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Editorial

Investigating outbreaks in neonatal intensive care units: A crucial battle in the cradle of care

Investigación de brotes en unidades de cuidados intensivos neonatales: una batalla crucial en la cuna de los cuidados

Progress in neonatal intensive care has significantly improved the survival rates of infants with extremely low birth weight and critical illnesses. However, these same advancements have paradoxically raised the risk of hospital-acquired infections (HAI). It becomes a true nightmare when these HAI evolve into outbreaks, impacting numerous infants simultaneously, especially considering they are entirely preventable. When such outbreaks take place in a Neonatal Intensive Care Unit (NICU), they can result in catastrophic consequences for the affected patients and cause considerable distress among the medical staff.[1]

In the current issue of Enfermedades Infecciosas y Microbiología Clínica, two outbreaks, that occurred in a NICU of the same hospital between 2019 and 2022, are reported.[2,3] Reading both publications consecutively reveals the commitment and systematic approach of a multidisciplinary team dedicated to addressing one of the most challenging situations in infection control: managing an outbreak.

The first article describes an outbreak of *Serratia marcescens* (SM).[2] Over 10 months, a total of 25 patients were identified (20 with infection and 5 colonized), the majority of whom had a mild infection (conjunctivitis), but nearly half suffered severe forms such as bacteremia or pneumonia. Fortunately, there were no deaths attributable to SM infection, yet the mortality rate in the cohort was 12%.

Pulsed-field gel electrophoresis allowed for the identification of a predominant pulsotype. All patient isolates, except for one, were identical to each other and matched one of the environmental isolates, which came from a sink used as a washbasin for incubators and other neonatal equipment.

Control measures were applied sequentially as new cases were added to the outbreak. The interventions that we might call "standard" (commonly applied in any type of outbreak, i.e., the formation of a multidisciplinary task force, screening of potential asymptomatic colonized individuals, contact precautions, cleaning, and reinforcement of hand hygiene) were not enough to control the outbreak. It was necessary the implementation of more comprehensive cleaning measures after a few months, the individual use of containers for sanitary products (eye drops and creams), and actions on the environment (changing of sink traps). Despite these sequential actions, cases continued to emerge. Eventually, it was necessary to reduce the nurse and auxiliar personnel ratio per neonate and increase the cleaning staff, likely highlighting the importance of cross-transmission through the hands of healthcare professionals and the environmental colonization.

The authors acknowledge that this was a prolonged outbreak with a high number of cases registered. Several factors could justify this: a late detection (the outbreak was identified when there were already 7 cases) and the absence of an identifiable source. The limited number of screening cultures performed is striking (only two rounds on 04/29 and 05/22). This low intensity in the search for colonized patients who could act as reservoirs may also partly explain the long duration of the outbreak.

The second article by the same group describes an outbreak caused by *Klebsiella oxytoca* (KO) and conducts a meta-analysis of 9 KO outbreaks in NICUs reported in the literature.[3] This time, the outbreak was controlled in just 5 months, affecting 6 children with infection and 15 with colonization. There were no deaths, in contrast to the mortality rate of 22% described in the studies analyzed in the meta-analysis.

It is noteworthy that a high percentage of the outbreaks analyzed in the meta-analysis achieved to identify a source. In most outbreaks, several lineages were circulating, which could be related to their prolonged duration (in nearly half, the outbreak lasted more than a year). The outbreak described by the authors again incorporates control measures in a phased manner. It is an outbreak with a complex transmission dynamic with 7 lineages circulating simultaneously (4 with case clustering and 3 with individual cases).

Both publications describe how the children accumulate several risk factors such as low birth weight, prematurity, exposure to devices like catheters, and prolonged stays in the ICU. These coincide with those published in the literature, which also includes the use of antimicrobials.[4]

Not surprisingly, both outbreaks were due to Enterobacterales. The prevalence of Enterobacterales in NICU outbreaks makes sense, considering that these bacteria are part of the normal stool microbiota.[1] They are transmitted to newborns at birth or may be acquired during their time in the nursery. *Klebsiella* spp. has the

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ability to endure on skin surfaces and exhibit greater resilience to drying out compared to other Enterobacterales. Remarkably, there are few outbreaks caused by *K. oxytoca* described, and the present review is especially interesting for this reason. On the other hand, *Serratia* spp., once merely viewed as harmless normal microbiota, are now recognized for their capacity to produce infections in NICUs, both in endemic and epidemic circumstances.[1]

NICUs have some distinguishing features that set them apart from other hospital settings: the presence of parents in close contact with the children, acting as potential reservoirs and/or transmitters of multi-drug resistant organisms (MDRO),[5] the use of breast milk for feeding the children, with the handling involved in the extraction, preservation, and administration of the same, and the use of specific devices for these units, such as incubators. Currently, the practice of the kangaroo mother care (KMC)[6] method is widespread. It is an evidence-based intervention that significantly reduce the risk of hospital acquired infections and the duration of hospital stays, promote growth, and improve neonatal survival, and at the same time introduce elements to be considered in the study of any outbreak in NICUs. All these factors make outbreaks in NICUs require, if possible, greater involvement of the professionals and family members involved in the care of the neonates to try to identify potential transmission pathways.

Identifying the origin of outbreaks or potential secondary reservoirs is critical for control. However, in real life, it is tough to find out exactly where an outbreak started, and success in management relies on the systematic application of control measure bundles, as elegantly reviewed by the authors in both publications. As discussed above, these bundles include monitoring compliance with hand hygiene recommendations,[7] active surveillance of MDRO colonization rates,[8] establishing contact precautions (e.g., isolation in a single room or group cohorts of cases exposed to the same bacterial colonization), enhancing training for unit professionals and, in the case of the NICU, for parents, adjusting professional ratios, reinforcing environmental cleaning, and antibiotic management strategies. It has been widely described how customized multicomponent strategies are needed to lower the burden and transmission risk of multidrug-resistant organisms in health care settings in endemic and outbreak situations.[9,10]

Not surprisingly there is a high proportion of identified outbreak sources among published data. There is a clear publication bias since it is easier to publish outbreaks that include the communication of the potential reservoir, which in the case of Enterobacterales ranges from colonization and transmission through artificial nails, stethoscopes, rectal thermometers, the use of multi-dose preparations of intravenous drugs, rolling platforms used to transport patients between surfaces, suction tubes, washers, humidifiers, or disinfectants.[11] In the two outbreaks described in this issue of the journal, it seems that the use of multi-dose vials, especially eye drops and creams, could have played a decisive role. In fact, outbreaks associated with the dissemination of transmissible agents related to the use of these products have been described, as recently reviewed in a paper describing an outbreak due to *K. oxytoca*. The adoption of single-dose vials after the second outbreak suggests that this measure was not established after the first outbreak and could partly explain the different dynamics in both situations. Some old and new papers not included in the metanalysis of *K. oxytoca* outbreaks describe some of these related transmission mechanisms.[12–15]

The contrast in the duration of both outbreaks is quite remarkable. Several factors could account for this disparity: the species involved and their inherent transmissibility, the presence of a single pulsotype in the case of SM (implying a higher likelihood of a potential source and/or secondary reservoirs), but most significantly, in our estimation, the frequency of active screening cultures. Therefore, the incorporation of routine screening cultures in outbreak management requires particular attention. The issue may provoke debate, particularly when addressing NICUs, which are known for their substantial production of clinical samples. In an endemicity setting, the discourse often revolves around whether these clinical samples adequately monitor the unit's circulating ecology or if periodic screenings are necessary instead. This discussion, in our view, is settled with respect to outbreaks. Numerous studies conducted in an outbreak context have demonstrate how detection via active screening samples of patients for MDRO colonization upon admission and at regular intervals during hospitalization facilitates early identification and the implementation of contact precautions to diminish the likelihood of cross-infection during the outbreak.[16–20]

It's clear that the two publications handled things differently in this regard. Yet, it's hard to say how much not using control cultures in the SM outbreak affects its duration. Other elements may have contributed to the prolongation of the SM outbreak: it occurred during the summer months coinciding with the holiday period, implying rotation of professionals and sometimes higher staff ratios. At the same time, the authors report a high mobility of patients between units as well as fluid transit of external professionals in the units affected by the outbreak and inadequate professional ratios.

One of the most powerful tools for outbreaks management and infection control in general are regular cleaning and advanced disinfection methods, yet the latter come with limitations. No mention is made in either both articles to whole room disinfection devices. Recent research underscores the effectiveness of ultraviolet (UV) light, especially UVC, and hydrogen peroxide in automated room disinfection post-manual cleaning.[21] Despite their potential benefit, these techniques can be time-consuming, have some technical limitations, require empty rooms to ensure safety, and may pose toxicity risks to humans. Additionally, self-cleaning materials with copper and silver, have shown clear effectiveness in reducing microbial loads and MDRO infections, however they face also challenges such as increased costs and potential long-term environmental impacts. Thus, while innovative disinfection methods are needed in hospital infection control strategies, their practical implementation must carefully balance effectiveness with safety and operational constraints.[22]

In recent decades, it has been repeatedly described how sink drainage systems (including drains, drainage pipes, and/or air samples above the sink drain) can be hidden reservoirs or vehicles involved in the transmission dynamics of MDROs through aerosol generation.[23] Multiple interventions on these drainage systems, mainly in closed hospitalization units, have managed to control epidemic situations. These interventions include avoiding the use of room sink drains to dispose of biological fluids, reducing the number of sinks or changing traps, or installing disinfection or splash-proof devices.[23] However, with the available evidence, it is difficult to establish the directionality of this transmission and determine to what extent these wet reservoirs act simply as black boxes, accumulating information on the microbiota circulating in the unit, or are indeed the source that explains the dynamics of an outbreak. In this sense, not always actions on these devices have been able to end outbreaks, which somewhat shows that they are one more element in the multifactorial dynamics of MDRO transmission.

In conclusion, tackling outbreaks in Neonatal Intensive Care Units (NICUs) requires a systematic approach that blends both horizontal and vertical epidemiological strategies, underscoring the importance of comprehensive infection control programs alongside targeted interventions.[8] These presently published experiences with *S. marcescens* and *K. oxytoca* outbreaks illuminate the critical role of timely outbreak detection, active surveillance, regular and extensive cleaning and the necessity of investigating potential reservoirs, such as environmental stuff (multiple-dose vials, sink drainage systems and others), to understand the transmission dynamics fully. Nevertheless, hand hygiene remains the cornerstone of our defense against MDRO spread,[9] highlighting the ongoing challenge of maintaining high adherence levels among healthcare workers, particularly beyond the pandemic. Infection control in NICUs is a multifaceted battle, requiring the commitment of healthcare professionals and the implementation of customized, multicomponent strategies to protect our most vulnerable patients. The two studies published in this issue of the journal contribute to convincing us of the importance of infection control measures to ensure the safety and well-being of neonates in the cradle of healthcare.

During the preparation of this work the author(s) used [ChatGPT] in order to improve language and readability. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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References

1. Gastmeier P, Loui A, Stamm-Balderjahn S, Hansen S, Zuschneid I, Sohr D, et al. Outbreaks in neonatal intensive care units—they are not like others. Am J Infect Control. 2007;35:172–6, http://dx.doi.org/10.1016/j.ajic.2006.07.007.
2. Liébana-Rodríguez M, Portillo-Calderón I, Fernández-Sierra MA, Delgado-Valverde M, Martín-Hita L, Gutiérrez-Fernández J. Nosocomial outbreak caused by *Serratia marcescens* in a neonatology intensive care unit in a regional hospital. Analysis and improvement proposals. Enferm Infecc Microbiol Clin. 2023, http://dx.doi.org/10.1016/j.eimc.2023.04.001.
3. Liébana-Rodríguez M, Recacha-Villamor E, Díaz-Molina C, Pérez-Palacios P, Martín-Hita L, Enríquez-Maroto F, et al. Outbreaks by *Klebsiella oxytoca* in neonatal intensive care units: analysis of an outbreak in a tertiary hospital and systematic review. Enferm Infecc Microbiol Clin. 2023, http://dx.doi.org/10.1016/j.eimc.2023.04.004.
4. Decembrino L, Maini A, Decembrino N, Maggi I, Lacerenza S. Management of outbreaks in neonatal intensive care units. Early Hum Dev. 2014;90 Suppl. 1:S54–6, http://dx.doi.org/10.1016/S0378-3782(14)70018-0.
5. Kristóf K, Szabó D, Marsh JW, Cser V, Janik L, Rozgonyi F, et al. Extended-spectrum beta-lactamase-producing *Klebsiella* spp. in a neonatal intensive care unit: risk factors for the infection and the dynamics of the molecular epidemiology. Eur J Clin Microbiol Infect Dis. 2007;26:563–70, http://dx.doi.org/10.1007/s10096-007-0338-9.
6. WHO Immediate KMC Study Group. Immediate "kangaroo mother care" and survival of infants with low birth weight. N Engl J Med. 2021;384:2028–38. https://doi.org/10.1056/nejmoa2026486.
7. Montagnani C, Cocchi P, Lega L, Campana S, Biermann KP, Braggion C, et al. *Serratia marcescens* outbreak in a neonatal intensive care unit: crucial role of implementing hand hygiene among external consultants. BMC Infect Dis. 2015;15:11, http://dx.doi.org/10.1186/s12879-014-0734-6.
8. Orman A, Celik Y, Evik G, Ersöz G, Kuyucu N, Ozmen BO. Should perirectal swab culture be performed in cases admitted to the neonatal intensive care unit? Lessons learned from the neonatal intensive care unit. Children (Basel). 2023;10:187, http://dx.doi.org/10.3390/children1002018.
9. Cohen B, Saiman L, Cimiotti J, Larson E. Factors associated with hand hygiene practices in two neonatal intensive care units. Pediatr Infect Dis J. 2003;22:494–9, http://dx.doi.org/10.1097/01.inf.0000069766.86901.91.
10. Mody L, Gontjes KJ, Cassone M, Gibson KE, Lansing BJ, Mantey J, et al. Effectiveness of a multicomponent intervention to reduce multidrug-resistant organisms in nursing homes: a cluster randomized clinical trial. JAMA Netw Open. 2021;4:e2116555, http://dx.doi.org/10.1001/jamanetworkopen.2021.16555.
11. Calbo E, Garau J. The changing epidemiology of hospital outbreaks due to ESBL-producing *Klebsiella pneumoniae*: the CTX-M-15 type consolidation. Future Microbiol. 2015;10:1063–75, http://dx.doi.org/10.2217/fmb.15.22.
12. Eshetu B, Gashaw M, Berhane M, Abdissa A, McClure EM, Goldenberg RL, et al. Intravenous fluid contaminated with *Klebsiella oxytoca* as a source of sepsis in a preterm newborn: case report. Am J Infect Control. 2019;47:840–2, http://dx.doi.org/10.1016/j.ajic.2018.12.025.
13. Schneider JS, Froböse NJ, Kuczius T, Schwierzeck V, Kampmeier S. Sink drains in a neonatal intensive care unit: a retrospective risk assessment and evaluation. Int J Environ Res Public Health. 2023;20:6692, http://dx.doi.org/10.3390/ijerph20176692.
14. Venezia RA, Scarano FJ, Preston KE, Steele LM, Root TP, Limberger R. Molecular epidemiology of an SHV-5 extended-spectrum β-lactamase in *Enterobacteriaceae* isolated from infants in a neonatal intensive care unit. Clin Infect Dis. 1995;21:915–23, http://dx.doi.org/10.1093/clinids/21.4.915.
15. Jalakas-Pörnull K, Dornbusch K, Kühn I, Ransjö U, Jonsson C, Broberger U. Characterization of β-lactam-resistant *Klebsiella oxytoca* isolated in a neonatal intensive care unit. APMIS. 1991;99:530–6, http://dx.doi.org/10.1111/j.1699-0463.1991.tb05186.x.
16. Tacconelli E, Cataldo MA, Dancer SJ, De Angelis G, Falcone M, Frank U, et al. ESCMID guidelines for the management of the infection control measures to reduce transmission of multidrug-resistant Gram-negative bacteria in hospitalized patients. Clin Microbiol Infect. 2014;20:1–55, http://dx.doi.org/10.1111/1469-0691.12427.
17. Calbo E, Freixas N, Xercavins M, Riera M, Nicolas C, Monistrol O, et al. Foodborne nosocomial outbreak of SHV1 and CTX-M-15-producing *Klebsiella pneumoniae*: epidemiology and control. Clin Infect Dis. 2011;52:743–9, http://dx.doi.org/10.1093/cid/ciq238.
18. Ben-David D, Maor Y, Keller N, Regev-Yochay G, Tal I, Shachar D, et al. Potential role of active surveillance in the control of a hospital-wide outbreak of carbapenem-resistant *Klebsiella pneumoniae* infection. Infect Control Hosp Epidemiol. 2010;31:620–6, http://dx.doi.org/10.1086/652528.
19. Laurent C, Rodriguez-Villalobos H, Rost F, Strale H, Vincent JL, Deplano A, et al. Intensive care unit outbreak of extended-spectrum β-lactamase-producing *Klebsiella pneumoniae* controlled by cohorting patients and reinforcing infection control measures. Infect Control Hosp Epidemiol. 2008;29:517–24, http://dx.doi.org/10.1086/588004.
20. Venkatachalam I, How MKB, Ko KKK, Abdul Rahman NB, Conceicao EP, Aung MK, et al. Healthcare-associated multispecies outbreaks of OXA-48-positive carbapenemase-producing *Enterobacteriaceae* in a Singapore tertiary-care hospital. Infect Control Hosp Epidemiol. 2023;44:8–16, http://dx.doi.org/10.1017/ice.2022.28.
21. Ji B, Ye W. Prevention and control of hospital-acquired infections with multidrug-resistant organism: a review. Medicine (Baltimore). 2024;103:e37018, http://dx.doi.org/10.1097/md.0000000000037018.
22. van der Starre CM, Cremers-Pijpers SAJ, van Rossum C, Bowles EC, Tostmann A. The in situ efficacy of whole room disinfection devices: a literature review with practical recommendations for implementation. Antimicrob Resist Infect Control. 2022;11:149, http://dx.doi.org/10.1186/s13756-022-01183-y.
23. Volling C, Ahangari N, Bartoszko JJ, Coleman BL, Garcia-Jeldes F, Jamal AJ, et al. Are sink drainage systems a reservoir for hospital-acquired Gammaproteobacteria colonization and infection? A systematic review. Open Forum Infect Dis. 2020;8:ofaa590, http://dx.doi.org/10.1093/ofid/ofaa590.

Esther Calbo[a,b,c,*], Laura Gisbert[a], Maria López-Sánchez[b]
[a] *Servicio de Enfermedades Infecciosas Hospital Universitario Mútua de Terrassa, Spain*
[b] *Equipo Control de Infección, Spain*
[c] *Universitat Internacional de Catalunya, Spain*

* Corresponding author.
E-mail address: ecalbo@mutuaterrassa.es (E. Calbo).