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ABSTRACT BOOK

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EARLY MICROBIOLOGICAL DIAGNOSIS

BIOFIRE® JOINT INFECTION PANEL FOR SAMPLES OTHER THAN SYNOVIAL FLUID. A CASE SERIES

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Objectives. Early identification of infection-causing microorganisms through multiplex PCR panels enables prompt and targeted antibiotic therapy. This study aimed to assess the performance of the BioFire® Joint Infection Panel (BF-JIP) in analysing non-synovial fluid samples compared to traditional culture methods. To our knowledge this is the first study to evaluate BF-JIP in a broader context, beyond bone and joint infections. Some authors have explored the "off-label" use of other multiplex PCR panels. Micó *et al.* investigated the use of the blood FilmArray panel on non-blood samples (e.g. cerebrospinal, joint, pleural, ascitic and abscesses fluids, finding an overall concordance with culture-based methods of 75% [1]. Hirai *et al.* evaluated the blood

FilmArray panel for bone and joint infection, showing a sensitivity of 100% when considering only pathogens that are included in the panel [2].

Design. Retrospective cohort study.

Setting. Trieste University Hospital, Italy

Interventions. None

Methods and main results. We conducted a retrospective cohort study at Trieste University Hospital, Italy, including all hospitalized adult patients who had at least one non-synovial fluid sample tested by both the BioFire Joint Infection Panel (BF-JIP) and traditional culture methods (gold standard) between November 2022 and April 2024 (Figure 1). To assess the performance of the BF-JIP, a suite of statistical metrics was calculated, including percentage of positive agreement (PPA), percentage of negative agreement (NPA), positive predictive value (PPV), negative predictive value (NPV), enhanced detection, concordance (C), and accuracy (A). A total of 48 non-synovial fluid samples from 45 patients were evaluated, representing a diverse set of clinical scenarios. The patient cohort had a median age of 63 years, with a notable portion (67%) receiving antibiotic therapy at the time of sample collection. The types of samples included 24 abscess drainage fluids (e.g. cerebral, abdominal, skin and soft tissue abscesses, as well as infections related to breast implants), 10 biopsies (mainly bone tissue samples collected during surgical procedures), 6 pleural fluid samples, 5 cerebrospinal fluid (CSF) samples, 2 ascitic fluid samples, and 1 vitreous/aqueous humor sample. BF-JIP demonstrated an overall concordance rate of 85.4% with traditional culture methods, achieving particularly high accuracy in CSF samples, where it reached 100% concordance and accuracy (Table 1). Additionally, its accuracy was recorded at 89.6%.

The BF-JIP detected 42 bacteria and 2 fungi (Table 2), effectively identifying anaerobic bacteria in polymicrobial infections that traditional culture missed. This resulted in a 4.3% increase in

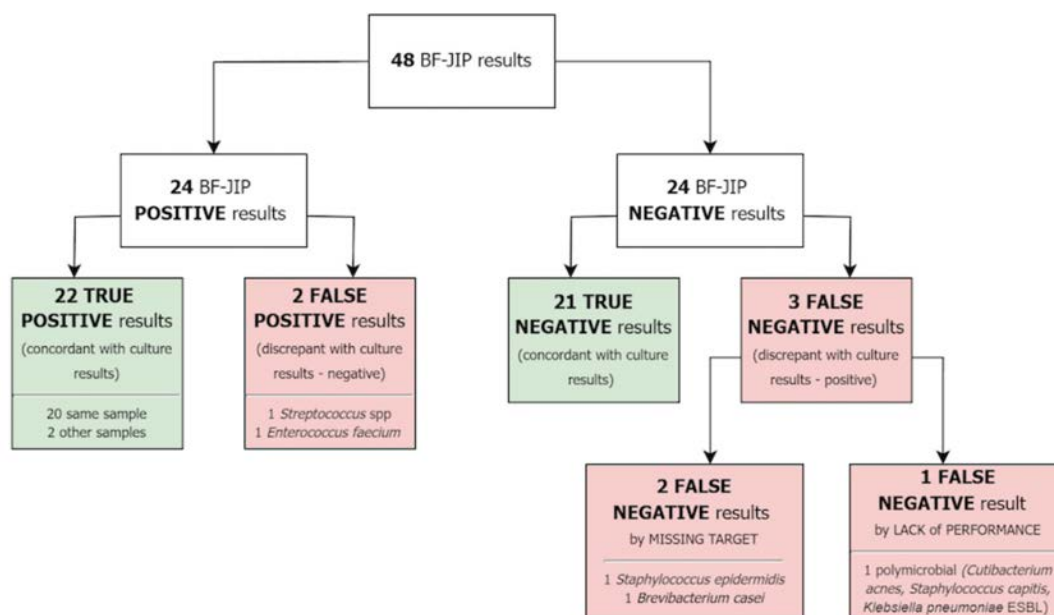


Figure 1. A) Pie chart representing sources of primary infection. B) Histogram representing age classes divided by gender. C) Boxplots showing MDW values dispersion at ICU admission and sites of primary infection.

the detection rate compared to standard culture methods. Even in patients undergoing antibiotic therapy, BF-JIP maintained robust performance. The comprehensive analysis confirmed BF-JIP's efficacy in critical samples such as CSF and abscess drainage fluids, highlighting its potential to improve patient management in complex clinical settings.

Conclusions. The BF-JIP demonstrated strong performance in detecting pathogens in non-synovial fluid samples, with high concordance (85.4%) and 4.3% enhanced detection compared to traditional culture methods. Notably, its accuracy was 89.6%, consistent with previous studies on synovial fluid where BF-JIP showed excellent sensitivity and specificity, as well as faster turnaround times [3,4].

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Table 1. Performances of the BF-JIP.

BF-JIP PERFORMANCES						
	PPA	NPA	PPV	NPV	C	A
All samples (n=48)	88.0%	91.3%	91.7%	87.5%	85.4%	89.6%
Abscess drainage fluid (n=24)	100%	90.9%	92.9%	100%	91.7%	95.8%
Biopsy (n=10)	57.1%	100%	100%	50%	70.0%	70.0%
Pleural fluid (n=6)	100%	75%	66.7%	100%	66.7%	83.3%
Cerebrospinal fluid (n=5)	100%	100%	100%	100%	100%	100%

A = accuracy; C = concordance; NPA = percentage of negative agreement; NPV = negative predictive value; PPA = percentage of positive agreement; PPV = positive predictive value.

Table 2. Microorganisms detected by the Biofire® Joint Infection panel (BF-JIP).

MICROORGANISMS DETECTED BY BF-JIP					
Gram +		Gram -		Yeasts	
<i>Staphylococcus aureus</i>	6	<i>Escherichia coli</i>	5	<i>Candida albicans</i>	2
<i>Streptococcus spp</i>	5	<i>Haemophilus influenzae</i>	2		
<i>Enterococcus faecium</i>	4	<i>Proteus spp</i>	1		
<i>Parvimonas micra</i>	3	<i>Citrobacter</i>	1		
<i>Anaerococcus prevotii</i>	2	<i>Enterobacter cloacae</i>	1		
<i>Finegoldia magna</i>	2	<i>Klebsiella pneumoniae</i>	1		
<i>Peptoniphilus</i>	2	<i>Pseudomonas aeruginosa</i>	1		
<i>Streptococcus pyogenes</i>	2				
<i>Bacteroides fragilis</i>	2				
<i>Peptostreptococcus anaerobius</i>	1				
<i>Enterococcus faecalis</i>					

RESUSCITATION AND MONITORING

PREDICTORS OF MORTALITY IN SEPTIC PATIENTS

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Objectives. Monocyte distribution width (MDW) represents monocytes volume dispersion around the mean value [1]. It is a known early marker for sepsis among patients recovered in ICU [2]. The primary aim of this study was to evaluate whether MDW could be an appropriate indicator of 30-days mortality among patients admitted to intensive care unit (ICU) with sepsis. The sec-

ondary objective was to verify whether MDW value at ICU admission correlates with mortality.

Design. Retrospective, single centre study.

Setting. ICU and ward.

Subjects. MDW values of patients diagnosed with sepsis admitted in ICU.

Interventions. None

Methods and main results. We retrospectively enrolled patients with a diagnosis of sepsis and admitted to ICU between August 15, 2023, and July 15, 2024, at Santa Maria della Misericordia Hospital, Udine, Italy. Only patients who underwent daily MDW evaluation during ICU recovery were included. Patients less than eighteen years old were not included. For each patient, demographic data, recovery length, site of infection and daily MDW values were collected. 43 patients met the eligibility criteria. The population accounted for 25 females (58.1%) and 18 males (41.9%), with a median age of 69.9±13.6 years (Figure 1). The mean recov-

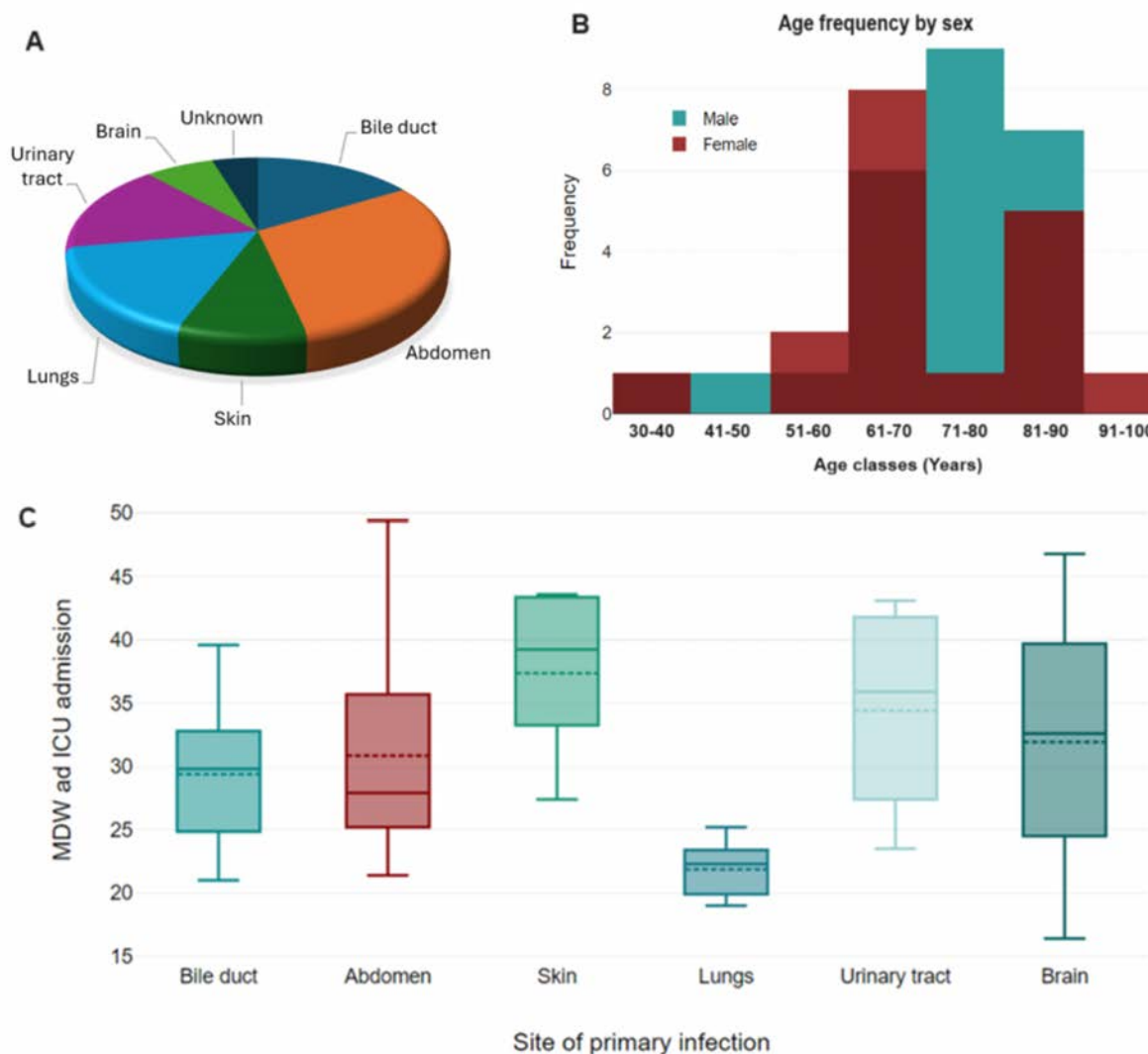


Figure 1. A) Pie chart representing sources of primary infection. B) Histogram representing age classes divided by gender. C) Boxplots showing MDW values dispersion at ICU admission and sites of primary infection.

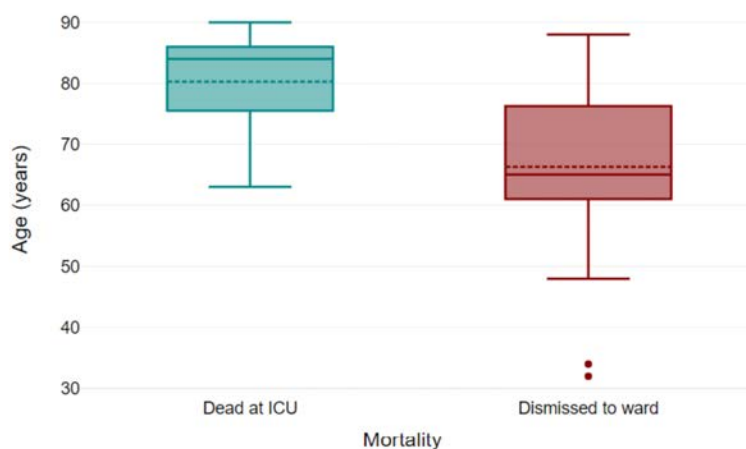


Figure 2. Boxplots representing ICU mortality sorted by age.

Table 1. Mortality and MDW values by primary infection site.

Infection site	n (%)	Death among ICU	Death within 30 days after ICU dismissal	Mean MDW at ICU admission
		n (%)	n (%)	n (%)
Bile duct	7 (16.28)	3 (42.86)	3 (42.86)	29.39
Abdomen	13 (30.23)	4 (30.77)	5 (38.46)	30.86
Skin	4 (9.30)	1 (25.00)	1 (25.00)	37.38
Lungs	7 (16.28)	1 (14.29)	1 (14.29)	30.69
Urinary tract	7 (16.28)	1 (14.29)	3 (42.86)	34.41
Brain	3 (6.98)	0 (0.00)	0 (0.00)	31.93
Unknown	2 (4.65)	1 (50.00)	1 (50.00)	32.90
Overall	43 (100.00)	11 (25.80)	14 (32.56)	31.94

Table 2. Statistical significance level between the analyzed variables.

Parameters		p-value
MDW at ICU admission	Death among ICU	0.780
Age		< 0.001
Maximum MDW among ICU		0.962
Infection site		0.711
MDW at ICU admission	Death within 30 days from ICU admission	0.437
Age		0.577
Maximum MDW among ICU		0.758
MDW at ICU dismissal		0.551

ery length was 11.7 ± 13.0 days. 11 patients (25.6%) died within ICU whereas 3 patients (7.0%) died after discharge to the ward; the overall mortality within 30 days after ICU admission was of 14 patients (32.6%). Abdominal infection was the most frequent source of sepsis (30.2%) as well as the main cause of 30-days mortality after recovery (38.5%) (Table 1 and Figure 1). Bile duct infection instead showed the highest ICU mortality (42.9%) (Table 1). Statistical analysis for continuous variables was conducted using Welch two sample t-test or Wilcoxon rank sum test with continuity correction, according to Kolmogorov-Smirnov normality test results. For categorical variables, chi-square test or Fisher's exact test were used. Our results demonstrate that MDW value at ICU admission does not correlate with ICU mortality (p-value 0.780), neither does the maximum value detected among ICU recovery (p-value 0.962) (Table 2). The primary outcome was not fulfilled: MDW values at ICU admission do not predict 30-days mortality (p-value 0.437). Similarly, MDW values at ICU discharge do not predict mortality in the further 30 days (p-value 0.551). According to our analysis, age is the strongest single predictor of ICU mortality ($p < 0.001$) but it does not predict mortality within 30 days after ICU dismissal (p-value 0.577). The mean age of patients who survived after ICU admission was 66.3 ± 13.2 years whereas the mean age of patients who experienced death among ICU recovery was about 80.3 ± 8.7 years (Figure 2).

Conclusions. Our study confirmed how MDW alone could not be used as a single predictor of mortality for septic patients [3], nei-

ther it could be employed as a single predictor of 30-days mortality after ICU discharge. Age > 65 years old is a risk factor for mortality among septic patients [4], condition attributable to comorbidities and lower organ function reserve. According to our evaluation, age is the strongest single predictor of ICU mortality.

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EARLY DIAGNOSIS AND TREATMENT OF ORGAN DYSFUNCTION

PROGNOSTIC ROLE OF THE ARTERIAL-VENOUS PCO₂ GAP CALCULATED ON PERIPHERAL VENOUS BLOOD IN SEPTIC PATIENTS IN THE EMERGENCY DEPARTMENT

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Objectives. The arterial-venous pCO₂ gap (A-VpCO₂ gap) is a marker used to evaluate tissue perfusion and cardiac output, typically considered normal when it is less than 6 mmHg. Traditionally, this measurement is calculated using central venous blood, and prior research has shown that an elevated A-VpCO₂ gap (>6 mmHg) is associated with poor prognosis in septic patients. However, in fast-paced and crowded environments like the Emergency Department (ED), obtaining central venous blood may not always be feasible. Recent studies suggest that peripheral venous blood could be a reliable alternative for calculating the A-VpCO₂ gap. The primary aim of this study was to assess whether the A-VpCO₂ gap, calculated using peripheral venous blood (A-PVpCO₂ gap), correlates with 7-day mortality in patients presenting with sepsis to the ED.

Design and setting. This study was a single-center, observational, prospective analysis conducted at the "Agostino Gemelli" University Hospital in Rome. Between May 2021 and May 2023, patients over the age of 18 who presented to the ED with sepsis

were enrolled. Upon arrival, each patient underwent simultaneous arterial and peripheral venous blood gas analysis. Data collected included vital signs, routine laboratory tests, and inflammatory markers.

Patients. Patients were classified into two groups based on the SOFA and APACHE-II scores: a low-risk group (SOFA <7, APACHE-II <15) and a medium-high-risk group (patients not meeting the low-risk criteria). Statistical significance was defined as a p-value of ≤ 0.05 .

Intervention: None

Results: A total of 121 patients were included in the study, with an average age of 72.6 years (± 13.2), and 71.5% of them were male. Several factors were statistically associated with 7-day mortality, including lower systolic blood pressure (101.1 \pm 24.0 vs 118.5 \pm 24.6 mmHg), lower diastolic blood pressure (59.9 \pm 13.0 vs 70.1 \pm 14.1 mmHg), lower C-reactive protein (CRP) levels (93.8 \pm 50 vs 185.3 \pm 119.1 mg/L), higher lactate levels (5.9 \pm 3.3 vs 2.3 \pm 4.4 mmol/L), and higher SOFA and APACHE-II scores (93% vs 51% and 71.4% vs 30.5%, respectively). Although the A-PVpCO₂ gap was higher in patients with worse outcomes (10.3 \pm 4.7 vs 7.8 \pm 5.7 mmHg), this difference was not statistically significant (p=0.08). ROC curve analysis (AUC=0.65) indicated that an A-PVpCO₂ gap of 6.75 mmHg was the most accurate cut-off value for predicting 7-day mortality, with a sensitivity of 92.9% and specificity of 50.5%. Additionally, Pearson correlation analysis showed a significant association between the A-PVpCO₂ gap and lactate levels (R=0.235, p=0.01).

Conclusions. The study suggests that the A-PVpCO₂ gap tends to be higher in septic patients with poorer outcomes, although this finding did not reach statistical significance. A cut-off value of 6.75 mmHg was identified as a potential marker for better prognosis, which aligns closely with the established cut-off of 6 mmHg for central venous blood and with previous studies (e.g., Wei Gao et al., 2018). The study's limitations include a small sample size, the absence of simultaneous A-VpCO₂ gap measurements using central venous blood, and patient heterogeneity within the ED setting. These factors suggest that further research with a larger and more controlled sample is necessary to validate the prognostic use of the A-PVpCO₂ gap in septic patients.

ANTIMICROBIAL THERAPY

A NEW DEVICE FOR THE TREATMENT OF SEPSIS: THE FUNCTIONALIZED CARTRIDGE

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Objectives. The efficacy of an antibiotic Functionalized Cartridge (FC) in reducing the circulating bacterial load during hemoadsorption treatment.

Design. Recent studies had proposed the utilization of drug- or antibiotic-FC in sepsis management. This *in vitro* study evaluated the impact of a FC on circulating bacterial load and compared it to a standard sepsis treatment using antibiotic and extracorporeal treatment with a Non-Functionalized Cartridge (NFC). The time to positivity (TTP), which provides indirect information on bacteria concentration, was used to evaluate the effect of treatments with FC and NFC.

Setting. *In vitro* hemoadsorption was performed using GALILEO testing platform (IRRIV Laboratory) with minimodule of HA380 cartridge (Jafron, Zhuhai, China).

Subjects. Staphylococcus aureus bacteria MSSA in heparinized blood

Interventions. None

Methods and main results. *S.aureus* were injected into 2L blood and incubated for 24h. After 24h, a sample was taken (T0) and the blood was divided into 4 bags: A and B of 700mL, X and Y, negative control of A and B respectively of 300mL. 70mg and 30mg of Vancomycin were inoculated into B and Y, respectively, and incubated together with other bags for 1h. A HA380 minimodule was functionalized with 1g of Vancomycin. Closed-loop hemoadsorption circuits were set up using two HA380 minimodules (FC and NFC) and circulations (FC with bag A and NFC with bag B) were maintained at 250 mL/min for 1h, while X and Y remained in incubation. 5 mL samples were drawn from all 4 bags at predefined time-points to measure Vancomycin concentration and injected into hemoculture to determine TTP. At the beginning (T1) and at the end (T2) of *in vitro* circulation, samples were taken. Then, 70mg of Vancomycin was added to bag B and 30mg to bag Y and, after 1h of incubation of all 4 bags, samples were taken (T3). Additionally, *in vitro* hemoadsorption with NFC and bag B were performed, while A, X and Y were placed in incubation. After 1h of treatment or incubation, samples were taken from the 4 bags (T4). Results are shown in Table 1.

Conclusions. Reduction of bacterial load, with increase of TTP, after hemoadsorption with FC. Prolonged effect on TTP using FC. TTP of B were affected by NFC adsorption and Vancomycin infusions. The study demonstrated that hemoadsorption with FC has an equal effect on bacterial concentration compared to standard therapy.

Table 1. Vancomycin concentration and TTP of the 4 bags at predefined time-point.

		Vancomycin Concentration (mg/L)	TTP (minute)
T0		7	133
T1	A	7	117
	B	201	293
	X	8	137
	Y	205	577
T2	A	12	293
	B	71	313
	X	7	133
	Y	206	653
T3	A	12	298
	B	234	698
	X	7	138
	Y	354	758
T4	A	12	304
	B	72	464
	X	7	134
	Y	343	924

SURGICAL SOURCE CONTROL

ASSESSMENT OF ANTIBIOTIC CONCENTRATIONS IN ABDOMINAL ABSCESES: PROTOCOL OF A PROSPECTIVE STUDY

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Objectives. In patients presenting with abdominal abscesses, the timely administration of antibiotics is essential for preventing further complications and ensuring effective treatment. However, a significant challenge in clinical practice is determining the appropriate type, administration method, and duration of antibiotic therapy. Secondly, it remains unclear whether antibiotics can be safely discontinued once the sepsis is resolved or must be continued until the abscess is fully treated. This uncertainty underscores the need for precise monitoring of antibiotic levels within both the blood and the abscess fluid. To address this issue, our study aims to measure and compare antibiotic concentrations in both blood and abscess fluid. The findings are expected to provide critical insights into optimizing antibiotic treatment, ultimately improving patient outcomes in the management of abdominal abscesses treatment.

Design. Prospective observational study

Setting. Academic Hospital

Patients. Adult patients with abdominal abscesses undergoing surgically or radiologically drainage after at least 24 hours of antibiotic therapy with piperacillin/tazobactam or meropenem.

Interventions. None

Methods and main results. The primary objective is to measure the antibiotic concentration in both blood and abscess fluid. Patients will receive standard antibiotic therapy in continuous infusion (18 g of piperacillin/tazobactam over 24 h, and 3 g of meropenem over 24 h). Blood and abscess fluid samples will be obtained after 24 hours after the start of antibiotic therapy (steady-state). Secondary objectives include: 1) evaluating the differences in antibiotic concentrations between blood and abscess fluid; 2) evaluating the above-mentioned concentrations in special populations (obese patients, those with liver disease, renal insufficiency, hypoalbuminemia). The study will likely reveal a range of drug concentrations in blood and abscess fluid that correlates with effective treatment. In special populations (i.e. patients with obesity, liver disease, renal insufficiency, hypoalbuminemia) we anticipate that altered pharmacokinetics may necessitate adjustments in antibiotic dosing to achieve therapeutic concentrations.

Conclusions. This study aims to refine the understanding of antibiotic distribution between blood and abscess fluid in patients with abdominal abscesses. By measuring and comparing drug concentrations in these compartments, the research will contribute valuable insights into optimizing antibiotic therapy. The findings are expected to guide clinicians in making more informed decisions regarding the choice and duration of antibiotic therapy and improving individualized patient care in the management of sepsis and abdominal abscesses.

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EARLY MICROBIOLOGICAL DIAGNOSIS

A RARE CASE OF DIZZINES

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Case History. Female patient, 50 years old, Ukrainian nationality, came to the emergency room for dizziness syndrome associated with weight loss of 12 kg in the last month. The anamnesis revealed worsening postural instability associated, sometimes, with dizziness and vomiting for approximately 3 months. The patient had normal vital signs and GCS15. Despite the therapy, headache and dizziness persisted, so she carried out haematochemical tests, results were normal, and head CT without contrast medium which highlighted multiple areas of tissue hypodensity surrounded by digitiform edema mostly located in the left cerebellar area, capsular nucleus bilaterally and left frontal cortico-subcortical, referable in the first instance to repetitive injuries. Therefore, she carried out a neurosurgical consultation which indicated the need for a total body CT scan and therapy with Dexamethasone and Mannitol. On suspicion of heteroplasic pathology with secondary effects, she was admitted to Internal Medicine for further investigation of the case. She performed routine blood chemistry, with findings of severe lymphocytopenia (400 u/L), sampling for oncomarkers and total body CT with contrast medium. Once lymphocytopenia was assessed, blood tests were carried out to exclude

an infectious origin of the lesions. There was positivity for HIV-Ab and IgG for Cytomegalovirus, Toxoplasma and Rubella. Having re-evaluated the CT images with the ward doctor, the residents on duty and the radiologist, given the finding of positivity to HIV Ab, the clinical suspicion of brain abscesses from Toxoplasma Gondii was advanced, for which empirical antibiotic therapy with Cotrimoxazole was started and an MRI was carried out. After infectious disease consultation he practiced prophylaxis for Mycobacterium Avium Complex. He therefore moved to the Infectious Diseases department of the Polyclinic where he began HAART therapy 10 days after the start of empirical antibiotic therapy, with the aim of avoiding immune reconstitution syndrome. Rachicentesis was not performed as it was contraindicated by the brain CT picture.

Discussion. *T. gondii* is a parasite that can infect humans in various ways including ingestion of raw meat containing tissue cysts or water contaminated with cat feces. Toxoplasmosis in HIV-positive patients is usually a consequence of the reactivation of the tissue cysts of the parasite. MRI is superior to CT in diagnosis, however Imaging techniques cannot distinguish toxoplasmosis from other neurological opportunistic infections. Lumbar puncture should be performed only if safe and feasible, and CSF characteristics are usually of little significance. Therapy should be started once the probable/presumptive diagnosis has been made and the response allows diagnostic confirmation. For treatment we recommend pyrimethamine (PYR) which is not always available and has reduced bioavailability in a malnourished patient, resulting in a wider use of TMP/SMX as first line. Immune reconstitution syndrome (IRIS) is uncommon in patients with cerebral toxoplasmosis and steroids remain the main therapeutic support, as they inhibit cellular destruction due to immune recovery. HAART is usually started within 2 weeks of starting treatment for cerebral toxoplasmosis.

EARLY MICROBIOLOGICAL DIAGNOSIS

CD169 AND HLA-DR IN BLOOD CELLS AND CIRCULATING EXTRACELLULAR VESICLES IN COVID-19 AS MARKERS INFECTION AND POST-ACUTE SEQUELAE MONITORING

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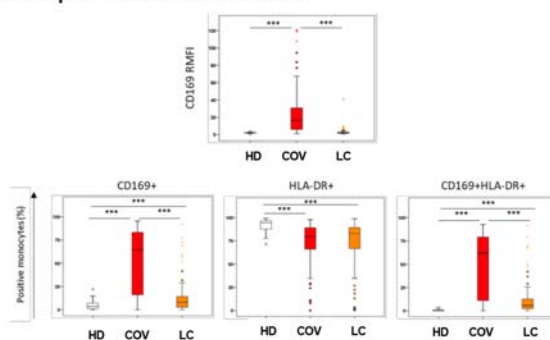
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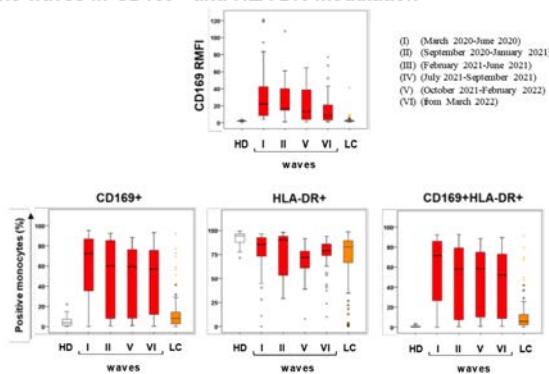
*Equally contribution

Objectives. An elevated inflammatory response and immune dysregulation are the main consequences of SARS-CoV-2 infection and characterize COVID-19 disease. This dysregulated inflammatory state persists even after infection, generating the post-acute

A) Persistence of circulating CD169+monocytes and HLA-DR downregulation underline the immune response impairment in LC individuals



B) Impact of the waves in CD169+ and HLA-DR modulation



C) Circulating microvesicles HLA-DR+ CD169+ in COVID-19 patients and LC individuals

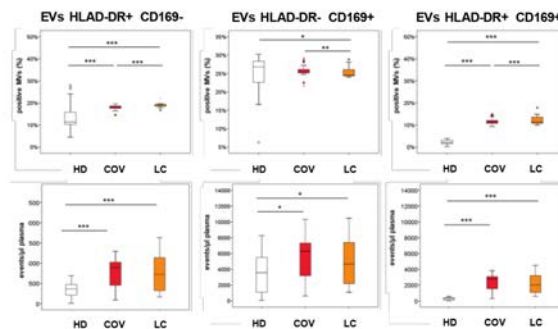


Figure 1. Analysis of CD169 RMFI and the percentage of HLA-DR+ and CD169+ in monocytes cells and in circulating MVs in COV, LC, and HD. **A)** Representation of CD169 RMFI, defined as the ratio of the mean fluorescence intensity (MFI) of CD169 in HLA-DR+ monocytes and lymphocytes, evaluated in COV (n = 133, red box), PASC (n = 132, orange box) and HD (n = 59, white box). **B)** impact of the SARS-CoV-2 waves in CD169 and HLA-DR modulation. **C)** Circulating MVs reported as % of CD169+ HLA-DR+ positive MVs and as events microliter/plasma. The Mann Whitney test was used to compare groups (**p ≤ 0.001; *p ≤ 0.01; *p ≤ 0.05).

sequelae of SARS-CoV-2 infection in Long COVID individuals (LC). The identification of innovative biomarkers to characterize acute COVID-19 and predict its long-term effects are needed. CD169+ macrophages play an important role in viral infections helping to differentiate viral vs bacterial infection (Bourgoin P *et al.* 2021) and recently has been demonstrated that CD169 was strongly overexpressed in the blood of COVID-19 patients (COV) in the early stage of SARS-CoV-2 infection (Bedin *et al.* 2021, Minutolo *et al.* 2021)

Design and Setting. Considering the close implication of CD169 expression in COVID-19, in the present study the analysis of CD169 was extended to a large cohort of COVID-19 patients and LC individuals both at blood cells and on circulating extracellular vesicles (EVs) in association with immune dysfunction, inflammatory markers and clinical features.

Patients. Blood samples from 133 COV, 132 LC (7-48 weeks' post-infection), and 59 Healthy Donors (HDs) were collected at Tor Vergata University Hospital of Rome in the period May 2020 and June 2023. Ethical approval for the collection and use of human samples was obtained from the Ethics Committee of 'Fondazione Tor Vergata', CORONA Virus Disease: Safety and efficacy of experimental treatment (COVID_SEET prot.7562/2020, 9 April 2020, experimental register 46.20).

Intervention. None

Methods and Main Results. Flow cytometry for Leukocytes subsets immunophenotyping and MVs characterization was performed by CytoFLEXs and CytoFLEX SRT. Serum inflammatory markers were assessed by Ella immunoassay system. Biomarkers were associated with clinical and biochemical parameters. Statistical analysis was performed by SPSS 23 software. As reported in Figure 1, CD169 RMFI was found significantly higher in COV than in HDs, and it correlated with CD8 T-cell senescence and exhaustion markers in COV. CD169 RMFI correlated with blood cytokine mRNA levels, inflammatory markers, and pneumonia severity in patients who were untreated at sampling, and was

associated with the respiratory outcome throughout hospitalization. We have also observed alterations of CD169 and HLA-DR expression and indices of inflammation upon different COVID-19 waves, and recently we also found the persistence of circulating CD169+HLA-DR+ monocytes in LC individuals (Fanelli *et al.* 2024). The analysis of CD169 and HLA-DR was extended at the level of circulating EVs in association with serum inflammatory markers and clinical features. In plasma, the percentage and number of HLA-DR+CD169+ EVs were significantly elevated in COV and persisted, although at lower level, in LC compared to HDs, correlating with coagulation factors and inflammatory indices in COV and with D-dimer in LC. Our results confirmed the CD169 and myeloid activation as predictive markers of COVID-19, and the persistence of myeloid activation in LC. A dynamic correlation among CD169 and HLA-DR expression was found at cellular level and EVs in association with inflammatory cytokines and coagulation factors, drawing attention to EVs phenotyping for monitoring emerging respiratory viruses associated diseases.

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RESUSCITATION AND MONITORING

SEPTIC SHOCK AND INFECTIVE ENDOCARDITIS FROM TOXIGENIC *CORYNEBACTERIUM DIPHTHERIAE*

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Objectives. We report the case of a patient who experienced septic shock and infective endocarditis (IE) with early septic emboli due to toxigenic *Corynebacterium diphtheriae* infection.

The aim of this study is to describe the therapeutic strategies adopted to deal with a rare infective disease which occurred with much atypical manifestations.

Design. Case report.

Setting. Intensive care unit (ICU).

Patients. Patient admitted to ICU with ascertained *C. diphtheriae* infection.

Interventions. None.

Methods and main results. Written consent was obtained from patient prior to the publication of this report. A 57-years-old male

was admitted to hospital due to persistent fever, headache and arthralgias. He referred recent business trip into foreign country but denied any raw food assumption or tick bite. Previous medical history and physical examination were otherwise unremarkable.

Once haemocultures were collected, empiric antibiotic therapy was started (Table 1). Samples lately tested positive for *Corynebacterium diphtheriae*. The strain was thus sent to Istituto Superiore di Sanità (ISS), which not only confirmed *C. diphtheriae* (biotype mitis) growth, but also detected diphtheria toxin gene in vitro expression, via Elek test (Figure 1). Therapy was thus modified according to antibiogram (Table 2) and diphtheria antitoxin infusion was started. Notably, otolaryngologist evaluation excluded upper airways involvement. Furthermore, oropharyngeal swabs repeatedly tested negative. Among recovery, the patient experienced desaturation, left hemiplegia, aphasia and lethargy. Brain computed tomography (CT) was carried out to assess the diagnosis; acute occlusion of the proximal tract of the middle right cerebral artery was identified, leading to thromboaspiration to be performed. Septic cerebral embolism diagnosis was assessed after sample culture tested positive for *C. diphtheriae*. To optimize central nervous system penetration, antibiotic therapy was thus shifted to meropenem. Concomitant elevation of I troponin subunit, in a patient already diagnosed with septic emboli and bacteriemia, arouse the suspect for IE; diagnosis was established due to trans-oesophageal echocardiography identification of mitral and aortic valves multiple vegetations. Given severe valves regurgitation, cardiac surgery was performed to allow valves replacement. Lately, due to the rise of liver necrosis enzymes and the rapid development of acute kidney injury, CT scans were extended to abdomen to detect any other site of embolization. Two ischemic lesion were identified in the spleen and in the left kidney whereas no pathologic areas were seen in the liver. After fifteen days of proper antibiotic therapy, there was no more clinical or microbiological detection of the pathogen.

Table 1. Antibiograms and therapeutic choices of the two main pathogens identified among recovery. MIC = minimal inhibiting concentration; S = sensitive; R = resistant; I = intermediate.

Antibiotic tested	Haemocultures	
	Pathogen: <i>C. diphtheriae</i>	Concentration: 10 ⁵ CFU/mL
	MIC	Efficacy profile
Amoxicillin	0.125	S
Cefotaxime	0.5	I
Ciprofloxacin	0.75	R
Clindamycin	0.38	S
Doxycycline	0.125	S
Erythromycin	0.047	S
Linezolid	0.19	S
Meropenem	0.064	S
G penicillin	0.094	I
Rifampicin	< 0.002	S
Tetracycline	0.19	S
Trimethoprim/ sulfamethoxazole	1.5	R
Therapeutic choice	Piperacillin/tazobactam 18g/daily + clindamycin 600mg 4/day + gentamicin 320mg/daily + meropenem 1g twice a day	

Table 2. Daily resume of most important diagnostic monitoring and therapies. ABT = antibiotic therapy; CT = computed tomography; IE = infective endocarditis; AKI = acute kidney injury; NSAID = non-steroidal anti-inflammatory drugs; β -DG = beta-D-glucan; MCA = mean cerebral artery; TOE = trans-oesophageal echocardiography; TnI = I troponin subunit.

Day	Signs/symptoms/tests	Diagnosis/therapy
0	Persistent fever, headache and arthralgias	<ul style="list-style-type: none"> - Acetaminophen + NSAID; - Haemocultures; - Empiric ABT: piperacillin/tazobactam 18g/daily + clindamycin 600mg 4/day + azithromycin 500mg/daily
2	<i>C. diphtheriae</i> isolated from haemocultures	<ul style="list-style-type: none"> - Isolation precautions; - ABT switched to: piperacillin/tazobactam 18g/daily + clindamycin 600mg 4/day + gentamicin 320mg/daily + diphtheria antitoxin.
	Neurological impairment	<ul style="list-style-type: none"> - Orotracheal intubation and ICU recovery; - Brain CT scan.
	Brain CT scan	MCA occlusion.
	MCA occlusion	Thromboaspiration.
	Hypotension	Norepinephrine and dobutamine started.
	TnI elevation	TOE → severe mitral and aortic valve impairment.
	AKI	Continuous renal replacement therapy.
4	Thromboaspiration sample cultures	<i>C. diphtheriae</i> detected → septic embolism diagnosis assessed → meropenem 1g twice a day added to ABT (to assess proper cerebral penetration)
	Liver impairment + AKI	Abdomen CT scan → spleen and renal ischemic lesions
	Brain control CT scan	Ischaemic and haemorrhagic evolution → decompressive craniectomy.
10	β -DG rise	Fungi infections suspected: liposomal-B amphotericin added to ABT.
19	15 days of proper ABT + no evidence of <i>C. diphtheriae</i>	ABT suspended. Antifungal therapy maintained.
38	Known IE with extensive vegetations	Cardiac surgery performed (not previously accomplishable due to unacceptable haemorrhagic risk, given recent brain surgery).

Phenotypic and molecular investigations carried out by ISS:	
The bacterial strain, isolated from blood culture, was confirmed as <i>C. diphtheriae</i> , mitis biotype, via Real-time PCR and API Coryne test.	
The diphtheria toxin gene search, by molecular methods, has given positive results.	
The toxigenicity test, using Elek test, performed to confirm the in vitro production of diphtheria toxin, gave a positive result.	
Genomic analysis (species identification, ST, resistance and virulence genes):	
<u>Methods</u>	
Species identification, sequence type (ST) determination and resistance gene detection were obtained using KmerFinder (https://cge.food.dtu.dk/services/KmerFinder/), MLST (https://cge.food.dtu.dk/services/MLST/) and DiphtOscan (https://gitlab.pasteur.fr/BERP/diphtoscan), respectively.	
Virulence factors were analyzed using "Virulence Factor Database (VFDB)" (http://www.mgc.ac.cn/cgi-bin/VFs/v5/main.cgi).	
<u>Results</u>	
The strain, confirmed <i>C. diphtheriae</i> , belongs to ST377, one of the main toxigenic and antibiotic-resistant clones reported in Europe.	
The following resistance genes were detected:	
<ul style="list-style-type: none"> - cmx (chloramphenicol resistance); - aph(6)-Ia, aph(3'')-Ib, aph(3')-Ia, aadA5 (aminoglycoside resistance); - sul1 (resistance to sulphonamides); - dfrA1 (resistance to trimethoprim). 	
The point mutation gyrA_S89F (conferring resistance to quinolones) was detected.	
As regards for virulence factors, were identified:	
<ul style="list-style-type: none"> - tox gene, coding for diphtheria toxin (DT); - the complete clusters of the genes involved in the acquisition of iron and heme: <ul style="list-style-type: none"> o Ciu iron uptake and siderophore biosynthesis (ciuA, ciuB, ciuC, ciuD, ciuE); o ABC transporter (fagA, fagB, fagC, fagD); o ABC-type heme transporter (htmTUV); o Siderophore dependent iron uptake system (irp6A, irp6B, irp6C) - complete cluster SpaA-type pili (spaABC-srtA) mainly involved in adhesion to pharyngeal epithelial cells - incomplete clusters of SpaD-type pili (spaDEF-srtBC) and SpaH-type pili (spaGHI-srtDE), mainly involved in adhesion to laryngeal and lung epithelial cells. 	

Figure 1. Phenotypic, genomic and molecular analyses performed by ISS on haemocultures samples.

Conclusions. Given an incidence of 0-0.1 cases per million people, diphtheria is considered as a rare disease in the European region [1]. The pathogen normally causes symptoms limited to oropharynx or upper airways but, following toxin diffusion and absorption, can induce systemic complications, such as myocarditis and neuritis [2]. Rarely, the pathogen can cause bacteraemia and endocarditis but in the majority of reported cases, non-toxigenic strains are involved [3,4].

This report describes an atypical and rare case of toxigenic *C. diphtheriae* infection, given lack of airways or skin impairment, septic shock, extensive cardiac valves aggression and early septic embolization.

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EARLY DIAGNOSIS AND TREATMENT OF ORGAN DYSFUNCTIONS

MANAGEMENT OF ACUTE PYELONEPHRITIS IN THE EDOU AND IN THE REGULAR WARD

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Contents. Pyelonephritis, according to the European Association of Urology 2023 guidelines, is suggested by fever (>38°C), chills, flank pain, nausea, vomiting, or costovertebral angle tenderness, with or without the symptoms of cystitis. While uncomplicated cases can be managed conservatively, complicated cases, including those with sepsis or persistent vomiting, require hospitalization for intravenous antibiotic therapy and proper hydration.

Table 1.

	Dati clinici			
	Totale	Pazienti in Reparto	Pazienti in OBI	p-value
	183			
Età media (anni ± ds)	53,21 ± 19.42	56,97 ± 18.99	45,56 ± 17.99	0,0001
Genere (M/F)	61 (33.33%) / 122 (66.67%)	47 (37.90%) / 77 (62.10%)	15 (24.59%) / 46 (75.41%)	0,07
Dolore fianco/dorso (si/no)	114 (62.30%) / 69 (37.70%)	72 (58.06%) / 52 (41.94%)	44 (72.13%) / 17 (27.87%)	0,06
Disuria (si/no)	43 (23.50%) / 140 (76.50%)	31 (25%) / 93 (75.5%)	13 (23.50%) / 48 (78.69%)	0,58
Ematuria (si/no)	16 (8.74%) / 167 (91.26%)	12 (9.68%) / 112 (90.32%)	4 (6.56%) / 57 (93.44%)	0,59
Altri disturbi urinari (si/no)	35 (19.13%) / 148 (80.87%)	23 (18.55%) / 101 (81.45%)	12 (19.67%) / 49 (80.33%)	0,85
Febbre (si/no)	130 (71.04%) / 53 (28.96%)	84 (67.74%) / 40 (32.26%)	47 (77.05%) / 14 (22.95%)	0,19
Litiasi urinaria (si/no)	30 (16.39%) / 153 (83.61%)	24 (19.35%) / 100 (80.65%)	7 (11.48%) / 54 (88.52%)	0,18
Progressi episodi (si/no)	78 (42.62%) / 105 (57.38%)	54 (43.55%) / 70 (56.45%)	24 (39.344%) / 37 (60.66%)	0,59
Progressa litotrissia (si/no)	15 (8.20%) / 168 (91.80%)	10 (8.06%) / 114 (91.94%)	5 (8.2%) / 56 (91.80%)	1
Portatore di stent (si/no)	26 (14.21%) / 157 (85.79%)	20 (16.13%) / 104 (83.87%)	6 (9.84%) / 55 (90.16%)	0,25
Portatore di nefrostomia/e (si/no)	28 (15.30%) / 155 (84.70%)	23 (18.55%) / 101 (81.45%)	5 (8.2%) / 56 (91.80%)	0,08
Portatore di catetere vescicale (si/no)	14 (7.65%) / 169 (92.35%)	11 (8.87%) / 113 (91.13%)	3 (4.92%) / 58 (95.08%)	0,39
Interventi progressi chirurgici su apparato urinario (si/no)	45 (24.59%) / 138 (75.41%)	38 (30.65%) / 86 (69.35%)	7 (11.48%) / 54 (88.52%)	0,004
Ureterocutaneostomia (si/no)	6 (3.28%) / 177 (96.72%)	3 (2.42%) / 121 (97.58%)	3 (4.92%) / 58 (95.08%)	0,39
Giordano positivo (si/no)	55 (30.05%) / 128 (69.95%)	33 (26.61%) / 91 (73.39%)	23 (37.7%) / 38 (62.3%)	0,12
Irradiazione del dolore in zona genitale (si/no)	26 (14.21%) / 157 (85.79%)	16 (12.9%) / 108 (87.1%)	10 (16.39%) / 51 (83.61%)	0,52
Frequenza cardiaca (media ± ds)	94.73 ± 19	96.23 ± 19	56.97 ± 18	0,49
PAS <90 (si/no)	7 (3.83%) / 176 (96.17%)	6 (4.83%) / 118 (95.17%)	1 (1.64%) / 60 (98.36%)	0,42
Sepsi (si/no)	30 (16.39%) / 153 (83.61%)	22 (17.74%) / 102 (82.26%)	9 (14.75%) / 52 (85.25%)	0,61

Objectives. The aim of this study is to assess whether there are differences in the treatment of pyelonephritis between hospital wards and the emergency department observation unit (EDOU), particularly in terms of length of hospital stay.

Design. We decided to build a retrospective, observational study in order to evaluate whether the length of hospitalization would change. Demographic characteristics, symptoms, physical examination findings, past medical history, laboratory tests, and imaging results were analyzed.

Setting. From February 27, 2021, to April 19, 2023, we collected data on all patients admitted to the Gemelli Hospital emergency department with a diagnosis of pyelonephritis.

Patients. We enrolled 183 patients, of whom 61 (48%) were males, with a mean age of 53 ± 19 years. 130 patients (71%) presented with fever, 114 (62%) with flank pain, and 94 (51%) with urinary symptoms. Upon physical examination, a positive Giordano sign was found in 55 patients (30%). The Charlson Comorbidity Index (CCI) was calculated for each patient. 78 patients had previously experienced a similar episode, and 74 were carriers of a septic focus (26 stents, 28 nephrostomies, 14 urinary catheters, 6 ureterocutaneostomies, 30 urinary lithiasis).

Interventions. None

Methods and main results. More than 70% of patients underwent ultrasound of the urinary tract, while just over 50% underwent abdominal CT scan with contrast. Laboratory tests revealed elevated markers of infection with an increase in white blood cell count, C-reactive protein, creatinine and procalcitonin. In 108 patients (59%), a urine culture was performed, resulting positive in 70%, and in 100 (55%), a blood culture was performed, resulting positive in 20%. The most frequently detected bacterium was *Escherichia coli* (32 patients, 36% of the total). Empirical antibiotic therapy, primarily piperacillin/tazobactam, was initiated in 80%

of patients, with 19 patients requiring an upgrade due to multidrug resistance. Results showed that 61 (33%) patients were admitted to the EDOU, and 122 to a ward. The average length of stay in the EDOU was significantly shorter (90 ± 47 hours) compared to the ward (240 ± 197 hours). In the univariate analysis, age ($p = 0.0001$), history of previous surgeries on the urinary system ($p = 0.004$), CCI ($p < 0.01$), gender ($p = 0.07$), and discharge within 72 hours ($p < 0.01$) were significantly associated with admission to EDOU. In the multivariate analysis, only discharge within 72 hours after correction for the aforementioned factors was found to be independently associated with admission to EDOU ($p < 0.001$, OR 15.51, 95% CI 4.1–57.36).

Conclusions. In conclusion, the EDOU serves a vital role in providing both observation and treatment for pyelonephritis patients, with shorter hospital stays compared to traditional wards. This contributes to optimizing patient care and resource utilization in the management of acute medical conditions.

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