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Editorial

Isolation strategy for controlling the spread of multidrug-resistant organisms: Is this still an essential option in hospitals?

Aislamiento de contacto en el control de la transmisión de bacterias multirresistentes: ¿sigue siendo esta una estrategia necesaria en los hospitales?

At a time in which antimicrobial resistance has become "the other pandemic" no longer exclusive to hospitals, new mass sequencing technologies have allowed a better understanding of the clonal relationship between isolates and, due to the pandemic SARS-CoV-2, we have seen how the improvement of our hygienic habits greatly influences the containment of the transmission of microorganisms, it is the moment to consider which and when containment measures are justified. Infection control measures are designed to interrupt the transmission of microbes from colonized and/or infected patients to other patients, hospital visitors and healthcare workers, who may subsequently transmit them to other patients or become infected or colonized themselves.[1,2] Normally, these measures include standard (SPs) and contact precautions (CPs) in patients infected or colonized by specific multidrug-resistant organisms (MDROs). SPs specifically include a horizontal approach, which is based on high compliance with hand hygiene, the use of personal protective equipment (gloves and gowns) when anticipating contact with blood or body fluids, and more rigorous environmental cleaning. On the other hand, vertical approaches are based on active surveillance bacterial cultures and CPs only for colonized or infected patients.[3] CPs are indicated if transmission of an infectious agent is not interrupted using SPs due to environmental contamination. They include the wearing of aprons or gowns and gloves for all interactions with the patient and potentially contaminated areas within the patient's direct environment, the use of patient-dedicated or single-use disposable noncritical equipment, and accommodations in single-bed rooms or cohorting in multi-bed rooms.

Making a little history, CPs were first recommended by the American Centers for Disease Control and Prevention (CDC) in 1970,[4] when methicillin-resistant *Staphylococcus aureus* (MRSA) emerged as a hospital pathogen. At that time, there was minimal surveillance of healthcare-associated infections (HAIs), hospitals were organized into rooms with multiple beds in which the toilet was shared, hand hygiene compliance was poor, alcohol-based hand rubs or chlorhexidine solutions to decolonize patients were not used, and effective environmental disinfection was not achieved satisfactorily.[2] After implementing the CDC measures, over the following years, more knowledge has been acquired about strategic approaches to infection prevention. One very well-known example is the Netherlands's successful "search-and-destroy" policy for preventing the further spread of MRSA in a healthcare setting. This strategy is applicable in countries with a low prevalence of MRSA, in which a strict isolation policy was a restrictive fundamental mainstay of the implemented strategy.[5] Contact isolation (CI), a term commonly used as a synonym for CP, of patients infected or colonized with an MDRO has been recommended for the management of infection control measures to prevent transmission in acute care hospitals by the CDC,[4] the Society for Healthcare Epidemiology of America (SHEA),[6] and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID),[7] among others. The scientific evidence that supports the recommendations of these clinical practice guidelines is drawn, almost in its entirety, from experiences in epidemic outbreaks, generally of great magnitude and affecting large areas of a given health institution. Despite the widespread use of CPs, there is little evidence to support their effectiveness in the prevention of MRSA or vancomycin-resistant enterococci (VRE) infections, especially in endemic situations.

Discontinuation of CPs for patients colonized by MRSA or VRE has not been associated with an increase in infection rates, particularly in hospitals with a strong horizontal infection prevention strategy, including high levels of compliance with hand hygiene.[8] At the present time, a great number of healthcare centers limit the use of CPs to manipulate patients with draining wounds, urinary or fecal incontinence or other situations that increase potential extensive environmental contamination and risk of transmission, and to the care of high-risk patients.[9] For *Clostridioides difficile*-infected patients, some institutions have also discontinued CPs, except for patients infected with hypervirulent ribotypes or with fecal incontinence.[10]

However, what are the situations and recommendations for multidrug-resistant gramnegative rod (MDR-GNB) infections? Extended-spectrum β-lactamase-producing *Enterobacterales* (ESBL-E), carbapenemase-producing *Enterobacterales* (CPE) and extensively drug-resistant (XDR) non-fermenter gramnegative bacilli, such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii* or

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other intrinsically multidrug-resistant bacteria, are disseminated worldwide, with very high prevalence in low- and middle-income countries.[3] In this sense, a strong recommendation to implement CPs for patients colonized by an MDR-GNB has been made by the ESCMID.[7] However, current recommendations do not specify when to initiate or to stop CPs, allowing for individual institutions to determine the best response for handling a specific MDRO based on the significance of the organism, endemic rates, patient population, and the institution's laboratory capabilities. The effectiveness of screening and CI in preventing the spread of MDROs has been a contentious issue in recent years.[11] Endemic MDRO occurrence is also frequently the result of inappropriate antimicrobial prescription, leading to excessive antimicrobial consumption and selective pressure.[2] In addition to the MDR-GNB-colonized patients found during active surveillance studies, MDR bacteria are also unexpectedly found in clinical cultures.[12]

The published literature shows a difference in the transmission risk of ESBL-E, suggesting that CPs may not be necessary for all ESBL-positive organisms. Colonization with this kind of organisms usually persists during hospitalization and often for months following discharge. This fact suggests that patients with a history of ESBL-E colonization should be considered at high risk of continued colonization.[13] For XDR organisms, such as CRE or non-fermenter bacteria, the difficulties in treatment and the fear of spread to susceptible patients, above all in immunocompromised and elderly patients, or the risk of generating large outbreaks, have motivated strongly preventive policies. Publications in the past decade have questioned the use of CPs because in-hospital transmission might not be the main driver of the spread of these MDR-GNBs, especially ESBL-E. Additionally, questions have been raised regarding the impact of CPs on quality care, particularly on care delivery and patient safety.[8] Several studies have demonstrated negative outcomes on patients and increased costs related to the use of CPs in hospitals. Recent evidence has suggested potential negative effects of isolation on patient mental well-being (higher scores for dissatisfaction, depression, anxiety and anger), feelings of loneliness and stigmatization. Moreover, patients in CI have been observed to experience half as much contact with healthcare workers as patients on an SP and are between 2 and 7 times more likely to experience a preventable adverse outcome (falls, pressure ulcers, and electrolyte errors) than patients not in CI. Furthermore, the use of CPs has been associated with an increase in workloads, costs of providers and even delays in diagnostic procedures, transfers between inpatient units and hospital discharge, and increased readmission rates.[8,9,14]

In the study related to this editorial, Hernández-García and colleagues[15] report the findings obtained in a Spanish reference hospital following their participation in the European R-GNOSIS (Resistance in Gram-Negative Organisms: Studying Intervention Strategies) project. This is a cluster-randomized crossover trial in which the main goal was to establish the benefits of CI over SPs for reducing the incidence of ESBL-E nosocomial colonization and infection in adult medical and surgical wards in different countries with an active surveillance culture program.[11] Hernández-García et al. performed this trial in two medical wards (Gastroenterology and Pneumology) and two surgical wards (Neurosurgery and Urology) during two one-year periods (2014–2016). In addition to the presence of ESBL colonization or infection, they investigated CPE intestinal colonization. During the first year, CI was implemented in the surgical wards, while only the SP was used in the medical wards. Both strategies were switched after a wash-out period of one month. All patients were screened on admission to the ward (or as soon as possible within the first 3 days), once a week during the stay, and on discharge for patients staying up to 3 days. A total of 15,556 rectal swabs were collected throughout the study period. Regarding ESBL-E, 730 nonduplicate isolates were recovered from 687 patients (total colonization rate 8.4%), and 198 non-duplicate CPE isolates were recovered from 162 patients (overall incidence 2%). The authors determined that 15.3% of ESBL-E carriers were simultaneously colonized with a CPE isolate and that 55.5% of CPE isolates were also ESBL-E producers. The most frequent ESBL-E species was *Escherichia coli* (78.5%), followed by *Klebsiella pneumoniae* (17%), and as expected, this order was inverted in the case of CPE (53.5% *K. pneumoniae* and 19.2% *E. coli*, as well as 11.1% *Enterobacter cloacae* complex). During the study period, the authors showed that for patients with ESBL-E, an SP strategy was non-inferior to a CP strategy, as the percentage of ESBL-E carriers tended to decrease over time, and nonsignificant differences were detected upon implementation or withdrawal of CI. Colonization with CPE was also invariable during the study, but the authors highlighted the differences observed at the ward level. CPE carriers were significantly more frequently detected in the medical wards in the first period and in the surgical wards in the second period, coinciding with the application of only SPs, suggesting that CI of colonized or infected ESBL-E patients had an indirect containment effect on the nosocomial acquisition of CPE. It should be noted that during the last part of the study, and coinciding with the withdrawal of CI, the authors detected an outbreak by NDM-1-*K. pneumoniae* producers in the neurosurgery ward associated with an increase in patients colonized with OXA-48-ST11-*K. pneumoniae* high-risk clone. This study had a high enrollment of eligible patients, the multicenter crossover design mitigated most confounding effects, and the authors performed genomic analysis to assess transmission. Despite this, two main limiting factors were described by authors: first, they emphasized that the study design was conceived to evaluate the effect of isolation policies on ESBL-E and not specifically on CPE. Second, they noted a high prevalence of community-acquired ESBL-*E. coli*, which limited its comparison with other ESBL-producing organisms that may have differences in transmissibility in the healthcare environment, as revealed in other studies in the low-endemic setting of Dutch hospitals of the R-GNOSIS project, in which CI was applied in addition to SPs for all known ESBL-E carriers.[16] In one of these studies, the investigators estimated that the absolute risk of acquisition of ESBL-E rectal carriage was 2.4–2.9%, with an ESBL-E rate of 2.8–3.8 acquisitions per 1.000 patient days, and that this risk was partly due to transmission between patients (undetected carriers, false-negative cultures if the MDRO proportion was very low, and noncompliance with recommended infection control measures). Other limitations included the single-center nature of this work, indicating that its results were dependent on a specific epidemiology. Consequently, the results can be extrapolated to centers with epidemiological characteristics and action protocols like those of the study hospital (a Spanish hospital with a third level of complexity). Additionally, the authors omitted patient and process information that could condition the results (differences in patient comorbidities or exposure to invasive procedures, average of antimicrobial consumption and length of stay of patients in both units, compliance with hand hygiene and CI, the proportion of isolated patients in individual rooms or in a cohort, and the existence of a homogeneous antibiotic policy in the respective units under study). Finally, transmission between patients might not be the main pathway for the spread of ESBL-E or CPE and could have condition the results of this study.

Most data on the effectiveness of CPs in hospitals are related to critical care settings or outbreak situations. Current European recommendations to limit control measures in endemic settings to ESBL-E other than *E. coli* are based on studies performed by Thompson et al, in which after eliminating the use of CP for patients colonized or infected with only ESBL-positive organisms, except in surgical site infections and CPE, an increased rate of healthcare-associated ESBL-positive infections or colonization was not found.[14] Kluytmans-van den Bergh and colleagues showed

that the isolation strategy in multi-bed rooms was non-inferior to the CP strategy in a single-bed room for preventing transmission of ESBL-E in 16 Dutch hospitals.[17] They noted a higher risk of transmission from patients with ESBL-Es that were not *E. coli* because environmental contamination was more frequently associated with non-*E. coli* species and might have a role as a secondary reservoir for cross-transmission. In a previous prospective cohort Dutch study, in which surveillance cultures were taken from contact patients when an MDRO was identified in the index patient roommate, no nosocomial transmission was documented using whole genome sequencing (WGS).[12] Finally, Tschudin-Sutter and colleagues found a remarkably low ESBL-E transmission rate (1.5%) from non-isolated index patients to roommates, with a mean contact period of 4.4 days in a large study performed in a Swiss university hospital. They concluded that nosocomial ESBL-E transmission rates were low when a high level of standard hygiene precautions was applied and that the community reservoir may be an important driver of the emergence and spread of ESBL-E, with an emphasis on the food chain.[18]

On the other hand, a site survey carried out in the 2014 ESCMID aiming to assess details of the CP and implementation barriers by experts from 32 European Union (EU) and 24 non-EU countries showed that 23.3% of EU and 34.7% of non-EU respondents did not consider any CP measures for non-*E. coli* ESBL.[19] In this sense, a more recent online survey conducted in 2017, which summarized the opinion of almost 500 experts belonging to 175 centers from 34 European countries, reflected high variability among European countries in terms of the implementation of CP measures. CPs to reduce the spread of MDR-GNB were applied by 96% of the participants but in a heterogeneous manner: regular universal screening at admission or discharge for all patients was performed in 22% and 18% of the centers, respectively, and CI of infected or colonized patients was performed in 71% of the scrutinized centers.[20]

A general multimodal effort is necessary to reduce MDRO transmission and consequently the load of the HAIs. Major compliance with the SP and other relevant preventive measures, such as hand hygiene and environmental cleaning, improves the practice of evidenced prevention bundles and educational programs, ensures a correct ratio of patient-healthcare workers and an adequate stewardship antibiotic program, and can avoid the implementation of other controversial measures, such as isolation precautions. A robust and reliable horizontal infection prevention program should be sufficient to limit the cross-transmission of all pathogens transmitted by patient contact with healthcare workers and with the inanimate environment in non-outbreak settings.[8] Evidence suggests that transmission occurs to a large degree in the community setting, not necessarily in healthcare facilities.[14] It is very likely that a certain proportion of these hospital-suspected acquisitions are community-acquired colonizations, becoming detectable during screening cultures. When designing infection-control policies, the intrinsic bacterial transmission capacity (i.e., high-risk clones) and the prevalence of MDRO species should also be considered.

Currently, the application of universal precautions with an emphasis on correct hand hygiene, environmental disinfection and educational preventive programs constitutes the mainstay in controlling the spread of all MDROs. Multiple transmission levels (strains, plasmids, and genes) and highly complex transmission dynamics have so far made it difficult to precisely establish the origin, routes and scope of the transmissions. New diagnostic technologies such as whole-genome sequencing might improve our knowledge and practices regarding infection control. Efforts need to be allocated to establish a comprehensive infection control strategy and an effective supplemental stewardship antimicrobial program leading to the prevention of the emergence and transmission of MDROs. Ultimately, there remains little to support the notion that the isolation strategy should be an essential option in hospitals for controlling the spread of endemic multidrug-resistant organisms.

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