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Commentary

Could we fight healthcare-associated infections and antimicrobial resistance with probiotic-based sanitation?

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Abstract

Healthcare-associated infections (HAI) affect every year about 4 million hospitalized patients in the EU, causing over 33 000 deaths as a direct consequence and over 1.1 billion € associated costs. Besides the persistent microbial contamination of the hospital environment, a major cause is the rampant antimicrobial resistance (AMR) of the HAI-associated pathogens. The hospital environment itself is in fact a reservoir of resistant pathogens, apparently not sufficiently controlled by conventional chemical-based sanitation. A recently published study, the SAN-ICA study, performed in Italy, suggests that the fight against AMR may involve probiotic-based sanitation approaches, as they might stably reduce AMR surface pathogens, finally reducing HAI incidence. Here we discuss the reported results and argue that their use may provide a novel approach which deserves exploration.

Key words

- healthcare-associated infections
- antimicrobial resistance
- hospital sanitation
- probiotics

Healthcare-associated infections (HAI) represent a global concern for human health, tightly associated with the growing antimicrobial resistance (AMR) of HAI causal pathogens. Since the discovery of penicillin in 1928, which opened the so-called "antibiotic era", the massive and sometimes inappropriate use of antibiotics in humans, animals and the environment (particularly in the healthcare settings) has led to the growth of AMR to alarming levels. Consistently with this, the current period has been defined as the "post-antibiotic" era [1], and more than 33 000 deaths from drug-resistant bacterial infections alone, acquired during hospitalization, are reported each year in Europe. This figure could rise tenfold by 2050, when it has been hypothesized that AMR might kill more than cancer [2].

In the hospital environment, due to the selective pressure exerted by the wide use of antimicrobials, AMR is associated with increased morbidity and mortality, as well as HAI-associated costs [3]. In fact, affecting up to 4 million patients each year in the EU, HAI directly cause over 1.1 billions € of additional sanitary costs [4]. Consistently with such concern, the WHO has defined the top-threatening HAI pathogens as the ESKAPE group, including *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterococcus faecalis/faecium*, all causing the majority of difficult-to treat HAI [5]. All of them are also included in the so-called "dirty dozen", a global priority list of drug-resistant bacteria which represent threats for the human health not only and not as much for their pathogenicity but rather for their AMR, which renders the therapeutical approach against the associated infections extremely challenging [5]. Targeting AMR is a critical focus for sustainable healthcare in the EU and worldwide, not only related to human health but also to veterinary medicine, agricultural livestock management, and food production.

Consistently with this, in the recent years actions have been taken to limit AMR and HAI occurrence, including increasing AMR awareness, surveillance, and infection prevention measures (AMR stewardship) [6].

Since the hospital environment represents a huge res-

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ervoir of resistant pathogens, a focus on the environmental hygiene was included as one of the key points in the fight against AMR in the 2017 EU anti-AMR plan [6]. In Italy, the importance of defining and maintaining adequate levels of environmental microbial contamination in the hospital environment has been recently highlighted in the 2018 guideline document by ANMDO, the Italian association of Medical Hospital Directors, to control the risk of contracting an HAI during hospitalization [7].

Controlling the hospital environment microbial contamination appears thus a key point, so far addressed by conventional sanitation procedures based on the use of chemical-based detergents and disinfectants. Nevertheless, several reports show the presence of persistent contamination in > 50% of sanitized hospital surfaces [8], mostly due to recontamination phenomena, which are continuous and cannot be prevented by conventional sanitizers.

In addition, some disinfectants have been reported to potentially contribute to the selection of resistant strains. For example, in Gram-negative species adapted to benzalkonium chloride a new resistance was most frequently found to ampicillin, cefotaxime, and sulfamethoxazole [9]. With the use of chlorhexidine a new resistance was often found to ceftazidime, sulfamethoxazole, imipenem, cefotaxime and tetracycline, as well as against colistin [9, 10]. Since colistin is considered a "last-resort" drug for the treatment of multi drug-resistant (MDR) Gram-negative bacteria, this effect appears particularly undesirable, also in light of recently reported data on the prevalence of the plasmid-driven colistin resistance in the hospital environment in Italy [11]. Cross-resistance to antibiotics was also found with triclosan, octenidine, sodium hypochlorite, and didecyldimethylammonium chloride.

Alternatives to disinfectants include ultraviolet (UV) light, hydrogen peroxide protocols, no-touch technologies, self-disinfecting surfaces, and use of metals like iron, copper or silver [12]. However, the effectiveness of such technologies is highly dependent on several parameters including the concentration, time of exposure, and the amount of original contamination, and lastly they have high costs of implementation and limited use to specific surface types.

On the other hand, the use of probiotics as a potential tool in reestablishing a healthy balance in potentially pathogenic microbiota has become more and more popular for human, veterinary and environmental application. The recent findings on the human, animal and environmental microbiota has profoundly stimulated the research in this direction, suggesting that drastic antimicrobial approaches may be doomed to failure, sometimes even further favouring the colonization of potentially pathogenic microbes [13]. At the same manner, at the environmental level, it is hypothesized that a "super-sanitation" might not represent the solution for pathogens elimination, whereas rather a replacement of pathogens with beneficial microorganisms might be more effective [14].

In a recently published study, the SAN-ICA study [15], this principle was investigated in the hospital environment, by using a "microbial-based" sanitation in substitution of the conventional chemical-based one. In particular, the sanitation method (named Probiotic Cleaning Hygiene System, PCHS) was based on the application of eco-sustainable cleansers additioned with probiotics belonging to the *Bacillus* genus, namely *B. subtilis*, *B. pumilus* and *B. megaterium* species. The system was applied in substitution of conventional disinfection in the Internal Medicine wards of six Italian public hospitals, where surface bioburden and HAI incidence was simultaneously analysed, comparing the 6-month initial period during which chemical sanitation was used with the 6-month period receiving PCHS. About 12 000 hospital inpatients were observed and over 30 000 environmental samples analysed. Overall, the authors report a stable 83% reduction of surface ESKAPE pathogens during the PCHS period compared to what detected during pre-PCHS phase. Of note, the sampling was performed seven hours after sanitation, to let recontamination occur. A likely mechanism of replacement by competitive exclusion was hypothesized, as the reduction of the pathogenic component of the surface microbiota was accompanied by a concomitant increase of probiotics (finally representing about 70% of total surface microbiota). Interestingly, the study reports an up to 99% decrease of the drug-resistance genes harboured by the residual contaminating population, compared to the chemical sanitation period, as detected by the resistome analysis of the entire microbial population. In particular, the resistances against aminoglycosides, fluoroquinolones, macrolides, methicillin, vancomycin, β-lactamases, and colistin were reported to be significantly decreased. The decrease of AMR is further detailed in a companion paper by the same authors [16], where a significant reduction of antimicrobial consumption (-60%) and related costs (-75%) is reported.

Most importantly in a patients-safety perspective, the use of PCHS was reported to be associated with a 52% reduction of HAI incidence compared with the use of conventional sanitation [15], and no infection caused by *Bacillus* in any of the hospitalized inpatients, confirming previous data on the safety of use of *Bacillus* probiotics [17, 18].

The SAN-ICA survey has diverse potential limitations, as indeed recognized by the authors themselves. The first potential bias is related to the study design, a pre-post intervention performed in the same hospitals, and further studies should include stepped wedge trials or cluster randomized trials. Another potential bias concerns the difficulty of performing double-blind surveys and controlling all the other factors potentially affecting HAI onset. Furthermore, collected data refer only to Internal Medicine wards, and more studies should be performed to verify the generalizability of the results in other type of wards and patients. Last, a potential for confounding is represented by the lack of measurement of hand hygiene over the study period, although the authors report that there was an agreement not to introduce measures to improve infection control in the enrolled hospitals.

Nevertheless, even taking into account these potential confounders, the effect in term of displacement of microbiota, and the size and characteristics of the HAI reduction seem significant and may deserve attention. This also in a cost-saving and sustainability perspective, due to the low environmental impact and cost of probiotic-sanitizers.

Overall, *Bacillus* spores have a long history of safe uses in humans, including food preparation, agriculture [19], animal farms [20], human therapy of the gut [21], and their administration was recently shown to be associated with *S. aureus* eradication in human gut [22].

However, there is still a lack of clear evidence on how exactly probiotics produce their benefits. It has been suggested that they can act by competitive exclusion (competition for nutrition and space), and/or secretion of antimicrobial compounds, but a combined effort at global level should be needed for implementing probiotic screening and regulation relative to their final use. One important point, especially in the light of the recent COVID 19 pandemics, would be to ascertain the potential antiviral activity of such ecological sanitation, an aspect still not elucidated.

It should be emphasised that, whatever the sanitation adopted, it would be advisable to monitor its effects in the treated environment, not only to verify its decontaminating effectiveness but also, perhaps more importantly, to prevent potential avoidable side-effects such as further AMR induction and spread. The use of the new molecular methodologies, such as next generation sequencing (NGS) or other molecular analyses, could be of great help in characterizing the microbiota and its evolution precisely and timely.

However, although with the highlighted limitations, the data reported in these studies are intriguing and suggest that microbial-based approaches may deserve further exploration. A fruitful debate may be opened on the possibility to consider the approaches modulating the environmental microbiota as something potentially able to balance it in such a way to contribute positively to the control of AMR and HAI.

Conflict of interest statement

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