Asian Journal of Basic Science & Research
Volume 6, Issue 4, Pages 15-24, October-December 2024

Antimicrobial Resistance to Colistin in Neonatal Intensive Care Units: A Mini-review of Mechanisms, Clinical Implications, and Strategies for Mitigation

Lawal Oyebimpe M.[1*], Akindele Folasade D.[2], Oluborode Ayomide V.[3], Olowe Niyi E.[4], Ajudua, Sharon C.[5], Babalola Gbenga J.[3], Ajaero Ugochi C.[6], Nwachukwu, Uju B.[7] & Okolie Lucy J.[8]

[1]Department of Zoology (Parasitology), University of Ilorin, Nigeria. [2]Department of Community Medicine, Osun State University, Nigeria. [3]Department of Internal Medicine, Federal Medical Center, Abeokuta, Nigeria. [4]Department of Veterinary Public Health, University of Ibadan, Nigeria. [5]College of Medicine, University of Lagos, Nigeria. [6]Department of Treatment Services, AIDS Healthcare Foundation, Nigeria. [7]College of Medicine, University of Nigeria Teaching Hospital, Ituku-Ozalla, Nigeria. [8]Department of Microbiology, Alex Ekwueme Federal University, Ndufu-Alike, Nigeria. Corresponding Author Email: lawalmaryam167@gmail.com[*]

DOI: http://doi.org/10.38177/AJBSR.2024.6402

Article Received: 09 August 2024 *Article Accepted: 21 October 2024* *Article Published: 25 October 2024*

ABSTRACT

Colistin resistance poses significant concern in Neonatal Intensive Care Units (NICUs) due to both intrinsic and acquired mechanisms of resistance such as *mcr* genes and adaptive phenotypes including biofilm formation pathways. For neonates, reduced susceptibility to colistin makes its clinical relevance severe, which leads to high mortality and morbidity, and longer hospitalization. Colistin which is one of the used antibiotics has been observed to have low efficacy against multidrug-resistant pathogens such as *Klebsiella pneumoniae* and *Escherichia coli* in NICU for infection management. Major strategies for infection control measures include, the prudent use of antibiotics and exploration for other alternatives like new molecules and bacteriophage. Future directions call for the development of new antibiotics effective against resistant strains, as the current pharmaceutical pipeline for neonates is inadequate. Further advancement in the application of rapid diagnostics could help with individualized therapies according to the resistance patterns, though the problem of cost and accessibility still arises. Long-term monitoring for Antimicrobial resistance (AMR) should be conducted to assess the effectiveness of its interventions, while policy measures should foster international cooperation and data sharing. Continued studies and policy modifications are needed to tackle colistin resistance among neonates.

Keywords: Antimicrobial resistance; Antimicrobial stewardship; Biofilms; Clinical implications; Colistin; Gram-negative bacteria; MCR genes; Multidrug-resistant; Neonatal intensive care units; Nosocomial pneumonia.

1. Introduction

Antimicrobial resistance (AMR) is a challenging issue in the national and global arena especially in human healthcare facilities where antibiotic therapies are frequently applied. According to WHO, AMR is as one of the most critical and emerging global health challenges, which have been worsened by misuse or overuse of antibiotic. Hospital-acquired infections remain a major concern, especially in the Intensive Care Units where liberal use of broad-spectrum antibiotics has resulted to increased emergence and spread of resistant bacteria. These resistant pathogens include Methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant *Pseudomonas aeruginosa* causing severe infections that are hard to manage, therefore, increasing the number of hospital days, hospital costs, and mortality (Waele et al., 2018). Besides the mentioned clinical impacts, AMR also results in increased financial burden to the health care systems since the focus is geared towards the use of more expensive and toxic antibiotics, not forgetting the costs incurred to implement measures to control the spread of resistant bacteria such as isolation (Mohsen et al., 2017). The emergence of the multidrug-resistant organisms makes the challenge even worse since there are few available treatments that physicians can prescribe to their patients (Ramirez & Cantey, 2019). Hence the need for antimicrobial stewardship programs (ASPs) to guide the use of antimicrobials to fight resistance and at the same time enhance patient outcomes (Ting et al., 2020).

Neonatal Intensive Care Units (NICUs) are especially at high risk of AMR because patients in them are often neonates with considerably compromised health and relatively high risk of infection. Newborns particularly

preterm or low birth weight infants are immunocompromised and are therefore at a higher risk of bacterial infections that needs antibiotics. Regular intake of antibiotics, especially for prophylactic purposes, contributes to the development of antibiotic resistant strains of bacteria making infections control a challenge especially for infants in NICU (Ahmed et al., 2018). This is worsened by the fact that there are few antibiotics available that are safe and effective for use in neonates especially when it comes to managing conditions caused by multidrug-resistant organisms (MDROs) (Liu et al., 2021). *Klebsiella pneumoniae* and *Escherichia coli*, which are top isolates in NICUs, for example, have been increasingly reported to be resistant to antibiotics belonging to the colistin group (Shah et al., 2022). The effects of AMR on NICUs health wise are severe as it leads to more deaths, longer hospitalization and high healthcare costs. To cope up with this challenge, enhanced infection prevention and control and provision of antimicrobial stewardship are important in the prevention of the spread of resistant bacteria and reduction of neonatal morbidity and mortality (Rallis et al., 2023).

1.1. Significance of Colistin

Colistin, otherwise referred to as polymyxin E, is one of the earlier administered antibiotics in the 1950s that was used in the treatment of infections by Gram-negative bacteria. However, because of the observed nephrotoxicity and neurotoxicity effects, colistin was rarely used in the 1970s when safer antibiotics were discovered. It has been used predominantly as topical administration or for cystic fibrosis patients suffering from chronic *Pseudomonas aeruginosa* infections for decades. With increasing reports of antibiotic resistance especially among gram-negative bacteria including *Acinetobacter baumannii, Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, colistin was again used in clinical practice for MDR infections (Li et al., 2006). Nevertheless, the re-emergence of colistin in the clinical setting underlined the importance of this antimicrobial agent against infections caused by MDR Gram-negative bacteria though with certain dangers (Loho & Dharmayanti, 2015). In the last few decades, colistin has gained renewed importance due to the absence of new antibiotics and the emergence of MDR pathogens in healthcare facilities (Karaiskos et al., 2013). The application of colistin however is associated with the problem of nephrotoxicity which needs constant observation and dose-interval adjustments, particularly in the cases of severely ill patients (Vu et al., 2022).

The epidemiologic shift of neonatal infections in the NICUs entails the emergence of MDR gram-negative bacteria for which colistin administration has become mandatory. Because of the appearance of pathogens such as *Acinetobacter baumannii* and *Klebsiella pneumoniae* which are resistant to many antibiotics, colistin plays a crucial role even with adverse effects (Çağan 2017). Colistin is usually prescribed in combination with other antibacterial agents, with the hope of increasing its efficiency and at the same time reducing the chances of resistance development. For instance, in NICUs, colistin is prescribed when there is no other antibiotic drug to prescribe because it is regarded as the last resort in treating serious infection in newborns (Nakwan et al., 2019). An application of colistin in NICUs proves the necessity for further investigation of the resistance patterns and the search for new strategies in MDR infections control (Ignak et al., 2020). Furthermore, the increasing use of colistin in NICUs may contribute to the risk of acquiring colistin-resistant strains that will further limit the management of MDR infections in neonates (El-Mokhtar et al., 2021).

1.2. Study Objectives

The following are the objectives of this study: (1) to identify the mechanisms underlying colistin resistance in Neonatal Intensive Care Units (NICUs), (2) to assess the role of colistin as a last-resort antibiotic in the treatment of multidrug-resistant infections in neonates, (3) to explore the clinical consequences of colistin antimicrobial resistance on neonatal health, (4) to investigate preventive strategies and measures to mitigate colistin-resistant strains in NICUs, and (5) to review the impact of increased colistin use on the emergence of colistin-resistant bacteria in NICUs.

2. Mechanisms of Colistin Resistance in Neonatal Pathogens

2.1. Intrinsic Resistance

The intrinsic resistances to colistin include *Proteus mirabilis*, *Burkholderia cepacia* and *Neisseria meningitidis* species which modify their lipopolysaccharides (LPS) through the addition of 4-amino-4-deoxy-L-arabinose (L-Ara4N) or phosphoethanolamine (pEtN), which reduces the binding site affinity of colistin (Gogry et al., 2021). Other species such as *Hafnia alvei* display intrinsic resistance due to the changes in outer membrane glycosides (Turbett et al., 2023), while *Proteus vulgaris* acquires resistance by mutations in the arn operon to allow the addition of L-Ara4N to lipid A (Baron et al., 2017). Such mechanisms explain the challenges of managing infections with intrinsically resistant bacteria mainly within NICU, as highlighted by Rallis et al. (2018).

2.2. Acquired Resistance

The primary source for acquired colistin resistance in bacterial pathogens particularly in neonatal intensive care unit is through genetic mutation affecting antibiotic target. One of them is the mcr genes that encode enzymes that affect the lipid A part of lipopolysaccharides (LPS), thereby decreasing the efficacy of colistin. The first reported mcr gene was mcr-1 which was detected in *Escherichia coli* in 2015 signalling the presence of plasmid mediated colistin resistance (Liu et al., 2015). Since then other mcr variants ranging from mcr-2 to mcr-10 have been identified in different bacterial species (Mello et al., 2018). Many of these genes are found on plasmids that enhance horizontal gene transfer (HGT) among bacteria (Brauer et al., 2016). This accelerated rate of colistin resistance especially in NICUs remains a major threat to public health because these plasmids can become integrated into bacterial chromosome and thus remain resistant even in the absence of selective pressures (Borowiak et al., 2017; Carroll et al., 2019).

2.3. Adaptive Resistance

Adaptive resistance of microbes in NICU pathogens entails biochemical pathways which are initiated by the presence of factors such as antibiotic pressure. While permanent resistance is long-standing, adaptive resistance occurs temporarily but may have a huge effect on the treatment outcomes. Stress-triggered mechanisms involve the action of some efflux pumps such as the AcrAB-TolC in *Escherichia coli* that ejects antibiotics from bacterial cells thus decreasing their efficiency (Li et al., 2015). Bacteria also change their membrane permeability depending on stress where modification of the lipid A profile of *Pseudomonas aeruginosa* reduces colistin's binding affinity (Baron et al., 2016). Another adaptive mechanism that is attributed to resistance in NICUs is biofilm formation.

Biofilms are complex organized community of bacterial cells embedded in a protective self-produced matrix attached to a substrate for example a medical device. Such a matrix shields bacteria against antibiotics and the immune system, resulting in chronic infections and reservoirs of resistant bacteria (Donlan, 2001). Several pathogens including *Staphylococcus aureus* and *Pseudomonas aeruginosa* are known to form biofilms within NICU hence complicating the management of infections and increasing the risk of recurrent infections (Vuotto et al., 2014).

3. Clinical Implications of Colistin Resistance in NICUs

3.1. Epidemiology of Colistin-Resistant Infections

Colistin-resistant pathogens are increasingly becoming prevalent in NICUs across the globe, particularly in areas with high incidences of AMR. In India, a retrospective study pointed out that 30% of *Klebsiella pneumoniae* isolated in NICU were resistant to colistin thus showing the emergence of resistance was a growing issue in South Asia (Shah et al., 2022). Likewise, a multicenter study conducted in China showed that a large percentage of cases of neonatal bloodstream infections were due to colistin-resistant *K. pneumoniae* and *E. coli*, and these rates were significantly different across different regions and NICUs (Liu et al., 2021). In Vietnam, colistin resistance has also been reported in the nosocomial pathogens in NICUs, particularly *K. pneumoniae* making the situation even worse when finding an appropriate strategy for treatment (Berglund et al., 2018). These studies suggest that colistin resistance is not only prevalent in a certain region, but has become a threat to neonatal health around the world.

In NICUs, the rates of colistin resistance have been rising in the past decade with an observable trend in many areas. A research study done in the United States on *Escherichia coli* that was isolated from NICUs between 2009 and 2017 revealed fairly constant yet high rates of antibiotic non-susceptibility including colistin resistance (Flannery et al., 20201). In Turkey, a 10-year meta-analysis has shown an increasing trend of resistance rates among the *Pseudomonas aeruginosa* isolates in the ICUs including resistance to colistin, which also pointed to a broader trend of the increasing resistance in critical care settings (Acar et al., 2019). Furthermore, a study in Vietnam, of carbapenem-resistant *Klebsiella pneumoniae* identified colistin resistance, although rare, was present and could rise with antibiotic pressure (Peters et al., 2019). These reports collectively stress the apparent need for constant monitoring and intervention measures aimed at containing the spread of colistin-resistant pathogens in NICU settings.

3.2. Impact on Neonatal Outcomes

More recently, increased instances of colistin-resistant infection are being recorded in NICUs and a few strong evidences have been enlisted in Table 1. In India, the case of colistin-resistant carbapenemase-producing *Klebsiella pneumoniae* was detected in five out of seven NICU neonates. Major consideration was given to early detection of cases, standard isolation measures, as well as environmental inspection to avoid deterioration of such events (Pathak et al., 2023). Similarly, in Pakistan *Klebsiella pneumoniae* and other Gram-negative bacteria were noted to cause increased mortality, especially among the neonates. The study also highlighted the need to take a rational approach in the use of colistin, especially in combination with other antimicrobials to ensure the patients benefit from it (Ambreen et al., 2020). *Burkholderia cepacia* and extended-spectrum beta-lactamase (ESBL) producing

Klebsiella pneumoniae have been noted to cause outbreaks in The Gambia through contaminated intravenous fluids and antibiotics respectively and hence, constant monitoring and genomic sequence analysis should be done to confirm the source of the infections as mentioned in the study by Okomo et al. (2020). The levels of antimicrobial resistance were also revealed in South Africa where 53 neonates got colistin-resistant carbapenemase-producing *Enterobacterales* infection that resulted in high rates of mortality as mentioned by Abrahams et al. (2023), which further confirmed the importance of implementing effective infection control measures as well as optimizing the antibiotics prescribing practices. Furthermore, Nosocomial pneumonia due to *Escherichia coli* in neonates in Egypt also reveals the need for enhanced surveillance and accurate diagnostic methods in a shorter period (El-Mokhtar et al., 2021).

Table 1. Summary of Selected Case Studies

Author(s) & Year	Location	Pathogen	Details of Outbreak	Lessons Learned
Pathak et al., 2023	India	*Klebsiella pneumoniae*	Outbreak of colistin-resistant, carbapenemase-producing *Klebsiella pneumoniae* in a NICU, affecting 5 out of 7 neonates.	Early detection, strict infection control measures, and environmental screening are crucial in containing such outbreaks.
Ambreen et al., 2020	Pakistan	*Klebsiella pneumoniae* and other Gram-negative bacteria	Colistin-resistant infections in neonates led to increased mortality and complications, highlighting the limited treatment options available in NICUs.	Early and appropriate use of colistin in combination with other antibiotics may improve outcomes, but requires careful monitoring of adverse effects.
Okomo et al., 2020	The Gambia	*Burkholderia cepacia* and *Klebsiella pneumoniae*	Sequential outbreaks of *Burkholderia cepacia* and ESBL-producing *Klebsiella pneumoniae* in a NICU, linked to contaminated IV fluids and antibiotics.	Genomic analysis identified the sources of outbreaks, highlighting the need for regular monitoring and strict clinical practices.
Abrahams et al., 2023	South Africa	*Enterobacterales* (CRE)	Outbreak of colistin-resistant, carbapenemase-producing *Enterobacterales* in a NICU, involving 53 neonates.	Colistin was used safely, but high mortality rates necessitate urgent infection control measures and better antibiotic stewardship.
El-Mokhtar et al., 2021	Egypt	*Escherichia coli*	Emergence of colistin-resistant *Escherichia coli* causing nosocomial pneumonia in neonates, with high morbidity.	Highlighted the need for enhanced surveillance and rapid diagnostics to manage resistant infections effectively in NICUs.

4. Strategies for Mitigating Colistin Resistance in NICUs

Overcoming colistin resistance in NICUs cannot be achieved solely through infection control measures without addressing the corresponding antibiotic stewardship or therapeutic interventions. Basic precautions and measures like wearing of gloves, hand washing, disinfection of objects and surfaces, and isolation of carriers are very crucial in preventing the spread of resistant bacteria. However, the sustainability of these practices rely on compliance of the healthcare workers and constant supervision. Antibiotic stewardship programs are equally as important in avoiding the overuse and misuse of colistin, but these programs face challenges such as timing to give effective treatment with the risk of propagating resistance. Despite these, antibiotic stewardship has achieved a certain measure of success, although its effectiveness may be hampered by factors like delays in access to diagnostics, which often lead to the use of empiric antibiotics that are mostly broad-spectrum in nature.

In addition to traditional approaches, obtaining the best results from pharmaceutical therapy and identifying novel therapeutic approaches to combat colistin-resistant bacteria deserves attention. Colistin in combination with other antibiotics has also been observed to be effective though a major drawback is seen in the toxicity of colistin and the

development of resistance to other antibiotics that are combined with colistin. Novel antibiotics and non-antibiotic therapies like bacteriophages and CRISPR-Cas9 technology offer promising outcomes, but clinical approaches are still in the developmental stage and are surrounded by implementation challenges. However, phage therapy and gene editing methods need to overcome the problem of specificity, routes of administration, and questions regarding their long-term efficacy to become part of the standard of care for the NICU.

4.1. Research Gaps

There is a significant research gap in the development of new antibiotics that can target colistin-resistant strains among NICU patients. Despite some novel antimicrobials being under development, others take years to be approved and their long-term efficacy and safety for use among neonates remains uncertain. It is therefore necessary to have effective antibiotics that could either substitute for colistin or complement its use. Although pharmaceutical pipelines for neonates still seem scarce, high costs and inherent difficulties in devising the drugs are some of the reasons why the development has been slow. Furthermore, new strategies such as host-directed therapies and immune-modulators are only theoretical at the moment, and clinical evidence is insufficient to integrate them into practice. Another important area of focus is the rapid detection of resistance since this has major implications for treatment regimens. Conventional strategies to assess the cause of the disease are time-consuming and hence do not enable commencement of the right treatment which hastens the development of resistant infections.

5. Conclusion

The present review shows that colistin resistance in NICUs results from chromosomally mediated determinants such as *mcr* genes and other distinct processes including biofilm formation and stress-induced resistance. In clinical practice, colistin-resistant infections in neonates are associated with higher mortality, longer length of hospitalization, and limited therapeutic options for clinicians. This study outlined key mitigation measures such as infection prevention and control measures, the utilization of antibiotics, combination therapy, and the search for new classes of antimicrobial agents or non-antibiotic therapeutic agents. Based on the findings from this study, NICU-acquired colistin resistance must be tackled to enhance neonatal prognosis and contain AMR in the most susceptible demographic group. Because of the immature immune system of neonates, colistin resistance reduces treatment's efficacy in severe infections, thus demanding attention from clinicians and public health experts. Further studies about new antimicrobials, new rapid diagnostic methods, and therapeutic strategies are required urgently. Also, international cooperation is needed for policies, and putting better surveillance systems in place. In particular, these strategies are recommended regarding colistin resistance in neonates, where coordinated scientific, political, and clinical approaches should be a priority on the global agenda.

6. Future Suggestions

Some solutions have been recommended and may include next-generation sequencing as well as the use of CRISPR-based diagnostics that can help identify resistant pathogens in a shorter period. Such developments might help to use targeted therapies for certain diseases by matching them to the resistance patterns of the infections. However, integrating such diagnostics in NICUs presents some difficulty because of high expenses, restricted use

of technology, and specialized craftsmanship. The specific pattern of NICU antimicrobial resistance requires sustained, long-term monitoring of many healthcare institutions performing suboptimal AMR surveillance. It also becomes challenging to monitor the dynamics of resistance, evaluate the effectiveness of measures taken in controlling resistance and forecast potential dangers. International collaboration is also essential in tackling AMR, especially in the developing world where colistin resistance is quickly emerging but the surveillance and control measures are scarce. Among the policy implications are enhanced cooperation between countries, data exchange, and an integrated set of protocols for using antimicrobials in neonates. Additionally, creating better conditions for developing new pharmaceuticals, with the help of reforms in the national legislation, may contribute to developing new methods for fighting resistant infections.

7. Abbreviations

AMR - Antimicrobial Resistance; ASPs - Antimicrobial stewardship programs; ESBL - Extended-spectrum beta-lactamase; HGT - Horizontal gene transfer; ICU - Intensive Care Units; LPS - Lipopolysaccharides; MDR - Multidrug-resistant; MDROs - Multidrug-resistant organisms; MRSA - Methicillin-resistant *Staphylococcus aureus;* NICU - Neonatal Intensive Care Units.

Declarations

Source of Funding

This study did not receive any grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing Interests Statement

The authors declare no competing financial, professional, or personal interests.

Consent for publication

The authors declare that they consented to the publication of this study.

Authors' contributions

Conceptualization: LOM.; Writing – original draft: LOM., AFD., OAV., ONE., ASC., BGJ., AUC., NUB., OLJ.; Data extraction: LOM and OLJ.; Writing – review – editing: LOM., AFD., OAV., ONE., ASC., BGJ., AUC., NUB., OLJ.

References

Abrahams, I., Dramowski, A., Moloto, K., Lloyd, L., Whitelaw, A., & Bekker, A. (2023). Colistin use in a carbapenem-resistant Enterobacterales outbreak at a South African neonatal unit. Southern African Journal of Infectious Diseases, 38(1): 487. https://doi.org/10.4102/sajid.v38i1.487.

Acar, A., Karaahmetoglu, G., Akalın, H., & Altay, A.F. (2019). Pooled prevalence and trends of antimicrobial resistance in *Pseudomonas aeruginosa* clinical isolates over the past 10 years in Turkey: A meta-analysis. Journal of Global Antimicrobial Resistance, 18: 64–70. https://doi.org/10.1016/j.jgar.2019.01.032.

Ahmed, F., Raj, A., Nahar, L., & Hasan, Z. (2018). Antimicrobial resistance of bacterial pathogens in a Neonatal Intensive Care Unit. Bangabandhu Sheikh Mujib Medical University Journal, 11: 25–28. https://doi.org/10.3329/bsmmuj.v11i1.35133.

Ambreen, G., Salat, S.M., Hussain, K., Raza, S.S., Ali, U., Azam, I., Iqbal, J., & Fatmi, Z. (2020). Efficacy of colistin in multidrug-resistant neonatal sepsis: experience from a tertiary care center in Karachi, Pakistan. Journal of Infectious Diseases, 105(9): 830–836. https://doi.org/10.1136/archdischild-2019-318067.

Baron, S., Hadjadj, L., Rolain, J.M., & Olaitan, A.O. (2016). Molecular mechanisms of polymyxin resistance: Knowns and unknowns. International Journal of Antimicrobial Agents, 48(6): 583–591. https://doi.org/10.1016/j.ijantimicag.2016.06.023.

Baron, S., Leulmi, Z., Villard, C., Olaitan, A., Telke, A., & Rolain, J. (2017). Inactivation of the arn operon and loss of aminoarabinose on lipopolysaccharide as the cause of susceptibility to colistin in an atypical clinical isolate of *Proteus vulgaris*. International Journal of Antimicrobial Agents, 51(3): 450–457. https://doi.org/10.1016/j.ijantimicag.2017.11.017.

Berglund, B., Hoang, N.T., Tärnberg, M., Le, N., Welander, J., Nilsson, M., Khu, D., Nilsson, L., Olson, L., Le, H.T., & Larsson, M. (2018). Colistin- and carbapenem-resistant *Klebsiella pneumoniae* carrying *mcr-1* and blaOXA-48 isolated at a paediatric hospital in Vietnam. Journal of Antimicrobial Chemotherapy, 73(4): 1100–1102. https://doi.org/10.1093/jac/dkx491.

Borowiak, M., Fischer, J., Hammerl, A.J., Hendriksen, S.R., Szabo, I., & Malorny, B. (2017). Identification of a novel transposon-associated phosphoethanolamine transferase gene, *mcr-5*, conferring colistin resistance in d-tartrate fermenting *Salmonella enterica subsp. Enterica serovar paratyphi B.* J Antimicrob Chemother, 72(12): 3317–3324. https://doi.org/10.1093/jac/dkx327.

Brauer, A., Telling, K., Laht, M., Kalmus, P., Lutsar, I., Remm, M., Kisand, V., & Tenson, T. (2016). Plasmid with colistin resistance gene *mcr-1* in extended-spectrum-β-lactamase-producing *Escherichia coli* strains isolated from pig slurry in Estonia. Antimicrobial Agents and Chemotherapy, 60: 6933–6936. https://doi.org/10.1128/aac.00443-16.

Çağan, E., Kıray Baş, E., & Asker, H. (2017). Use of colistin in a Neonatal Intensive Care Unit: A cohort study of 65 patients. Medical Science Monitor: International Medical Journal of Experimental and Clinical Research, 23: 548–554. https://doi.org/10.12659/msm.898213.

Carroll, L., Gaballa, A., Guldimann, C., Sullivan, G., Henderson, L., & Wiedmann, M. (2019). Identification of novel mobilized colistin resistance gene mcr-9 in a multidrug-resistant, colistin-susceptible *Salmonella enterica* serotype Typhimurium isolate. mBio, 10(3). https://doi.org/10.1128/mbio.00853-19.

Donlan, R.M. (2001). Biofilms and device-associated infections. Emerging Infectious Diseases, 7(2): 277–281. https://doi.org/10.3201/eid0702.010226.

El-Mokhtar, M.A., Daef, E., Hussein, A., Hashem, M., & Hassan, H. (2021). Emergence of nosocomial Pneumonia caused by colistin-resistant *Escherichia coli* in patients admitted to Chest intensive care unit. Egyptian Journal of Clinical Microbiology, 10(3): 226. https://doi.org/10.3390/antibiotics10030226.

Flannery, D., Akinboyo, I.C., Mukhopadhyay, S., Tribble, A., Song, L., Chen, F., Gerber, J., & Puopolo, K. (2021). Antibiotic susceptibility of *Escherichia coli* among infants admitted to NICUs across the United States from 2009 to 2017. Jama Pediatrics, 175(2): 168–175. https://doi.org/10.1001/jamapediatrics.2020.4719.

Gogry, F., Siddiqui, M., Sultan, I., & Haq, Q. (2021). Current update on intrinsic and acquired colistin resistance mechanisms in bacteria. Frontiers in Medicine, 8. https://doi.org/10.3389/fmed.2021.677720.

Ignak, S., Coskun, Y., Yalcin, D., & Akman, İ. (2020). The efficacy and nephrological side effects of treatment with colistin in neonates. Anadolu Klinik, 25: 174–179. https://doi.org/10.21673/anadoluklin.680958.

Karaiskos, I., Galani, L., Baziaka, F., & Giamarellou, H. (2013). Intraventricular and intrathecal colistin as the last therapeutic resort for the treatment of multidrug-resistant and extensively drug-resistant *Acinetobacter baumannii* ventriculitis and meningitis: A literature review. International Journal of Antimicrobial Agents, 41(6): 499–508. https://doi.org/10.1016/j.ijantimicag.2013.02.006.

Li, J., Nation, R., Turnidge, J., Milne, R., Coulthard, K., Rayner, C., & Paterson, D. (2006). Colistin: The re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections. The Lancet Infectious Diseases, 6(9): 589–601. https://doi.org/10.1016/s1473-3099(06)70580-1.

Li, X.Z., Plésiat, P., & Nikaido, H. (2015). The challenge of efflux-mediated antibiotic resistance in Gram-negative bacteria. Clinical Microbiology Reviews, 28(2): 337–418. https://doi.org/10.1128/cmr.00117-14.

Liu, J., Fang, Z., Yu, Y., Ding, Y., Liu, Z., Zhang, C., He, H., Geng, H., Chen, W., Zhao, G., Liu, Q., Wang, B., Sun, X., Wang, S., Sun, R., Fu, D., Liu, X., Huang, L., Li, J., Xing, X., Wang, X., Gao, Y., Zhu, R., Han, M., Peng, F., Geng, M., & Deng, L. (2021). Pathogens distribution and antimicrobial resistance in bloodstream infections in twenty-five neonatal intensive care units in China, 2017–2019. Antimicrobial Resistance and Infection Control, 10. https://doi.org/10.1186/s13756-021-00989-6.

Liu, Y., Wang, Y., Walsh, T., Yi, L., Zhang, R., Spencer, J., Doi, Y., Tian, G., Dong, B., Huang, X., Yu, L., Gu, D., Ren, H., Chen, X., Lv, L., He, D., Zhou, H., Liang, Z., Liu, J., & Shen, J. (2015). Emergence of plasmid-mediated colistin resistance mechanism *MCR-1* in animals and human beings in China: A microbiological and molecular biological study. The Lancet Infectious Diseases, 16(2): 161–168. https://doi.org/10.1016/s1473-3099(15)00424-7.

Loho, T., & Dharmayanti, A. (2015). Colistin: An antibiotic and its role in multiresistant Gram-negative infections. Acta Medica Indonesiana, 47(2): 157–168. https://www.actamedindones.org/index.php/ijim/article/view/52.

Mello, M., Vieira, J., Simões, F., Freire, S., Moraes, R., & Pratte-Santos, R. (2018). Microbial resistance to colistin in consequence of mutations in the *MCR-1* gene of *Escherichia coli*. MOJ Public Health, 7. https://doi.org/10.15406/mojph.2018.07.00206.

Mohsen, L., Ramy, N., Saied, D., Akmal, D., Salama, N., Haleim, M., & Aly, H. (2017). Emerging antimicrobial resistance in early and late-onset neonatal sepsis. Antimicrobial Resistance and Infection Control, 6. https://doi.org/10.1186/s13756-017-0225-9.

Nakwan, N., Chokephaibulkit, K., & Imberti, R. (2019). The use of colistin for the treatment of multidrug-resistant Gram-negative infections in neonates and infants: A review of the literature. Pediatric Infectious Disease Journal, 38(11): 1107–1112. https://doi.org/10.1097/inf.0000000000002448.

Okomo, U., et al. (2020). Investigation of sequential outbreaks of *Burkholderia cepacia* and multidrug-resistant extended spectrum β-lactamase producing *Klebsiella species* in a West African tertiary hospital neonatal unit: A retrospective genomic analysis. The Lancet Microbe, 3: 119–129. https://doi.org/10.1016/s2666-5247(20)30061-6.

Pathak, S., et al. (2023). Outbreak of colistin-resistant carbapenemase-producing *Klebsiella pneumoniae* in a NICU. Frontiers in Cellular and Infection Microbiology, 13. https://doi.org/10.3389/fcimb.2023.1051020.

Peters, L., Olson, L., Khu, D., Linnros, S., Le, N., Hanberger, H., Hoang, N.T., Tran, D.M., & Larsson, M. (2019). Multiple antibiotic resistance as a risk factor for mortality and prolonged hospital stay: A cohort study among neonatal intensive care patients with hospital-acquired infections caused by gram-negative bacteria in Vietnam. PLoS ONE, 14(4): e0215666. https://doi.org/10.1371/journal.pone.0215666.

Rallis, D., Giapros, V., Serbis, A., Kosmeri, C., & Baltogianni, M. (2023). Fighting antimicrobial resistance in neonatal intensive care units: Rational use of antibiotics in neonatal sepsis. Antibiotics, 12(3): 508. https://doi.org/10.3390/antibiotics12030508.

Ramirez, C., & Cantey, J. (2019). Antibiotic resistance in the Neonatal Intensive Care Unit. NeoReviews, 20(3): e135–e144. https://doi.org/10.1542/neo.20-3-e135.

Shah, M., McAleese, S., Kadam, S., Parikh, T., Vaidya, U., Sanghavi, S., & Johnson, J. (2022). Emerging antibiotic resistance patterns in a neonatal intensive care unit in Pune, India: A 2-year retrospective study. Frontiers in Pediatrics, 10. https://doi.org/10.3389/fped.2022.864115.

Ting, J., Roberts, A., Tilley, P., Robinson, J., Dunn, M., Paquette, V., Lee, K., Shah, V., Yoon, E., Richter, L., Lodha, A., Shivananda, S., Thampi, N., Autmizguine, J., & Shah, P. (2020). Development of a national neonatal intensive care unit-specific antimicrobial stewardship programme in Canada: Protocol for a cohort study. BMJ Open, 10. https://doi.org/10.1136/bmjopen-2020-043403.

Turbett, S., Bronson, R., Worby, C., McGrath, G., Hodgkins, E., Becker, M., Belford, B., Kogut, L., Oliver, E., Ryan, E., Larocque, R., Earl, A., & Pierce, V. (2023). Intrinsic resistance to colistin in the genus *Hafnia*. Journal of Clinical Microbiology, 61. https://doi.org/10.1128/jcm.01326-22.

Vu, T., Dang, N., & Nguyen, T. (2022). An investigation on the use of colistin in critically ill patients at a teaching hospital in Ho Chi Minh City. Indonesian Journal of Pharmacy, 33: 4. https://doi.org/10.22146/ijp.4359.

Waele, J., Akova, M., Antonelli, M., Cantón, R., Carlet, J., Backer, D., Dimopoulos, G., Garnacho-Montero, J., Kesecioglu, J., Lipman, J., Mer, M., Paiva, J., Poljak, M., Roberts, J., Baño, J., Timsit, J., Zahar, J., & Bassetti, M. (2018). Antimicrobial resistance and antibiotic stewardship programs in the ICU: Insistence and persistence in the fight against resistance. A position statement from ESICM/ESCMID/WAAAR round table on multi-drug resistance. Intensive Care Medicine, 44: 189–196. https://doi.org/10.1007/s00134-017-5036-1.