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Timeline of infection and sepsis in a major burn patient with AKI on CRRT

Abstract

Introduction: In extended ICU stays for severe burn patients, beta-lactam de-escalation in Gram-negative infections is routinely used to prevent resistance. *Candida spp.* and yeast invasive infections are also common due to immunosuppression.

Objective: To assess anidulafungin's effectiveness against invasive fungal infections in immunosuppressed burn patient, and report ciprofloxacin efficacy against *Pseudomonas aeruginosa* (meropenem-and amikacin-resistant) on Day 41 of ICU admission in a septic burn patient with AKI receiving CRRT.

Methodology: Approved by the hospital's Ethics Committee (Brazilian Platform 07525118.3.0000.0068), this case involved a 31-year-old male (160 kg, 171 cm) with severe burns (25% TBSA), multiple injuries, and morbid obesity following an engine explosion at work. Admitted to ICU, he had a SAPS*3 score of 61/49% risk of death and Sofa 9.

Results: The patient experienced severe oil burns, necessitating multiple surgical interventions. The complexity of infections and complications led to a prolonged hospital stay. Burn patients are at high risk for invasive infections due to factors such as underlying conditions, burn extent (TBSA), delays in wound excision, and pathogen characteristics. Diagnosing burn wound infections is complex because the responsible organisms depend on time from injury and location. Common pathogens include *Staphylococcus* and *Pseudomonas* species; fungal infections like *Candida* sepsis also occur. In this case, the patient had an invasive *Fusarium solani* infection, complicating recovery. The patient's severe oil burns required several surgeries, including evisceration of the left-eye, resulting in a prolonged hospital stay due to infection complexity.

Conclusion: Antibiotic therapy was adjusted based on infections and resistance, with TDM and MIC results guiding treatment selection. Pharmacokinetic monitoring ensured therapeutic drug levels. Fungal infections were treated with anidulafungin. Culture became negative by ICU Day 51 following ciprofloxacin and anidulafungin therapy. Precision medicine, using real-time anti-infective serum monitoring and culture results, enabled effective dosing adjustments and was crucial in treating multi-drug-resistant infections and improving outcomes in major burn patients.

Keywords: ICU immunosuppression and prolonged stay, major burn sepsis, inflammatory biomarkers, invasive fungal infections, anti-infectives TDM/MIC data & PK/PD

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Abbreviations

AKI, Acute kidney injury; ARDS, acute respiratory distress syndrome; $AUC^{ss}\tau$, area under the curve at the steady state serum levels; (C^{ss}), at the time dose interval (tau: τ) BAL, bronchoalveolar lavage (BAL) fluid; BSI, Blood stream infection; CLSI, Clinical & Laboratory Standard Institute, database USA; c-RP, c-Reactive Protein; CRRT, continuous renal replacement therapy; CVVHDF, continuous veno-venous hemodialysis filtration; [$t_{(1/2)\beta}$], elimination half-life/biological half-life; GNB, gram-negative bacteria; GPB, gram-positive bacteria; ICU, intensive care unit; MIC, minimum inhibitory concentration; MV, mechanical ventilation; N/L ratio, neutrophils to lymphocytes ratio; PD, pharmacodynamics; PK, pharmacokinetics; PK/PD, pharmacodynamics based on pharmacokinetics; SAPS3, simplified acute physiology score 3; SIRS, systemic inflammatory response syndrome; SOFA score, sequential organ failure assessment score, previously known as the sepsis-related organ failure assessment score; TBSA, total burn surface area; TDM, therapeutic drug monitoring

Introduction

Infection is the most frequent complication and the leading cause of death among burn patients. The physiological changes that occur after a burn make these individuals especially vulnerable to infections and the development of burn wound sepsis. Accurate diagnosis and effective management of these infections depend on a combination of approaches, including a thorough physical examination and analysis of the pathological characteristics of the burn wound. Prolonged intensive care unit (ICU) admission frequently leads to a state of immunosuppression. Patients with major burns are particularly susceptible to this phenomenon, such as ongoing critical illness, repeated surgical interventions, and persistent infection risks contribute to a weakened immune response. Extended ICU stays are often necessary for the management of severe complications, including recurrent infections and multiple organ dysfunctions. This immunosuppressed state further increases vulnerability to opportunistic fungal and yeast pathogens, complicating recovery and prolonging hospitalization. Management of burn sepsis requires a multifaceted approach that includes the use of local wound dressings,

prompt surgical excision of the burn wound, and the administration of systemic anti-infective complex therapy.[1–6]

Subject

The primary objective of this study was to examine the clinical course of a young patient who sustained major burn injuries at work, focusing on the progression of infection and burn sepsis during ICU hospitalization. The patient developed acute kidney injury (AKI) and required continuous renal replacement therapy (CRRT), which added complexity to his management. This investigation centered on evaluating the effectiveness of anidulafungin in treating invasive fungal infection in major burn patient immunosuppressed. Additionally, the study aimed to document the efficacy of ciprofloxacin administered on Day 41 of ICU admission for the treatment of sepsis caused by *Pseudomonas aeruginosa* that was resistant to both meropenem and amikacin, in the context of ongoing AKI and CRRT.

Case report - ICU admission to the burn center

On January 15th, patient DMS, protocol number 371, a 31-year-old male with a height of 171 cm and a weight of 160 kg, classified as morbidly obese, sustained extensive burn injuries due to direct contact with flames during a workplace accident.

Medical history – comorbidities - ICU admission and injury details: He was initially admitted to the hospital and received emergent medical care on January 16th at 2:00 AM at a tertiary public hospital. Following this, he was immediately transferred to the Intensive Care Unit (ICU) of the Plastic Surgery and Burns Center at the Hospital of Clinics, Faculty of Medicine, University of São Paulo, in São Paulo, SP, Brazil. Upon arrival at the ICU, the patient was found to have burns covering 25% of his total body surface area (TBSA). The affected regions included the face, neck, nape, upper chest, bilateral scapular and forearm areas, as well as the upper airways, indicating the presence of an inhalation injury. He also suffered severe bilateral eye injuries. Clinical assessment revealed the patient was experiencing hypovolemic/distributive shock, moderate acute respiratory distress syndrome (ARDS), and acute renal failure that continuous dialysis requirements. His severity scores at admission were SAPS*3 of 61 with a 49% risk of death, and a SOFA score of 9.

Immediate medical management - resuscitation & surgical debridement: Upon admission to the intensive care unit, the patient presented in a critically compromised condition due to extensive burn injuries. Immediate and comprehensive medical intervention was required to address life-threatening complications and stabilize his vital functions. The initial approach focused on cardiopulmonary resuscitation, a crucial step to restore and maintain adequate cardiac and respiratory activity. Once the patient's vital signs were stabilized, surgical debridement was undertaken. This procedure involved the removal of devitalized and necrotic tissue from the affected areas, which is essential to minimize the risk of infection and promote optimal wound healing in burn patients.

Airway, respiratory, and renal complications: Due to ongoing hypoperfusion, orotracheal intubation was performed to secure the airway and initiate mechanical ventilation. The patient was diagnosed with hypovolemic-distributive shock and developed acute respiratory distress syndrome (ARDS), further complicating respiratory management. Renal function was severely compromised, evidenced by acute kidney injury with creatinine clearance dropping below 25 mL/min, necessitating continuous renal replacement therapy (CRRT) to manage fluid and electrolyte balance. Additionally, the patient suffered from severe bilateral ocular injuries, including a perforated and infected ulcer in the left eye, requiring specialized ophthalmologic attention.

Diagnosis and early microbiological investigation of septic shock: On the third day following ICU admission, clinicians suspected the development of septic shock in the patient. In response to this critical condition, blood and site-specific cultures were obtained before initiating any antibiotic therapy. This approach aimed to facilitate a comprehensive microbiological investigation and maximize the likelihood of accurately identifying causative pathogens. The diagnostic workup specifically targeted the potential presence of Gram-positive bacteria, such as *Streptococcus* and *Staphylococcus* species, as well as Gram- negative bacteria, including species of the *Enterobacteriaceae* family. The decision to pursue this broad- spectrum investigation was guided by c-RP and N/L ratio, biomarkers daily obtained to support the clinical context of a systemic inflammatory response syndrome (SIRS), which is frequently associated with severe infections in burn patients.

Role of biomarkers in guiding broad-spectrum microbiological investigation: In the assessment and management of severe infection in major burn septic patient the clinical team relied on specific inflammatory biomarkers to guide their diagnostic approach. The decision to initiate a broad-spectrum microbiological investigation was informed by daily measurements of C-reactive protein (c-RP) and the neutrophil-to-lymphocyte (N/L) ratio. These biomarkers served as valuable predictors of ICU-mortality and provided real-time insight into the patient's inflammatory status. Monitoring c-RP and N/L ratio helped support and confirm the clinical context of systemic inflammatory response syndrome (SIRS), a condition frequently observed in patients with severe burn injuries who are at increased risk for developing life- threatening infections. This targeted use of biomarkers ensured that the investigation and subsequent treatment strategies were closely matched to the evolving clinical picture.[2–6]

Clinical approach – anti-infective therapy initiates on ICU-day 3

On the third day, following admission to the Intensive Care Unit, the patient experienced a notable decline in clinical status. In response to this deterioration, the medical team initiated a targeted anti-infective treatment regimen. Prior to starting any antibiotics, blood and site-specific cultures were obtained to accurately identify the causative pathogens and guide therapy. The antimicrobial strategy included vancomycin, which was selected to treat suspected Gram-positive bacterial strains, and piperacillin/tazobactam, aimed at Gram-negative organisms. Additionally, doxycycline was administered due to the suspicion of ocular infection present at admission. This comprehensive approach was designed to address the broad spectrum of potential infectious agents and provide coverage for both systemic and localized infections, optimizing the chances of clinical improvement. Microbiological cultures detected *Staphylococcus epidermidis* (vancomycin susceptible, MIC 1 mg/L) and *Proteus mirabilis* (PTZ resistant, meropenem susceptible, MIC 0.25 mg/L). Based on these findings, PTZ was stopped and meropenem (1g every 12 hours by 3-hour infusion) was started. Additionally, sodium colistinemethate was initiated, with dosing calculated based on the patient's ideal body weight. The combined therapy was given on days 3–23 and again on days 24–33 in two 10-day cycles. Antimicrobial adjustments were based on susceptibility data to improve bacterial eradication and manage infection changes.[1,3–5] (Table 1)

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Table 1 General anti-infective therapy septic shock episodes and management of fungal infections

ATB-AF/LD: loading dose	Dose regimens	Daily dose (mg/kg)	Dose tau (mg/kg)
Anidulafungin LD 200 mg	150 mg q24h 1hr.-inf. MO	2.11	2.11
Anidulafungin LD 200 mg	100 mg q24h 1hr.-inf n-MO	1.41	1.41
Ciprofloxacin LD 400 mg	400 mg q12h 1hr.-infusion	11.27	5.65
Colistinemethate LD 300 mg	150 mg q12h 0.5hr.-infusion	4.23	2.17
Doxycycline LD 200 mg	100 mg q12h Nasoenteric tube	2.82	1.41
Meropenem LD 1 g	1g q/8h 3hrs.-infusion	42.25	14.08
Meropenem LD 1 g	AKI/CRRT 1g q12h 3hrs.-inf.	28.17	14.08
Metronidazole LD 500 mg	500 mg q12h Nasoenteric tube	14.08	7.04
Piperacillin/tazobactam	4.5g q12h 3hrs.-infusion	126.76	63.38
Vancomycin LD 1g	1g q12h 1hr.-infusion.	28.17	14.08
Vancomycin LD 1g	AKI/CRRT:1g q24h 1hr.-inf	14.08	14.08

Abbreviations: AKI, acute kidney injury; CRRT, continuous renal replacement therapy; ATB, antibiotic therapy; IBW, hydrophilic ATBs dose regimens were based on ideal body weight; TBW, total body weight for dose regimens of lipophilic agents; AF- anidulafungin therapy was based on TBW, total body weight> 145kg for morbid obesity; n-MO: non morbid obesity (TBW 90-120 kg).

Septic shock episodes and management of fungal infections: On day 17 of ICU admission, the patient developed septic shock attributed to enterocolitis caused by Clostridioides infection. In response, metronidazole therapy was promptly initiated and continued for one week, from day 17 through day 23, to target the underlying infection. During this period, the patient experienced an additional episode of septic shock on the same day. By day 21, cultures isolated *Klebsiella pneumoniae*, which was found to be susceptible to meropenem (MIC 0.25 mg/L), guiding further adjustments in antibiotic therapy.

Given the high risk of fungal infections in the context of severe burns and repeated septic episodes, antifungal therapy was introduced. Anidulafungin was prescribed in response to the isolation of *Fusarium solani* from a corneal scraping on day 23 and *Candida parapsilosis* from tracheal secretions on day 27.

This antifungal regimen was maintained through ICU Day 51 to ensure comprehensive management of invasive fungal infections in this critically ill patient.[7] (Figure 1)

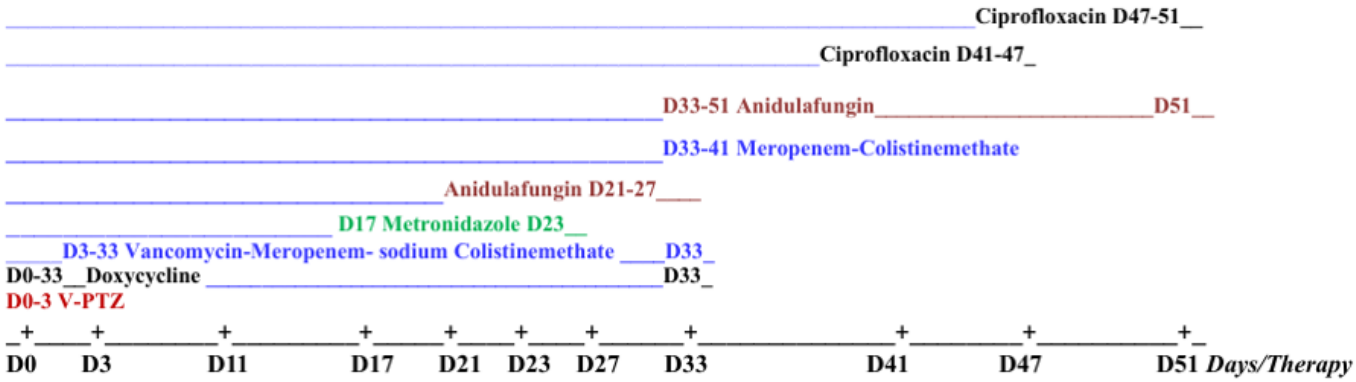

Figure 1 Anti-infective therapy - Microbiology of isolates.

D3 *P. mirabilis*: Piperacillim/tazobactam: PTZ/R MIC 32 mg/L, MIC 0.25 mg/L Meropenem/S GNB – Enterobacterales

D3 *Staphylococcus epidermidis; S. aureus* MIC 1.0 mg/L Vancomycin/S - GPB

D11 *Klebsiella pneumoniae* MER: Meropenem/S MIC 0.25mg/L - GNB – Enterobacterales

D17 *Clostridium difficile* Metronidazole/S Enterocolitis clostridioides

D21 *Klebsiella pneumoniae* Meropenem/S MIC 0.25mg/L - GNB – Enterobacterales

D23 *Fusariun solani* Anidulafungin/S MIC data: no available consensus - Fungal invasive infection

D27 *C. parapsilosis* Anidulafungin/S MIC data: no available consensus - Fungal invasive infection

D33 *Klebsiella pneumoniae* Meropenem/S MIC 0.5 mg/L - GNB – Enterobacterales

D41 *C. albicans; C. tropicalis* - Anidulafungin /S MIC data: no available consensus – Fungal infection

D41 *P. aeruginosa* Meropenem/R Ciprofloxacin/S MIC 0.5 mg/L – GNB - non-Enterobacterales

D41 *S.aureus* Ciprofloxacin/S - MIC 1.0 mg/L GPB

PK/PD target recommended was attained for coverage against Gram-positive, Gram-negative susceptible strains isolated:

PTZ --MER 100%*f*ΔT>MIC Ciprofloxacin AUC^{ss}_{24}>125 Vancomycin AUC^{ss}_{24}>400 up to-600

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Precision medicine and inflammatory biomarkers monitoring

Individualized therapeutic drug monitoring: Here, precision medicine was implemented through individualized therapy guided by serum therapeutic drug monitoring (TDM). By measuring how long each antibiotic took to reach steady-state levels after a loading dose, dosing was tailored to the patient's pharmacokinetics, optimizing effectiveness and reducing toxicity risk.[2–6]

Renal and inflammatory biomarker surveillance: Daily monitoring of renal and inflammation biomarkers, including C-reactive protein (c-RP) and neutrophil-to-lymphocyte ratio (N/L ratio), guided patient management in the ICU. These markers informed mortality risk assessment and supported timely treatment adjustments for improved outcomes.[2–6] (Table 2)

Table 2 Biomarkers monitored to predict ICU mortality for best clinical outcome

Laboratory data	Reference	ICU Admission Day 1 Jan.16th	Hospital discharge
Biomarkers	**CLSI database**	**ICU Discharge (93 days)**	**March 8th (98 days)**
Scr mg/dL (male)	0.7-1.2	2.5	0.95
Clcr ml/min	90-120	43	113
c-RP mg/L	<5.0	17.4	15.9
WBC*10^3/mm^3	4.00-11.00	32.82	9.31
Neutrophils*10^3/mm^3	2.5-7.5	27.23	6.31
Lymphocytes*10^3/mm^3	1.5-3.5	2.2	2.42
N/L-ratio	1.67-2.14	12.38	2.61
N/WBC-ratio	0.63-0.68	0.82	0.68

Abbreviations: Scr, Serum creatinine; Clcr, creatinine clearance; c-RP, c-reactive protein; WBC, total blood white cells; N/L-ratio, neutrophils/lymphocytes ratio: N/WBC-ratio, neutrophils/total white blood cells ratio; CLSI, Clinical & Laboratory Standard Institute (USA)

Surgical interventions: Jan 24 - March 18/April 3

The patient was admitted to a tertiary plastic surgery and burns center and underwent several procedures, including debridement and grafting for wounds on the left upper limb, face, tracheostomy site, both upper limbs, and sacral pressure ulcers.

I. **January 24 (Day 10):** First debridement on the left upper limb. Postoperatively, the patient developed SIRS due to septic-hemorrhagic shock. Cultures identified *K. pneumoniae* (meropenem- susceptible). Extubating failed on day 13, requiring re-intubation. By January 31 (day 17), pseudomembranous colitis was suspected and treated with metronidazole.

II. **February 5 (Day 22):** Second debridement covered the face and tracheostomy site. The patient experienced shock and immunosuppression. Anidulafungin was started due to fungal infection risk. Cultures of *Candida parapsilosis, Fusarium solani*, later confirmed in corneal scrapings.

III. **February 12 (Day 29):** Partial debridement and grafting were performed on both arms, using thigh skin as donor material.

IV. **February 18 (Day 35):** Evisceration of the left eye was undertaken for invasive *Fusarium solani* infection, continuing antifungal therapy.

V. **February 21 (Day 38):** Debridement and partial grafting were performed on upper limbs, ears, and trunk. Cultures revealed multidrug-resistant *K. pneumoniae*, leading to a change in antibiotics. Ciprofloxacin cycles eliminated *Pseudomonas aeruginosa* and ciprofloxacin-sensitive *Staphylococcus aureus*.

VI. **March 18 up to April 3:** For a sacral pressure ulcer, sequential debridement's, VAC dressings, and a surgical flap were performed.

The patient left the ICU after 93 days and the hospital after 98 days, having lost 70 kg. This summary covers key surgeries, complications, microbiology results, and treatment changes.

Conclusion

Antibiotic therapy was adjusted based on infections and resistance, with TDM and MIC results guiding treatment selection. Pharmacokinetic monitoring ensured therapeutic drug levels. Fungal infections were treated with anidulafungin. Culture became negative by ICU Day 51 following ciprofloxacin and anidulafungin therapy. Precision medicine, using real-time anti-infective serum monitoring and culture results, enabled effective dosing adjustments and was crucial in treating multi-drug-resistant infections and improving outcomes in major burn patients.

Limitations

This clinical study was a CASE REPORT, conducted in the ICU with a patient with several sepsis infections during the treatment of each septic shock, with a single-center design. Microbiological confirmation was done from day 3 in the ICU up to day 51 confirmed by negative cultures. Prolonged hospitalization was expected especially for survived patient in the ICU due to the extent of total body surface area burned (TBSA), nine surgical interventions, and ten septic shocks. A total of 15 isolates from cultures in a period of 51 days were distributed as follows: Gram-positive bacteria [GPB-3 isolates: *S. aureus* (n=2), *Staphylococcus epidermidis* (n=1)]; Gram-negative bacteria [GNB-7 isolates: *P. mirabilis* (n=1), *K. pneumoniae* (n=3), *C. difficile* (n=1), *P. aeruginosa* (n=2)], and invasive fungal infections caused by *Candida spp* (n=3) and *Fusarium solani* (n=2) as a function of a patient with an extended ICU period of immunosuppression at the Burn Center of the tertiary public hospital.

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Authors' contributions

All authors contributed equally to this work based on their specialty. DSG contributed to the study related to ethical approvals at the hospital and the Brazilian Platform for clinical projects, data acquisition, interpretation, and critical review of the manuscript content. SRCJS contributed to the conception and design of the study, acquisition and interpretation of data, writing of the manuscript with critical review for important intellectual content. DCSP, EDC, EMSJ and JMSJ contributed to clinical data acquisition, interpretation, and critical review of clinical data in the manuscript for important intellectual content. ASGA, GAF, TCO contributed to the critically ill patients care in the ICU, blood collection of viable samples for serum anti- infectives serum measurements, and blood collection for laboratorial data acquisition related to biomarkers. MJS, TVC, KBV contributed to the revision of "detailed information of articles included in the text", and especially at the last revision related to references included. PR, NJCD and NMS contributed to the critical revision of data for important intellectual new contents. PRA and MSS contributed to the discussion on anti-infective TDM, specifically regarding anidulafungin, a key lipophilic echinocandin used for *Candida spp*. and *Fusarium solani*. All authors read and approved the final manuscript version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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