

# The use of prophylactic vancomycin to prevent MRSA colonization: Does this double-edged sword promote future vancomycin resistance or is it a safe preventative strategy that should be used in all patients in the context of MRSA endemicity?

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Since its discovery in 1880, *Staphylococcus aureus* (SA) has been a major human pathogen and has been shown to cause a large variety of serious infections involving, in particular, the respiratory system, bloodstream, and soft tissues. In 1961, only 2 years after the introduction of methicillin, SA acquired resistance to this new agent.<sup>1</sup> During the following decades, methicillin-resistant *Staphylococcus aureus* (MRSA) became highly prevalent in hospital settings, causing increased morbidity, mortality, and healthcare costs. In intensive care units (ICU), the burden related to MRSA is even higher. Indeed, a recent study that was<sup>2</sup> conducted in 125 Italian intensive care units confirmed that MRSA was the main causative pathogen of ICU-acquired infections, particularly ventilator-associated pneumonia.

Over the past several years, many efforts have been made to manage MRSA infections and control colonization rates. Education programs for the healthcare personnel, improved hand hygiene, environmental disinfection, the isolation of carriers, the implementation of lower patient-nurse ratios, the use of protective clothing, and the use of active screening protocols have all been strongly recommended and implemented worldwide. Unfortunately, preventive measures have often failed to control endemicity, and the prophylactic

use of vancomycin has become an appealing strategy to eradicate MRSA and to prevent MRSA-related infections in the ICU setting.

In this issue of *Minerva Anestesiologica*, Silvestri *et al.* report the results of an interesting three-year study conducted in a single ICU, characterized by MRSA endemicity.<sup>3</sup> Authors assessed the effects of two different interventions to control oropharyngeal MRSA colonization and prevent respiratory infections. First, the authors applied topical vancomycin to the oropharynx of patients shown to be colonized with MRSA at the time of admission. During the second phase of the study, all ICU patients received topical vancomycin, irrespective of their initial colonization status, and until they were extubated. Similarly to previous studies,<sup>4-8</sup> the authors found that the prophylactic use of topical vancomycin significantly decreased MRSA carriage rates. Moreover, when use of vancomycin was extended to all patients the authors demonstrated a significant risk reduction in the development of lower respiratory tract infections.

The prophylactic use of antibiotics to modulate oropharyngeal and digestive bacterial colonization has been a topic of active debate from almost 40 years. Researchers who advocate the broad use of selective digestive decontamination

(SDD) have shown consistent benefits,<sup>9, 10</sup> but they have always encountered strong opposition from scientists who have emphasized the daunting risks of antimicrobial resistance. The use of vancomycin for prophylaxis raises even more concerns because vancomycin is still a first-line agent against MRSA, which makes it different from the antimicrobial agents that are used to treat Gram-negative pathogens and fungi in standard SDD. Several studies have evaluated the efficacy and safety of the use of prophylactic vancomycin in decreasing MRSA carriage and infection rates.<sup>4-8, 11</sup> Pooling data from those studies, more than 1000 patients received prophylactic vancomycin and surveillance samples were assessed until ICU discharge. Neither vancomycin-intermediate *Staphylococcus aureus* (VISA) nor vancomycin-resistant *Staphylococcus aureus* (VRSA) were identified in any of these studies. Only one study<sup>5</sup> reported a time-limited outbreak of vancomycin-resistant *Enterococcus* (VRE) that was controlled through the implementation of infection control procedures.

Several key issues must be considered to correctly interpret the findings presented by Silvestri *et al.* as well as previous contributors and to develop a safe strategy for preventing ICU-acquired MRSA infections.<sup>3</sup> First, in favor of the approach proposed by the authors, it should be acknowledged that antimicrobial resistance often develops when antibiotics do not exert full bactericidal activity. No previous reports that have examined the use of prophylactic vancomycin have demonstrated increased resistance of MRSA to vancomycin. However, early stages of vancomycin resistance are often not recognized with current standard assays and indeed the authors did not perform tests to identify vancomycin heteroresistant SA (hVISA) in any of the previous studies. Several investigators have suggested that hVISA appears to be present in the first stage that precedes the occurrence of intermediate resistance.<sup>12</sup> Parent strains of VISA cells are susceptible to vancomycin, while subpopulations of daughter cells express vancomycin intermediate resistance and are often not detectable through standard testing methods. Population analysis profiling,<sup>13</sup> which is the current gold standard to test for hVISA, is still a labor-intensive assay, but several simplified versions of the original technique are now avail-

able,<sup>14</sup> and the use of these assays is highly advisable in future studies in this field. Of note, Silvestri *et al.* observed vancomycin minimum inhibitory concentrations (MIC) that were always lower than 1 µg/mL, and based on those findings, it is unlikely that heteroresistant clones would have been identified if more sensitive tests had been performed. Unfortunately, in previous reports, detailed MIC values were not reported and therefore the low MIC values found by Silvestri *et al.* cannot be substantiated in other studies.<sup>3</sup> Second, in critically ill intubated patients, MRSA colonization depends not only on the prevalence of the pathogen within the environment, but also on host defenses. The use of vancomycin as prophylactic strategy for all patients is a measure to modulate the prevalence of MRSA within the environment, assuming that all patients are at the same risk for acquiring MRSA and developing infections. However, in reality, patients at risk of acquiring MRSA are often colonized prior to ICU admission and re-colonized following discharge, irrespective of the treatments they received during their ICU admission, and several comorbidities are associated with an increased risk of MRSA acquisition. The use of vancomycin for all patients is an attempt to compensate for our current limitations with regard to the early detection of MRSA carriers and populations at risk of being colonized by MRSA. MRSA colonization has been shown to be associated with previous stays in long term care facilities, invasive devices, prolonged and complicated surgeries, and older age. Interestingly, in the current study by Silvestri *et al.*, a statistically significant imbalance in age existed between the two study periods, favoring the second phase, when all patients were treated upon admission.<sup>3</sup> The early detection of patients at risk of carrying MRSA could facilitate the use of interventions only in patients who indeed require preventive measures due to their increased risk of MRSA infection and could thereby narrow the use of prophylactic vancomycin. Third, the findings by Silvestri *et al.* also highlight the fact that the standard microbiological methods that are used to identify MRSA carriers are ineffective.<sup>3</sup> In an effort to control endemicity, it simply does not make sense to wait two or three days to properly identify patients carrying MRSA. Recent

studies<sup>15-17</sup> have assessed the efficacy of new real-time polymerase chain reaction tests that can detect MRSA within hours and could therefore greatly improve our ability to identify, isolate, and treat MRSA carriers in a timely manner. Further research is mandatory to improve the accuracy of those rapid tests so that MRSA can be better controlled in the future. Finally, concerning the use of prophylactic vancomycin in settings in which VRE is present, the horizontal transmission of resistance from VRE to MRSA has been confirmed,<sup>18</sup> which clearly confirms the risk of the use of vancomycin prophylaxis in ICUs in which both MRSA and VRE are endemic.

In conclusion, in several previous studies, vancomycin was safely applied to treat MRSA colonization and to prevent lower respiratory infections. The prophylactic use of vancomycin could be considered as a potentially useful strategy to reduce the risks associated with MRSA colonization and infection, but only when the strict implementation of infection control measures has failed. However, the use of prophylactic vancomycin should nonetheless be indicated for patients who are at increased risk of infection and may ultimately benefit from the strategy, as with any other medical intervention. Identification of the population at risk and active screening through rapid tests may therefore be the safest approach through which to promptly apply infection control measures and wisely use prophylactic topical vancomycin in the future.

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