line antibiotic, and corticosteroid, with reduced serum calcium, the probability of death increases significantly. Our findings underscore the gravity of close monitoring at these points and the niches for early interventions.

**Key words:** Septic shock; severe acute malnutrition; sepsis; malnutrition; blood transfusion.

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### Introduction

Septic shock – a medical emergency – is associated with high mortality in developed and developing countries [1,2] and is one of the leading causes of death in under-five children worldwide [3]. However, in developing countries, where poor sanitation, insufficient immunization coverage, water contamination, diseases like diarrhea, pneumonia, and malnutrition remain prevalent, the efficient management of septic shock in young children becomes even more challenging [4–6].

With timely diagnosis, appropriate antibiotics, and early fluid resuscitation, it is possible to significantly reduce the mortality in septic shock [7–9] even though few recent studies in children without severe malnutrition suggest that aggressive fluid bolus (crystalloid solution) in septic shock may increase the mortality [10]. The diagnosis of septic shock is heavily dependent on detecting the appropriate clinical features. But the clinical diagnosis becomes difficult if both hypovolemic and septic shock is present simultaneously

in a child having diarrhea. However, in hypovolemia alone, the clinical condition improves rapidly along with the fluid resuscitation, while septic cases often remain unresponsive [11]. Moreover, in children with severe malnutrition, such clinical signs often remain absent – due to their low immune response – which further complicates the situation [12].

For children with severe acute malnutrition, World Health Organization (WHO) recommends that during septic shock, blood transfusion should be given as early as possible at a rate of 10 mL/kg over 3 hours with antibiotics therapy and micronutrient supplementation [10]. But despite the full implementation of this protocol [10,12], the mortality in septic shock remains high in such cases – as we also observed in the Dhaka hospital ICU in International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b). As enough data regarding the response of blood transfusion in severely malnourished-children during septic shock is still lacking, our objective was to evaluate the factors

associated with death in children who developed septic shock and received a blood transfusion in the background of severe malnutrition, besides assessing the effect of early, i.e., within 3 hours of diagnosing septic shock vs. late - i.e., after 3 hours - blood transfusion upon outcome in these children.

## Methodology

### *Ethical statement*

This study had a retrospective design and solely comprised of chart analysis, where complete anonymity was ensured. A waiver of approval for chart analysis from the Institutional Review Board - Research Review Committee and Ethical Review Committee - was obtained.

### *Study design*

In our retrospective chart analysis, all severely malnourished children of either sex, from 2 to 59 months of age, who received a blood transfusion for septic shock due to the unresponsiveness to the fluid resuscitation at the intensive care unit (ICU) of icddr,b Dhaka hospital between 2013 to 2017, were enrolled. Those children who died were labeled as cases, and those who survived were identified as controls. Patients receiving blood transfusion due to indications other than septic shock, or who left against medical advice, or those who were not severely malnourished, were excluded from the analysis, followed by a subsequent comparison of variables between these two groups.

### *Definitions*

All patients met criteria for fluid-refractory septic shock, defined by, when age-specific tachycardia, with hypo ( $< 35.0$  °C) or hyperthermia ( $\geq 38.5$  °C), or abnormal white blood cell (WBC) count were present, along with the presumed presence of infection, with age-specific hypotension that did not resolve with 20 mL/kg of fluid bolus with Normal saline or, Ringer's lactate solution or, Cholera saline - maximum of 40 mL/kg - administered over 2 hours [13,14]. A child was declared to have severe malnutrition when weight-for-age z-score (WAZ) was  $< -3$  (severe-underweight), and/or weight-for-length z-score (WLZ) was  $< -3$  (severe wasting) and/or had bipedal pitting edema [7,15].

### *Study settings*

We conducted this study in icddr,b Dhaka hospital in Bangladesh, which provides treatment for approximately 160,000 patients annually, irrespective of age, sex, and socio-economic condition. Diarrhoea is

the entry point of admission in this hospital, while most patients come from urban and peri-urban Dhaka. Patients are shifted to ICU immediately when critical complications - such as respiratory distress, severe pneumonia with hypoxemia or respiratory failure, repeated hypoglycemia, severe sepsis, septic shock, altered level of consciousness - were found [14,16].

### *Patient management*

Severely malnourished children who required hospital admission but did not have any features of sepsis received parenteral ampicillin and gentamicin. Once the signs of sepsis appeared, the antibiotics were switched to the second-line - i.e., ceftriaxone instead of ampicillin - while, gentamicin was continued. However, in presence of pneumonia, superimposed on sepsis, gentamicin was replaced by levofloxacin in the second-line, according to the standard hospital guideline. If a patient did not respond - i.e., the patient's condition did not improve after 48 to 72 hours or deteriorated within 24 hours of initiating the second-line - the antibiotics were changed to the third-line, i.e., ceftazidime and amikacin. If a patient still remained unresponsive, meropenem or imipenem was started as the fourth-line antibiotic. As these are the sequence of choice of the antibiotics for the treatment of sepsis cascades in severely malnourished children in Dhaka hospital of icddr,b, understandably in an advanced stage of sepsis cascade - i.e., by the time of the development of septic shock - most of the patients received fourth-line antibiotic as well as the blood transfusion. Children who had severe acute malnutrition and severe sepsis that did not respond to fluid resuscitation - with Normal saline or, Ringer's lactate solution or, Cholera saline (sodium 133 mMol/L, potassium 13 mMol/L, chloride 98 mMol/L, and acetate: 48 mMol/L) - were labeled as septic shock, who also received - in both cases and controls - antibiotics therapy and micronutrient supplementation following hospital guidelines based on the local evidence [13]. In these children with septic shock, whole human blood was transfused at a rate of 10 mL/kg over 3 hours. Corticosteroid was also indicated in such patients who exhausted all other interventions including blood transfusion and inotropes. However, in most cases, whole human blood was not readily available. Therefore, inotropes support - dopamine, if no improvement adrenaline, and if no improvement nor-adrenaline - was started immediately without any delay. The transfusion was given later, once it was made available [14,17] All relevant investigations were carried out simultaneously and the vital signs, blood glucose, and SpO<sub>2</sub> level were closely

and critically monitored, and parameters such as BP and urine output were checked periodically, to take rapid countermeasures to maintain Mean Arterial Pressure (MAP) > 50 mm Hg, and/or urine output (UO) > 1 mL/kg/hr.

### Data collection

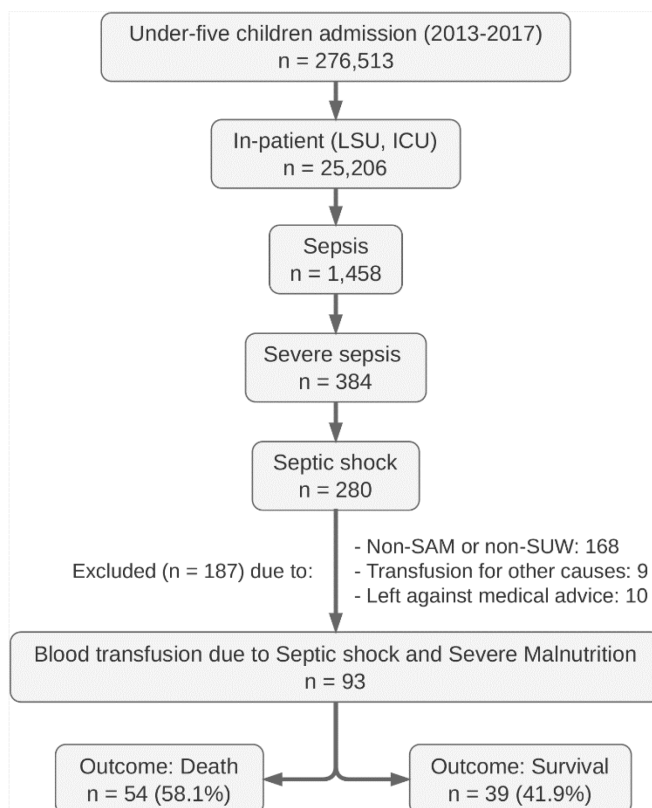
After preparing the case-record forms (CRFs), we collected relevant patient data from SHEBA – a digital patient management system at icddr,b Dhaka hospital. The variables included patients' demographic information, chief complaints during admission (e.g., diarrhoea, cough, fever, respiratory distress, lethargy along with the duration of each category), clinical features (e.g., tachypnea, lower chest-wall-indrawing, hypoxemia, and crackles in lungs, dehydration, nutritional edema, abdominal distension), clinical diagnosis (e.g., sepsis, sclerema, severe pneumonia, hospital-acquired infection and/or pneumonia, convulsion, electrolytes imbalance, severe malnutrition, invasive and/or persistent diarrhoea, acute renal failure, ARF), characteristics of laboratory

investigations on admission (i.e., electrolytes, blood counts, and blood cultures), received medications (first, second, third and fourth-line antibiotics, inotropes, hydrocortisone), transfusion within 3 hours of diagnosing septic shock – early blood transfusion – of developing or detecting septic shock and the outcome, i.e., death or survival, at different time points.

### Statistical analysis

We checked the difference in proportions of the explanatory variables relative to the outcome, i.e., death or survival, and carried out the Chi-square tests of independence to see whether these differences are statistically significant, i.e.,  $p$ -value < 0.05. However, we considered Fisher's exact test instead, where the expected counts were < 5. Afterward, we did logistic regression analysis to assess whether the outcome variables were significantly ( $p$ -value < 0.05) influenced by multiple explanatory variables in combination or alone. We carried out the data analysis in R (version 4.0.4) and prepared the graphs and figures using R and draw.io (version 10.5.9).

**Figure 1.** Flowchart of under-five children admitted in icddr,b Dhaka hospital from 2013 to 2017.



SUW (severe-underweight): weight-for-age z-score (WAZ) < -3, SAM (severe acute malnutrition, also called severe wasting): weight-for-length z-score (WLZ) < -3.

## Results

### Summary of descriptive statistics

Out of 276,523 under-five children admitted to icddr,b Dhaka hospital between 2013 to 2017, we found 93 severely malnourished children who developed septic shock and received the blood transfusion (Figure 1). Although there were differences in proportions in the demographic, clinical, and laboratory information between the cases and controls, only a few were statistically significant, i.e.,  $p$ -value < 0.05 (Table 1). We found that there was significantly more use of fourth-line antibiotics ( $p = 0.045$ ) and corticosteroids ( $p = 0.0003$ ) in cases. We also found that in cases – i.e., those who died - the serum potassium (median: 3.5 vs. 3.99) and calcium (mean: 1.96 vs. 2.10) levels were less than the survivors, while these differences were not statistically significant ( $p$ -value  $\geq 0.05$ ). We also found that the use of dopamine as the only inotrope agent was significantly more in survivors and those children who developed respiratory failure had a significantly higher rate of mortality (both  $p$ -value < 0.001).

### Factors associated with death in septic shock

During the logistic regression analysis (Table 2), we found, the use of fourth-line antibiotics (OR = 14.801, 95% CI = 2.029, 175.9;  $p$ -value = 0.02) was significantly associated with cases, i.e., death in septic shock in both adjusted (variables listed below Table 2) and unadjusted logistic regression analysis.

**Table 1.** Summary of differences in proportions of characteristics of cases and controls.

Characteristics	Death (Cases) n = 54	Survival (Controls) n = 39	p
	n (%)	n (%)	
Age in months (Median, IQR)	5.58, 5.85	4.44, 7.8	0.18
Weight in kg (Mean ± SD)	4.04 ± 1.39	4.27 ± 1.81	0.49
Male gender	29 (54)	19 (49)	0.79
Safe drinking water	18 (49)	13 (39)	0.59
Complete immunization	32 (71)	17 (53)	0.17
Normal Vaginal Delivery (NVD)	30 (71)	23 (72)	1.00
Exclusively breastfed	11 (23)	5 (16)	0.62
Diarrhoea	49 (92)	38 (97)	0.39
Cough	35 (65)	23 (59)	0.72
Tachypnea (Fast breathing)	25 (46)	20 (51)	0.79
Respiratory rate (Mean ± SD)	44.9 ± 18.6	48.2 ± 17.1	0.39
SpO <sub>2</sub> (Mean ± SD)	91.7 ± 11.4	92.6 ± 10.3	0.70
Crackles in lungs	33 (61)	20 (51)	0.46
Chest in-drawing	36 (67)	20 (51)	0.20
Hypoxemia	14 (26)	11 (28)	0.99
Dehydration	21 (39)	17 (44)	0.81
Nutritional edema	18 (33)	7 (18)	0.16
Abdominal distension	15 (28)	7 (18)	0.39
Convulsion	14 (26)	8 (21)	0.72
Sclerema	18 (33)	8 (21)	0.26
Severe pneumonia	45 (83)	31 (79)	0.84
Ileus	13 (24)	5 (13)	0.28
Acute watery diarrhoea	42 (77)	35 (90)	0.22
Invasive diarrhoea	12 (22)	8 (21)	1.00
Blood culture isolates	19 (40)	10 (28)	0.37
Serum Na <sup>+</sup> (Mean ± SD)	140.49 ± 20.4	141.29 ± 15.6	0.84
Hypernatremia	16 (30)	11 (28)	1.00
Hyponatremia	25 (47)	16 (41)	0.71
Serum K <sup>+</sup> (Median, IQR)	3.5, 2.14	3.99, 2.28	0.05
Hyperkalemia	7 (13)	10 (26)	0.21
Hypokalemia	26 (49)	12 (31)	0.12
Serum TCO <sub>2</sub> (Mean ± SD)	11.22 ± 6.35	11.38 ± 5.63	0.90
Metabolic acidosis	43 (81)	35 (90)	0.40
Serum Creatinine (Median, IQR)	60.7, 69.7	51.0, 40.4	0.62
Acute Renal Failure (ARF)	15 (29)	5 (13)	0.13
Serum Ca <sup>+</sup> (Mean ± SD)	1.96 ± 0.37	2.10 ± 0.40	0.08
Hypocalcemia	35 (69)	23 (59)	0.47
Serum Mg <sup>++</sup> (Median, IQR)	1.06, 0.358	1.1, 0.225	0.65
Hypermagnesemia	27 (54)	22 (56)	0.99
Hemoglobin (Mean ± SD)	9.19 ± 2.83	10.13 ± 3.28	0.15
Moderate anemia	29 (56)	17 (44)	0.35
Total White Blood Cell count (Mean ± SD)	21.77 ± 11.5	23.44 ± 12.4	0.51
Neutrophil (Mean ± SD)	56.83 ± 16.4	54.17 ± 15.3	0.43
Neutropenia	7 (13)	7 (18)	0.77
Thrombocytopenia	14 (33)	8 (26)	0.71
Hypoglycemia (Median, IQR)	8.1, 6.3	6.4, 3.7	0.16
First-line antibiotics	37 (69)	31 (79)	0.35
Second-line antibiotics	48 (89)	32 (82)	0.53
Third-line antibiotics	31 (57)	17 (44)	0.27
Fourth-line antibiotics	23 (43)	8 (21)	0.045*
Dopamine	6 (11)	16 (49)	< 0.001*
Corticosteroids	22 (41)	2 (5)	< 0.001*
Early blood transfusion (in 3 hours)	7 (13)	1 (3)	0.13
Blood transfusion delay 12 hours	23 (43)	14 (37)	0.74
Blood transfusion delay (Median, IQR)	13.4, 16.4	20.5, 19.3	0.12

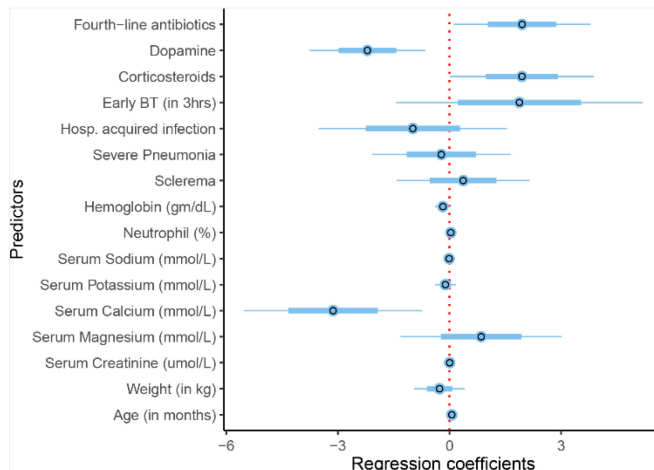
\*Statistically significant findings (p-value &lt; 0.05).

We also found that the use of dopamine alone was negatively associated with death (OR = 0.107, 95% CI = 0.016, 0.512; *p*-value = 0.010), while the development of respiratory failure was positively associated with death (OR = 17.018, 95% CI = 2.633, 171.063; *p*-value = 0.006) in both unadjusted and adjusted model. The serum calcium was also negatively associated with death (OR = 0.030, 95% CI = 0.002, 0.357; *p*-value = 0.010), but only in the adjusted model, while the use of corticosteroid was found positively associated with death (OR = 12.719, 95% CI = 3.391, 83.292; *p*-value = 0.001) in the unadjusted model (Table 2, Figure 2). When we plotted the unadjusted regression model, we found that the probability of death increases when S. Calcium level drops below 2.29 mmol/L, although this model was not statistically significant (*p*-value = 0.083) (Figure 3).

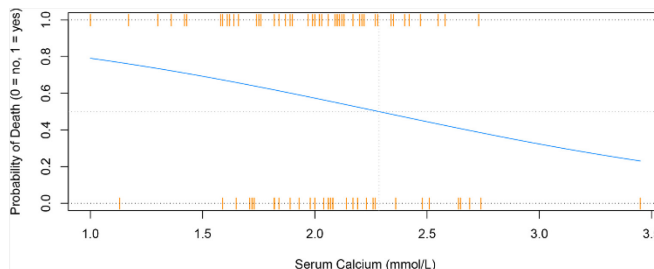
**Discussion**

We observed a 58.1% case-fatality rate (CFR) in severely malnourished under-five children who developed septic shock and received a blood transfusion. And we found CFR ranging from 40% to 69% in other studies in Bangladesh where the children were severely malnourished, had pneumonia, and developed septic shock [18]. Although the septic shock is very difficult to manage even in a resourceful setting, in a background of severe malnutrition and limitation of resources, it becomes even more challenging [1,2]. In our study, we found, i. the severely malnourished children who died, more often required to change the antibiotics leading to the use of the fourth-line antibiotics – i.e., imipenem or meropenem – followed

**Figure 2.** Factors associated with deaths in septic shock in severely malnourished under-five children.



**Figure 3.** Regression plot of the probability of deaths vs. serum calcium level (mmol/L) in septic shock in severely malnourished under-five children.



**Table 2.** Summary of logistic regression analysis.

Characteristics	Unadjusted		Adjusted	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Fourth-line antibiotics	2.875 (1.150; 7.765)	0.03*	7.037 (1.289; 51.005)	0.03*
Dopamine	0.132 (0.042; 0.360)	< 0.001*	0.110 (0.021; 0.454)	0.004*
Corticosteroids	12.719 (3.391; 83.292)	0.001*	7.022 (1.247; 62.966)	0.04*
Early blood-transfusion (in 3 hours)	5.511 (0.923; 105.398)	0.12	6.551 (0.405; 313.127)	0.26
Hospital acquired infection	1.500 (0.369; 7.484)	0.58	0.373 (0.028; 4.349)	0.44
Severe pneumonia	1.290 (0.44; 3.739)	0.64	0.803 (0.120; 4.997)	0.81
Sclerema	1.937 (0.759; 5.290)	0.18	1.446 (0.247; 8.570)	0.68
Hemoglobin (mg/dL)	0.900 (0.774; 1.034)	0.15	0.839 (0.666; 1.030)	0.11
Neutrophil count (%)	1.011 (0.984; 1.039)	0.43	1.035 (0.992; 1.085)	0.13
Serum Sodium (mmol/L)	0.998 (0.975; 1.021)	0.84	0.990 (0.952; 1.031)	0.63
Serum Potassium (mmol/L)	0.933 (0.755; 1.124)	0.47	0.897 (0.677; 1.218)	0.44
Serum Calcium (mmol/L)	0.355 (0.102; 1.094)	0.08	0.044 (0.003; 0.396)	0.009*
Serum Magnesium (mmol/L)	0.904 (0.242; 3.376)	0.88	2.343 (0.306; 24.628)	0.43
Serum Creatinine (µmol/L)	1.005 (0.994; 1.017)	0.36	1.006 (0.988; 1.023)	0.53
Weight (in kg)	0.911 (0.697; 1.187)	0.49	0.765 (0.382; 1.489)	0.43
Age (in month)	0.998 (0.942; 1.058)	0.93	1.064 (0.932; 1.219)	0.35

\*Statistically significant findings (*p*-value < 0.05).

by the corticosteroid, ii. when the septic shock could not be managed with dopamine alone, their chance of mortality increased significantly, iii. reduced serum calcium is positively associated with deaths in septic shock, and iv. a lack of difference of effects of early, i.e., within 3 hours of diagnosing septic shock, vs. late blood transfusion, i.e., after 3 hours, in severely malnourished under-five children having septic shock.

We strictly adhered to the rational use of antibiotics, thus we can say that the patients who died from septic shock were highly prone to receiving these two interventions, i.e., the fourth-line antibiotics and the corticosteroid therapy due to the higher disease severity. It is important to note that these patients died even after receiving adequate fluid resuscitation according to the standard hospital guidelines [13] and interventions including antibiotics following the Surviving Sepsis Guideline [7,9,12].

During the multivariate analysis, we found that whenever we added vasopressors – i.e., adrenaline and noradrenaline – in addition to dopamine to manage the septic shock in our severely malnourished septic shock children, the probability of death increased significantly, underscoring the extreme level of caution, care, and effort are required to save such children's lives in this stage. However, as we followed the same sequence of inotrope administration for all patients, from this data it was not possible to determine which inotropic agent had a better impact over the others, as indicated elsewhere [19,20].

Although serum calcium was diminished in both cases and controls (Table 1), reduced serum calcium was found associated with death in severely malnourished children during septic shock ( $p$ -value < 0.01). In the unadjusted model, we also found that at a serum calcium level below 2.29 mmol/L the probability of death increases ( $p$ -value = 0.083) in severely malnourished children during septic shock (Figure 3), highlighting the possibility of early intervention at this point [21,22]. However, a careful approach is needed as some of the previous studies recommended against calcium supplementation during sepsis [23].

As all subjects received the blood transfusion, we could not evaluate the effectiveness of the blood transfusion. Instead, we tried to assess whether early (within 3 hours of diagnosing septic shock) or late blood transfusion (after 3 hours) had any differential impact upon the outcome. In our study, we could not find any statistically significant difference of effect, although Bachou *et al.* argued in a previous study that the blood transfusion in malnourished hospitalized children was associated with high mortality [24]. In

such context, a carefully designed prospective study is needed to better understand the impact of early blood transfusion and the inotropic agents individually in septic shock in severely malnourished children.

We had several limitations in our study. Being a retrospective chart analysis, we had only a few variables of interest to analyze, e.g., we did not have enough data to calculate the PRISM III or PELOD scores. We failed to assess albumin level, phosphorus level, initial lactate level, arterial blood gas analysis due to limitation of resources and had to do the liver function tests only when a patient was clinically indicated. We also lack the data on which titration of a given inotrope a septic shock patient stabilized and when. Also, our sample size was quite small, preventing us from achieving more statistical robustness, and we could not match our cases with the controls.

## Conclusions

In summary, our data suggest that when a severely malnourished under-five child develops septic shock that can not be managed with dopamine alone, where fourth-line antibiotics and corticosteroids have to be given, in presence of reduced serum calcium, the probability of death increases significantly. Such events underscore the gravity of extreme vigilance in such situations and the possibilities of early interventions.

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