To the Editor—We read the study by Shopsin et al. [1] with interest. As far as we are aware, this study provides the first accessory gene regulator (agr) functional analysis for isolates of Staphylococcus aureus recovered from colonized individuals. These authors observed that agr-dysfunctional isolates colonized 15% (9%) of 160 screened subjects and suggest that agr-dysfunctional strains were fit for transmission.

We support the notion that agr-dysfunctional S. aureus is fit for transmission, as well as the idea that these strains actually acquire particular advantages in a healthcare setting, compared with agr-functional strains. This hypothesis is supported by these authors’ finding that prior hospitalization was strongly associated with colonization with agr-dysfunctional S. aureus [1].

The expression of agr results in a virulence phenotype marked by exotoxin production, which is important in the formation of abscesses and tissue invasion [2]. Genetically engineered agr-knockout strains have attenuated virulence in animal models of such infections [2, 3]. Undoubtedly, agr expression and the resulting production of the various exoproteins that enable virulence come at a large metabolic price for the organism. The price of such metabolic demand may exceed the benefit in a healthcare setting, particularly if one examines the hosts in such an environment. Patients frequently have intravascular catheters that allow free access to the host, surgical wounds have already compromised skin integrity, vascular disease compromises the delivery of blood-dependent host response factors (e.g., leukocytes, complement, and antibodies), and antistaphylococcal host defenses are further impaired by other immunocompromised states, whether pharmacologic or pathologic. All of these factors combine to create a situation in which S. aureus would potentially be less hindered and would therefore require fewer virulence “tools” to cause disease. Would the metabolic price of agr be worth it in the healthcare setting? We certainly know that passage of bacteria in vitro, where exotoxin production is not required for nutrient acquisition, results in the selection of less virulent organisms and a selective advantage for subpopulations that relinquish virulence.

In addition to the arguments above, however, recent evidence suggests that loss of agr function confers potential advantages in a healthcare setting beyond the decrease in metabolic costs. Loss of agr has been associated with increased biofilm production and polystyrene adherence, potential advantages in an environment where the majority of bloodstream infections are catheter associated [4, 5]. Reduced agr expression increases the expression of fibronectin-binding protein, which is required for mammalian cell adhesion and, therefore, is important in the mechanism of colonization [6]. Such phenotypes may also allow for intracellular uptake and evasion of host defenses, allowing for recurrence of infection in sites with poor antimicrobial access. Our laboratories have generated considerable data demonstrating that agr dysfunction confers a survival advantage under vancomycin selection pressure whereby loss of agr function, coupled with subinhibitory vancomycin exposure, readily selects for vancomycin heteroresistance and tolerance [4, 7]. Finally, agr-dysfunctional S. aureus has been linked to prolonged bacteremia [8].

It appears, therefore, that loss of agr expression would be a potential “win-win” situation for a nosocomial pathogen. Although it has never been precisely studied, several studies have shown diminished agr function among clinical S. aureus isolates obtained in a hospital setting. One study performed prior to the widespread prevalence of community-acquired methicillin-resistant S. aureus (MRSA) infection (meaning that MRSA infection was almost exclusively nosocomial) found that among isolates from patients with bacteremia, 41% of MRSA isolates but only 27% of methicillin-susceptible S. aureus isolates were agr dysfunctional (P = .03) [4]. A subsequent study performed after the emergence of community-acquired MRSA infection showed that agr dysfunction rates among healthcare-associated strains was 48% but only 3% among community-associated strains of MRSA [9].

In conclusion, we wish to agree with Shopsin et al. [1] that agr-dysfunctional strains can be viably transmitted between patients and that hospitalization is a risk factor for colonization with agr dysfunctional strains. In addition, we also wish to point out that agr dysfunction offers potential advantages to S. aureus in a healthcare setting. Further work that evaluates the physiologic role of agr in S. aureus will be important to our understanding of staphylococcal virulence and antimicrobial resistance as well as the epidemiology of staphylococcal infection.

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