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Keywords: duration, catheter, intravenous, PICC, CVC, MDRO, multidrug resistance

Article

Differences in the Duration of Peripherally Inserted Central Catheter Placement Leading to CLABSI Versus Colonization by Multi-Drug Resistant Pathogens: A Single Centre Retrospective Cohort Study

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Abstract: Background: While it is established that intravenous catheter placement duration is strongly linked to the risk of catheter colonization and bloodstream infections, there are still substantial knowledge gaps concerning the varying durations of PICC placement that lead to either infection or colonization by common pathogens, particularly MDR pathogens. The present study aims to compare the dwell time required for MDR pathogens to colonize with the time required to cause Central Line-Associated Bloodstream Infections (CLABSIs) in critically ill patients with PICCs and compares it with non-MDR pathogens, shedding light on the significance of preventive procedures to control MDR infections in clinical settings. **Methods:** Data from critically ill patients with PICCs admitted consecutively to «Metropolitan» Hospital in Athens, Greece, from May 2017 to May 2020 were retrospectively analysed. **Results:** In this study, 86 hospitalized patients, consisting of 56 (65.1%) males and 30 (34.9%) females, with a mean age of 55.67±21.1 years (range 16-91 years), presented with both CLABSIs and colonization following PICC placements. Specifically, 42 (48.8%) of them presented with CLABSIs, while 44 (51.2%) presented with colonization. Among the total participants, an MDR pathogen was isolated from 26 (30.2%) PICCs, while other pathogens were isolated from 60 (69.8%). The mean duration of catheter dwell time for all participants was 20.94±14.22 days (range 3-72 days). When analysed separately for each group, the dwell time for PICCs with CLABSIs was 25.73±16.19 days and 16.36±10.28 days for those with colonization (T test, p=0.002). Additionally, the mean dwell time for PICCs infected by non-MDROs was 22.48±15.64 days whereas for PICCs with MDROs, it was 17.38±9.5 days (T test, p=0.005). In PICCs with CLABSIs, the mean indwelling time for MDR pathogens was 21.50±12.31 days, while for non-MDROs, it was 27.73±16.98 days (T test, p=0.417). In PICCs with colonization, the mean dwell time for MDR pathogens was 15.55±7.73 days, while for non-MDROs, it was 16.92±11.85 days (T test, p=0.124). Among PICCs with MDR pathogens (n=26), the mean duration in CLABSIs events (n=18) was 21.5±12.31 days and in colonization events 15.55±7.73 days, (n=8) (T test, p=0.146). **Conclusions:** The present study reveals that colonization of PICCs exhibited a shorter dwell time compared to those with CLABSIs. Moreover, PICCs infected by MDROs had a shorter mean dwell time than those with non-MDROs. These findings underscore the importance of considering infection status and microbial resistance patterns when evaluating PICC dwell times.

Keywords: duration; catheter; intravenous; PICC; CVC; MDRO; multidrug resistance

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1. Introduction

The use of peripherally inserted central catheters (PICCs) has become increasingly prevalent in modern medical practice. This popularity can be attributed to several factors, such as their ease of insertion, versatility in applications including medication administration and venous access, perceived safety, and cost-effectiveness compared to other central venous catheters (CVCs) [1,2]. Moreover, the establishment of nursing-led PICC teams has facilitated their widespread use across various healthcare settings [3].

However, despite the numerous advantages [4–6] associated with PICCs compared to traditional central line catheters, they still carry a notable risk of catheter-related infections, which can lead to serious complications and compromise patient outcomes [7]. Moreover, with the emergence and spread of multi-drug resistant (MDR) pathogens, the occurrence and management of catheter-related infections has become increasingly challenging [8]. MDR organisms pose a significant threat to patient safety and healthcare systems globally, requiring close surveillance and stringent infection control measures.

One crucial factor influencing the risk of CLABSI is the duration of catheter placement [9–11]. This risk stems from various factors, including the potential for biofilm formation on the catheter surface, which provides a favourable environment for bacterial colonization and subsequent bloodstream infection. On the other hand, colonization of catheters without subsequent bloodstream infection is also a concern, as it can serve as a precursor to central line-associated bloodstream infections if the microorganisms gain access to the bloodstream.

Previous studies suggest that the risk of colonization also increases with prolonged catheter dwell times [12,13].

Building on this information, our recently published research [14] comparing the indwelling time of CVC and PICC placements leading to microbial colonization by MDROs in critically ill patients has shown that the indwelling time of PICC colonization rate was considerably lower than CVCs, while MDROs arose later during catheterization in PICCs compared to CVCs. In this context, significant knowledge gaps remain regarding the duration of PICC placement leading to either infection or colonization by common pathogens, and most importantly by MDR pathogens.

To address this critical gap in knowledge, the present study conducted a single-center retrospective cohort analysis to investigate differences in the duration of PICC placement leading to CLABSI versus colonization by MDR pathogens in critically ill patients. Furthermore, it aims to compare these findings with infections caused by non-MDR pathogens, offering insights into the dynamics of infection development and the complex interplay between pathogen colonization, infection development, and antimicrobial resistance, in order to highlight the importance of preventive measures in controlling MDR infections within clinical environments.

2. Methods

2.1. Study Design

We conducted a retrospective analysis of data from consecutive admissions of critically ill patients at Metropolitan Hospital, a tertiary care private hospital in Athens, Greece, spanning from May 2017-May 2020. Data collection involved the utilization of a check-box form following catheter insertion to document various details, including the patient's diagnosis, the operator's name, chosen site, insertion and removal dates, ICU discharge or death dates, use of mechanical ventilation, arterial catheters, parenteral nutrition, vasopressor support, and daily clinical assessments for potential catheter-related infections (e.g., induration, discharge, erythema, and tenderness). Initial data entry was conducted by the catheter-inserting operator, with subsequent entries made by nursing personnel on subsequent days. Monitoring of data collection occurred by the infection control nurse 3–4 times per week. Data were retrospectively collected from three sources: (1) the ICU database, providing demographic and clinical data related to patient admission and clinical course; (2) the clinical laboratory; and (3) the hospital infection control team database. Ethical approval for this observational study was obtained from the hospital's institutional review board.

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2.2. Catheter Care

Highly skilled nursing personnel proficient in all facets of catheter care maintained standardized catheter care protocols. To reduce the risk of dressing contamination, thorough visualization of all insertion sites was conducted. Dressings were replaced every few days or more frequently as deemed clinically necessary. Nursing staff utilized iodine solution to cleanse the skin site and catheter hub during dressing changes and also replaced the intravenous accessory tubing. Moreover, strict adherence to sterile insertion techniques was observed by the nursing staff.

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2.3. Indications for Catheter Removal

Catheters were removed in the following circumstances: (a) suspicion of infection, (b) when no longer needed.

2.4. Culture Techniques

All catheters were subjected to pathogen examination either routinely after removal or if infection was suspected. The process involved disinfecting the skin around the catheter entry site followed by excising the proximal 4–5 cm portion of the tip using sterile scissors. The excised specimen was then placed in a sterile container and promptly transported to the microbiology laboratory within 15 minutes at room temperature. Analysis of both the intradermal and intravascular portions of the catheter was conducted using the semiquantitative culture technique described by Maki et al. [15]. According to this technique, a positive catheter tip culture was defined as the presence of ≥15 colony-forming units (CFUs) of any organism. Blood cultures were incubated in aerobic and anaerobic broth media using the Becton Dickinson BACTEC system. Identification of isolates and determination of antimicrobial resistance patterns were performed using the VITEK®2 Automated Compact System. Additionally, an E-test was conducted to confirm resistance phenotypes reported by the VITEK System, following standard laboratory procedures.

2.5. Definitions

Definitions used in the study were as follows:

Peripherally inserted central catheters (PICCs) were categorized as catheters inserted into the basilic, cephalic, or brachial veins of the upper extremities, with tips terminating in the superior vena cava or right atrium.

Multidrug-resistant organisms (MDROs) were identified as microorganism species exhibiting antimicrobial resistance to at least one antimicrobial drug in three or more antimicrobial categories. This definition encompassed both Gram-positive and Gram-negative bacteria.

Catheter-associated bloodstream infection (CLABSI) was defined as a laboratory-confirmed bloodstream infection (a positive blood culture with no other apparent source of infection) occurring in the presence of a CVC or within 48 hours of CVC removal.

Catheter colonization was considered the presence by a semi-quantitative culture of ≥15 CFU of at least a single organism per catheter, according to Maki.[15]

3. Results

3.1. Participants Characteristics

A total of 86 patients underwent PICC catheterization during their hospital stay, comprising 56 (65.1%) males and 30 (34.9%) females, with a mean age of 55.6 +/- 21.1 years (ranging from 20 to 92 years). Out of these, 44 (51.2%) developed CLABSIs, while 42 (48.8%) were colonized. Among all isolates, 60 (69.8%) were non-MDROs and 26 (30.2%) were MDROs. The average duration of catheterization was 20.94 ± 14.22 days (ranging from 3 to 72 days). The detailed clinical characteristics of the patients are outlined in Table 1.

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Table 1. Study populations' demographic and clinical characteristics upon admission and during hospital stay.

Patients' characteristics (n=86)	N (%)
Respiratory disorders	23 (26.7)
Diabetes mellitus	20 (23.2)
Hypertension	48 (55.8)
Cerebrovascular diseases	40 (46.5)
Gastrointestinal disease	19 (22)
Kidney disease	18 (20.9)
Oncological Disorders	20 (23.2)
Cardiovascular disease	25 (29.0)
Immune deficiency/ suppression	45 (52.3)
During hospital stay	
ICU admission	50 (58.1)
Total parenteral nutrition	35 (40.7)
Mechanical ventilation	31 (36.0)
Death	15 (17.4)
Sepsis	15 (17.4)
APACHE II at inclusion (mean +/- SD)	12.9+/- 7.5

3.2. Comparison of the Duel Times between PICCs Subgroups

When analysed separately for each group, the dwell time for PICCs with CLABSIs was 25.73±16.19 days and 16.36±10.28 days for those with colonization (T test, p=0.002). Additionally, the mean dwell time for PICCs infected by non-MDROs was 22.48±15.64 days whereas for PICCs with MDROs, it was 17.38±9.5 days (T test, p=0.005). In PICCs with CLABSIs, the mean indwelling time for MDR pathogens was 21.50±12.31 days, while for non-MDROs, it was 27.73±16.98 days (T test, p=0.417). In PICCs with colonization, the mean dwell time for MDR pathogens was 15.55±7.73 days, while for non-MDROs, it was 16.92±11.85 days (T test, p=0.124). Among PICCs with MDR pathogens (n=26), the mean duration in CLABSIs events (n=18) was 21.5±12.31 days and in colonization events 15.55±7.73 days, (n=8) (T test, p=0.146).

3.3. MDRO Identification and Distribution in PICCs with CLABSIs and PICCs with Colonization

Table 2. displays the microbial identification and distribution in PICC CLABSIs and ICCs colonization subgroups. Among total PICCs group, the most frequently isolated microorganisms were MDR *Klebsiella pneumoniae* (n=14, 16.3%) *Candida non-albicans* (n=8, 9.3%) MDR *Acinetobacter baumannii* (n=10, 11.6%) and *Candida albicans* (n=9, 10.4%). No notable differences in prevalence were observed among isolates from the CLABSIs group, including *Candida non-albicans*, MDR *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*, all sharing the same number of isolations. In the colonized PICC group, the three most frequent pathogens were MDR *Klebsiella pneumoniae* (n=10, 22.7%) which was the predominant microorganism isolated, followed by MDR *Acinetobacter baumannii* (n=8, 18.2%) and *Candida albicans* (n=6, 13.6%).

Table 2. Pathogen distribution among PICC CLABSI and colonization subgroups.

BACTERIA	CLABSI No (%)	COLONIZATION No (%)
Candida albicans	3 (7.1)	6 (13.6)
Candida non-albicans	4 (9.5)	4 (9.1)
CnS	3 (7.1)	2 (4.5)
Enterococcus faecalis	2 (4.8)	-
Enterococcus faecium	-	4 (9.1)
Enterobacter cloacae	3 (7.1)	-

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Fungi	2 (4.8)	-
Klebsiella pneumoniae	4 (9.5)	-
Pseudomonas aeruginosa	4 (9.5)	2 (4.5)
Proteus mirabilis	1 (2.4)	2 (4.5)
MDR-Acinetobacter baumanni	2 (4.8)	8 (18.2)
MDR- Klebsiella pneumoniae	4 (9.5)	10 (22.7)
MDR- Pseudomonas aeruginosa	2 (4.8)	-
Staphylococcus aureus	4 (9.5)	-
MRSA	-	2 (4.5)
Staphylococcus haemolytic	2 (4.8)	2 (4.5)
Streptococcus salivarious	-	2 (4.5)
Serratia marcescens	2 (4.8)	-
Total	**42**	**44**

4. Discussion

To the best of the authors' knowledge, this is the first study to investigate variations in the duration of PICCs placement leading to CLABSI compared to colonization by MDR pathogens. Our findings suggest that PICCs infected by MDROs had a shorter mean dwell time than those with non-MDROs. Of particular interest is the identification of multi-drug resistant (MDR) pathogens in a substantial proportion of cases, accounting for approximately one-third of all isolated pathogens. This highlights the growing threat of antimicrobial resistance in healthcare settings and emphasizes the need for tailored treatment approaches and antimicrobial stewardship initiatives.

The analysis of dwell times for PICCs with CLABSIs and colonization reveals notable differences between the two groups, since PICCs associated with CLABSIs exhibited a longer mean dwell time compared to those with colonization, suggesting an association between prolonged catheterization and the development of bloodstream infections. This finding supports previous research indicating that a common etiology of CLABSI involves colonization of central venous catheters, potentially originating from the catheter hub or the surrounding skin [16,17]. Additionally, PICCs infected by MDR pathogens demonstrated a shorter mean dwell time compared to those with non-MDR pathogens. The same difference was exhibited when comparing the duration of catheter dwell time between PICCs infected with MDR and those infected with non-MDR pathogens separately in CLABSIs and colonization events, however not in a statistically significant level. While numerous studies have examined the connection between antimicrobial resistance and catheter-related infections, [18,19] it's worth noting that research in this area typically centers on overall infection rates, pathogen profiles, and risk factors. However, there is currently a lack of data specifically comparing dwell times between MDROs and non-MDROs.

Our research has demonstrated that the duration of PICCs placement plays a crucial role in the acquisition of MDR pathogens. Unlike conventional pathogens, which may require longer periods to colonize or infect the catheter, MDR pathogens seem to colonize and cause infection relatively quickly after catheter insertion. One possible explanation for the shorter duration of catheter placement for acquiring MDR pathogens is that these organisms may have a heightened ability to adhere to catheter surfaces and establish biofilms compared to other pathogens. Biofilm production has emerged as a potential virulence factor in various bacteria, gram-positives and gram- negatives, as well as fungal species (such as *Candida albicans* and non-albicans *Candida*), contributing to catheter colonization and catheter-related sepsis [20–22]. Especially in the case of *A. baumannii*, which emerged as the predominant MDR pathogen in our study, the chronicity and persistence of infections, coupled with its antibiotic resistance, are primarily associated with its ability to colonize and produce biofilms on diverse surfaces, including vascular catheters. [23,24] Moreover, biofilm-producing species have shown heightened resistance to multiple classes of antibiotics, [25,26] with a significant correlation observed between the capacity to form biofilms and antimicrobial resistance. This suggests a close association between microbial biofilm formation and multidrug resistance. The genetic mechanism underlying increased horizontal gene transfer, observed in both resistant bacteria and biofilm-

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producing bacteria, may serve as the foundation for this correlation. Another possible explanation for the observed associations between certain types of resistant organisms and shorter dwell times could be attributed to increased virulence or the efficacy of specific antibiotics in eliminating them. However, this association can be complex and influenced by various factors such as patient characteristics, antimicrobial usage, and infection prevention practices.

Moreover, our findings regarding the predominance of fungi in both colonization and CLABSI subgroups is concerning. *Candida* species represent a substantial portion of the isolates, pointing to the need for effective antifungal treatments. Despite their beneficial applications, venous catheters can increase the risk of fungal colonization, leading to local infections, venous inflammations, or, in rare cases, [27,28] disseminated infections. Invasive candidiasis remains a major cause of mortality among hospitalized patients [29] and is the fourth most common cause of hospital-acquired bloodstream infections in the United States [30]. While the rising prevalence of *Candida* bloodstream infections is largely linked to the use of CVCs, [31] often due to biofilm formation, [32] our findings also indicate a significant presence of these infections associated with PICCs.

Our study has specific limitations, the most significant of which is that it is subject to the general limitations of an observational design, implying the potential introduction of information bias.

5. Conclusions

In conclusion, our findings that the duration of catheter placement for acquiring MDR pathogens is shorter than acquiring other pathogens in PICCs highlights the need for proactive infection control measures and ongoing surveillance to minimize the risk of catheter-related infections. Our findings underscore the urgency of implementing stringent infection prevention and control measures from the moment of PICC insertion. Since MDR pathogens can colonize and cause infection relatively quickly, there is a narrow window of opportunity to prevent their transmission. Moreover, our study underscores the complex microbial landscape associated with PICC catheterization, highlighting the diversity of pathogens and the prominence of MDROs and Candida species. Future research efforts should focus on elucidating the specific mechanisms underlying biofilm formation by MDR pathogens and developing targeted interventions to disrupt biofilm formation and enhance catheter disinfection. Healthcare providers should balance the need for long-term intravenous access with the associated infectious risks, implementing strategies such as regular catheter site care, appropriate catheter removal when no longer needed, and adherence to evidence-based insertion and maintenance practices to mitigate these risks effectively.

Author Contributions: Vassiliki C. Pitiriga: Conceptualization, study design, Data analysis, Writing of the manuscript with input from all authors; **Elsa Campos:** Data collection and interpretation of results; **John Bakalis:** Data entry, Statistical analysis, and interpretation of results; **George Saroglou:** Writing – review & editing, Data analysis and interpretation of results; **Athanasios Tsakris:** Data analysis and interpretation of results, Writing – review & editing, Supervision. All authors have read and agreed to the published version of the manuscript.

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References

1. O'Grady NP, Alexander M, Dellinger EP, et al. Guidelines forthe prevention of intravascular catheter-related infections. Am J Infect Control 2002;30:476–489.2.
2. Mermel LA, Farr BM, Sherertz RJ, et al. Guidelines for the management of intravascular catheter-related infections. ClinInfect Dis 2001;32:1249–1272.

3. Safdar N, Maki DG. Risk of catheter-related bloodstream in-fection with peripherally inserted central venous catheters usedin hospitalized patients. Chest 2005;128:489–495.
4. Yamaguchi RS, Noritomi DT, Degaspare NV, Muñoz GOC, Porto APM, Costa SF, Ranzani OT. Peripherally inserted central catheters are associated with lower risk of bloodstream infection compared with central venous catheters in paediatric intensive care patients: a propensity-adjusted analysis. Intensive Care Med. 2017 Aug;43(8):1097-1104. https://doi.org/10.1007/s00134-017-4852-7. Epub 2017 Jun 5. PMID: 28584925.
5. Pitiriga V, Bakalis J, Theodoridou K, Kanellopoulos P, Saroglou G, Tsakris A. Lower risk of bloodstream infections for peripherally inserted central catheters compared to central venous catheters in critically ill patients. Antimicrob Resist Infect Control. 2022 Nov 9;11(1):137. https://doi.org/10.1186/s13756-022-01180-1. PMID: 36352414; PMCID: PMC9647909.
6. Evans M, Ryder MA. Invited Review: vascular access devices: perspectives on designs, complications, and management. Nutrition in Clinical Practice 1993;8:145–52.
7. Johansson E, Hammarskjöld F, Lundberg D, Arnlind H. Advantages and disadvantages of peripherally inserted central venous catheters (PICC) compared to other central venous lines: A systematic review of the literature. Taylor & Francis Online. 2013 Mar 11;52(5).
8. Pitiriga V, Bakalis J, Theodoridou K, Dimitroulia E, Saroglou G, Tsakris A. Comparison of microbial colonization rates between central venous catheters and peripherally inserted central catheters. Antimicrob Resist Infect Control. 2023 Aug 7;12(1):74. https://doi.org/10.1186/s13756-023-01285-1.
9. Lafuente Cabrero E, Terradas Robledo R, Civit Cuñado A, García Sardelli D, Hidalgo López C, Giro Formatger D, Lacueva Perez L, Esquinas López C, Tortosa Moreno A. Risk factors of catheter- associated bloodstream infection: Systematic review and meta-analysis. PLoS One. 2023 Mar 23;18(3):e0282290. https://doi.org/10.1371/journal.pone. 0282290. PMID: 36952393; PMCID: PMC10035840.
10. Sengupta A, Lehmann C, Diener-West M, Perl TM, Milstone AM. Catheter duration and risk of CLA-BSI in neonates with PICCs. Pediatrics. 2010 Apr;125(4):648-53. https://doi.org/10.1542/peds.2009-2559. Epub 2010 Mar 15. PMID: 20231192; PMCID: PMC4492110.
11. Pitiriga V, Bakalis J, Kampos E, Kanellopoulos P, Saroglou G, Tsakris A. Duration of central venous catheter placement and central line-associated bloodstream infections after the adoption of prevention bundles: a two-year retrospective study. Antimicrob Resist Infect Control. 2022 Jul 15;11(1):96. https://doi.org/10.1186/s13756-022-01131-w. PMID: 35841083; PMCID: PMC9284713.
12. Milstone AM, Reich NG, Advani S, Yuan G, Bryant K, Coffin SE, et al. Catheter dwell time and CLABSIs in neonates with PICCs: a multicenter cohort study. Pediatrics. 2013;132(6):e1609–15.
13. Dünser MW, Mayr AJ, Hinterberger G, Flörl CL, Ulmer H, Schmid S, Friesenecker B, Lorenz I, Hasibeder WR. Central venous catheter colonization in critically ill patients: a prospective, randomized, controlled study comparing standard with two antiseptic-impregnated catheters. Anesth Analg. 2005 Dec;101(6):1778-1784. https://doi.org/10.1213/01.ANE.0000184200.40689.EB. PMID: 16301258.
14. Pitiriga VC, Bakalis J, Campos E, Kanellopoulos P, Sagris K, Saroglou G, Tsakris A. Central Venous Catheters versus Peripherally Inserted Central Catheters: A Comparison of Indwelling Time Resulting in Colonization by Multidrug-Resistant Pathogens. Antibiotics (Basel). 2024 Jan 17;13(1):89. https://doi.org/10.3390/antibiotics13010089. PMID: 38247648; PMCID: PMC10812679.
15. Maki DG, Weise CE, Sarafin HW. A semiquantitative culture method for identifying intravenous-catheter-related infection. New Engl J Med. 1977;296:1305-1309.
16. N.P. O'Grady, M. Alexander, L.A. Burns, E.P. Dellinger, J. Garland, S.O. Heard, et al. Guidelines for the prevention of intravascular catheter-related infections. Am J Infect Control, 39 (2011), pp. S1-34.
17. E. Bouza, N. Alvarado, L. Alcala, M.J. Perez, C. Rincon, P. Munoz. A randomized and prospective study of 3 procedures for the diagnosis of catheter-related bloodstream infection without catheter withdrawal. Clin Infect Dis, 44 (2007), pp. 820-826.
18. W.-C. Liao, W.-S. Chung, Y.-C. Lo, W.-H. Shih, C.-H. Chou, C.-Y. Chen, C.-Y Tu, M.-W. Ho. Changing epidemiology and prognosis of nosocomial bloodstream infection: A single-center retrospective study in Taiwan. J. Microbiol. Immunol. Infect. (2021), 10.1016/j.jmii.2021.09.015
19. Bouhrour, N.; Nibbering, P.H.; Bendali, F. Medical Device-Associated Biofilm Infections and Multidrug-Resistant Pathogens. *Pathogens* 2024, *13*, 393. https://doi.org/10.3390/pathogens13050393
20. Li Y, Ni M. Regulation of biofilm formation in Klebsiella pneumoniae. Front Microbiol. 2023 Sep 7;14:1238482. https://doi.org/10.3389/fmicb.2023.1238482. PMID: 37744914; PMCID: PMC10513181.
21. Kreve S, Reis ACD. Bacterial adhesion to biomaterials: What regulates this attachment? A review. Jpn Dent Sci Rev. 2021 Nov;57:85-96. https://doi.org/10.1016/j.jdsr.2021.05.003. Epub 2021 Jun 12. PMID: 34188729; PMCID: PMC8215285.
22. Greene, C.; Vadlamudi, G.; Newton, D.; Foxman, B.; Xi, C. The influence of biofilm formation and multidrug resistance on environmental survival of clinical and environmental isolates of Acinetobacter baumannii. Am. J. Infect. Control. 2016, 44, e65–e71.

23. Yang, C.H.; Su, P.W.; Moi, S.H.; Chuang, L.Y. Biofilm formation in Acinetobacter Baumannii: Genotype-phenotype correlation. Molecules 2019, 24, 1849.
24. Ceparano, M.; Baccolini, V.; Migliara, G.; Isonne, C.; Renzi, E.; Tufi, D.; De Vito, C.; De Giusti, M.; Trancassini, M.; Alessandri, F.; et al. Acinetobacter baumannii Isolates from COVID-19 patients in a hospital intensive care unit: Molecular typing and risk factors. Microorganisms 2022, 10, 722.
25. Revdiwala S, Rajdev BM, Mulla S. Characterization of bacterial etiologic agents of biofilm formation in medical devices in critical care setup. Crit Care Res Pract. 2012;2012:945805.
26. Shin JH, Kee SJ, Shin MG, Kim SH, Shin DH, Lee SK, et al. Biofilm production by isolates of Candida species recovered from nonneutropenic patients: comparison of bloodstream isolates with isolates from other sources. J Clin Microbiol. 2002;40:1244–8.
27. Cateau E, Rodier MH, Imbert C. In vitro efficacies of caspofungin or micafungin catheter lock solutions on Candida albicans biofilm growth. J Antimicrob Chemother. 2008;62(1):153–5.
28. Letscher-Bru V, Herbrecht R. Caspofungin: the first representative of a new antifungal class. J Antimicrob Chemother. 2003;51(3):513–21.
29. Morgan J, Meltzer MI, Plikaytis BD, Sofair AN, Huie-White S, Wilcox S, et al. Excess mortality, hospital stay, and cost due to candidemia: a case-control study using data from population-based candidemia surveillance
30. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis. 2004;39(3):309–7.
31. de Grooth HJ, Timsit JF, Mermel L, et al. Validity of surrogate endpoints assessing central venous catheter-related infection: evidence from individual- and study-level analyses. Clin Microbiol Infect. 2019;26:563–571.
32. Cavalheiro M, Teixeira MC. *Candida* biofilms: Threats, challenges, and promising strategies. Front Med. 2018;5:28. https://doi.org/10.3389/fmed.2018.00028.