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When silver doesn't shine anymore: The threat of increasing resistance to antibiotics and silver antiseptics

In this issue of *New Microbes and New Infections*, Safain and colleagues report on resistance patterns of bacteria causing wound infections in Bangladesh. There were eight bacterial species identified with *Staphylococcus aureus* (25%), *Escherichia coli* (19%), *Klebsiella pneumonia* (16%), and *Pseudomonas aeruginosa* (11%) being most commonly identified. More than half of bacterial isolates had extremely high minimum inhibitory concentrations to silver, and the presence of one or more of three silver resistance genes was associated with the phenotypic resistance to silver. Among *S. aureus*, 73% were methicillin-resistant, and 43% were vancomycin-resistant. Carbapenem-resistance was common – 76% of *E. coli*, 69% of *K. pneumoniae*, and 22% of *P. aeruginosa*. Approximately half of the isolated bacteria carried both extended spectrum beta-lactamase (ESBL) resistance genes (CTX-M-1 being the most common) *and* silver resistance genes. Many wounds were co-infected by multiple organisms, and the authors rightly suggest that plasmids transmitted between bacteria might be spreading multiple resistance genes.

Many different sorts of biochemical agents have been helpful in the fight against bacterial infection. Antibiotics typically kill bacteria both within the body and on body surfaces by interfering with biological processes of bacteria. Some less complex compounds, often called "antiseptics," hinder bacterial growth on inanimate and bodily surfaces through more straightforward toxic effects. The distinctions between antibiotics and antiseptics, however, are blurred. Increasingly, bacteria manifest genetically-derived resistance to the static and cidal effects of many antibiotics and antiseptics. It is concerning that silver-resistance and ESBL-resistance co-occur and are potentially spreading through bacterial plasmids.

Silver has been used to prevent bacterial growth for over a century. Wounds, especially from burns, have been successfully treated with topical silver-containing compounds, and newborn eyes were treated with silver nitrate drops to prevent gonococcal conjunctivitis (partly through silver's inhibitory effect on the organisms and, presumably, partly by stimulating a mild chemical conjunctivitis to bolster the babies' inflammatory responses against colonizing bacteria). Plasmid-derived silver-resistance genes have been characterized during the past decade and a half with, until very recently, very low frequency of identification [1]. Now, increasing rates of silver-resistance among bacteria will make care of patients with burns more difficult.

Besides silver, the antiseptic class of chemicals used to decontaminate surfaces includes iodine-based products, chlorine-related chemicals, alcohol, and quaternary ammonia compounds. Iodine has been used widely in humans and animals for many years with only low levels of resistance and with prolonged effectiveness on surfaces [1,2]. Chlorhexidine has less broad antibacterial effect than do iodine-containing solutions, and resistance has been reported [2]. However, comparative data suggest that chlorhexidine should still be a first-line choice for surgical antisepsis of skin [3]. With widespread alcohol use during the COVID-19 pandemic, alcohol-resistance, with organisms living even on alcohol dispensers, has been identified [4]. The most alcohol-tolerant/resistant germs were *Bacillus cereus* and *Enterobacter cloacae*; the strains that survived despite alcohol exposure were also resistant to other antimicrobial classes [4]. Quaternary ammonia compounds, in wastewater, have been associated with the emergence of ammonia-resistant Gram-negative bacteria [5]. Newer antiseptics, such as polyhexamethylene biguanide, seem to have good antimicrobial coverage for use in wound care and have not been associated (yet, at least) with the emergence of resistant organisms [6].

Rightly, of course, current concerns about antimicrobial resistance are not only limited to antiseptics. As Safain and colleagues demonstrated in Bangladesh, antibiotic resistance, especially with ESBL organisms, is a major concern. ESBL- and carbapenemase-producing Enterobacterales are an increasing problem worldwide. According to the World Health Organization, ESBL- and carbapenemase-producing Enterobacterales belong to the critical priority pathogens for research and development of new antibiotics [7]. While ESBL-producing *E. coli* are increasingly prevalent in community-acquired infections, ESBL-producing *K. pneumoniae* and *P. aeruginosa* and carbapenemase-producing Enterobacterales in general are still mostly a health-care associated problem [8].

South Asia is considered a part of the world in which extended-spectrum beta-lactamases have emerged de novo [9]. Similarly, New Delhi metallo-betalacatamase-1 (NDM-1), a carbapenemase, has first been described in a Swedish patient who had previously obtained medical care in New Delhi, India [10] and has subsequently spread the world [11]. Today, prevalence of ESBLs and Carbapenemases are among the highest in South Asia: a meta-analysis published in 2022 looking at colonization rates with ESBL-producing *E. coli* in children found colonization rates between 9 and 60% [12]. Another study looking at ESBL- and metallo-beta-lactamase-producing *E. coli* in South Asia found pooled prevalences of 33% and 17%, respectively [13].

The combined resistance against antibiotics and antiseptics in wounds is worrisome: especially extensive wounds, like for instance burn wounds, do have a tendency to become colonized and infected with various bacteria and especially multidrug resistance is observed frequently in this setting [14,15]. The subsequent sepsis, facilitated by loss of skin barrier function and the need for invasive medical devices is one of the main reasons for death in these patients [15,16]. An important part of wound management to prevent colonization is the use of topical antimicrobial agents. According to a recently published systematic

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review [17], silver-containing dressings are recommended in most guidelines and silver sulfadiazine is the most recommended topical antimicrobial in resource limited settings. Consequently, resistance to antiseptics like silver will hamper the prevention of infection, which increases the need for antibiotic treatment, thereby further driving resistance development and associated mortality.

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