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Biology of Hand-to-Hand Bacterial Transmission

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ABSTRACT Numerous studies have demonstrated that adequate hand hygiene among hospital staff is the best measure to prevent hand-to-hand bacterial transmission. The skin microbiome is conditioned by the individual physiological characteristics and anatomical microenvironments. Furthermore, it is important to separate the autochthonous resident microbiota from the transitory microbiota that we can acquire after interactions with contaminated surfaces. Two players participate in the hand-to-hand bacterial transmission process: the bacteria and the person. The particularities of the bacteria have been extensively studied, identifying some genera or species with higher transmission efficiency, particularly those linked to nosocomial infections and outbreaks. However, the human factor remains unstudied, and intrapersonal particularities in bacterial transmission have not been yet explored. Herein we summarize the current knowledge on hand-to-hand bacterial transmission, as well as unpublished results regarding interindividual and interindividual transmission efficiency differences. We designed a simple *in vivo* test based on four sequential steps of finger-to-finger contact in the same person artificially inoculated with a precise bacterial inoculum. Individuals can be grouped into one of three observed transmission categories: high, medium, and poor finger-to-finger transmitters. Categorization is relevant to predicting the ultimate success of a human transmission chain, particularly for the poor transmitters, who have the ability to cut the transmission chain. Our model allowed us to analyze transmission rate differences among five bacterial species and clones that cause nosocomial infections, from which we detected that Gram-positive microorganisms were more successfully transmitted than Gram-negative.

INTRODUCTION

Oliver Wendell Holmes was the first to describe the direct transmission of possible infective ("pestilent") agents to puerperal women through the physician's contaminated hands (1). In 1855, he published a book entitled *Puerperal Fever, as a Private Pestilence* in the United States (2). Nevertheless, the worldwide recognition of this relevant observation was classically attributed to Ignaz Philipp Semmelweis, who published a scientifically based demonstration of the role of hand disinfection in his thesis titled "The Etiology, the Concept and the Prophylaxis of Childbed Fever," developing seminal observations carried out in the year 1847 (3). Both authors implicated, for first time, the role of human hands contaminated with "cadaverous particles" in the deadly transmission process. Their legacy persists today, with considerable influence on current medicine, in which hand hygiene remains a liturgy in surgical procedures and is also a general measure with a pivotal role in the prevention and control of communicable diseases (4, 5).

An interesting epistemological thought is that the overwhelming clarity, prestige, and influence of widely accepted and applied practices might repress fundamental

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research in this particular field—the idea that because it works beyond any reasonable doubt, there is no need to look for explanations. Semmelweis himself discarded as "irrelevant" the use of the microscope to explain his own results (6–10). These classical observations fostered the development of microbiology (11), but were not seminal for research on the biological bases of transmission of bacteria by hands, which remains largely unexplored.

HANDWASHING PREVENTS BACTERIAL TRANSMISSION

It is now accepted worldwide that adequate hand hygiene among hospital staff is the best measure to prevent nosocomial infections and outbreaks (12). To standardize the handwashing process by health care workers, in 2009, the World Health Organization published universal guidelines (13). Although numerous scientific studies have confirmed the clear relationship between proper hand hygiene on the part of the hospital staff and lower nosocomial infection rates, overall compliance is only ~40% (14).

Alcoholic solutions have recently been incorporated for hand hygiene. These solutions eliminate 99.99% of resident hand microbiota, whereas water washing only reaches 95% of the total decontamination (15, 16). It should be noted that these are indicative numbers, which are probably variable and dependent on the methodology of sampling and enumerating bacterial organisms (17, 18). Most importantly, we have minimal data from which to elucidate whether deeper hand microbiota decontamination is the recommended option to prevent bacterial transmission. As occurs in other microbiota localizations, the commensal native hand microbiota might play a crucial role in preventing the colonization and growth of external pathogens. In that sense, controlled reduction of hand microbiota density might be more recommendable than complete disinfection (19). The "mechanism" of bacterial killing with various procedures and the microecology of decontamination are also critical aspects that remain to be investigated.

MICROECOLOGY OF HAND SURFACES

In classical water washing, the majority of the bacterial reduction is due to the dragging effect, whereas alcohol solutions have an additional bactericidal effect by removing membrane lipids in both bacterial and human cells (15, 20). The real usefulness of these alcoholic solutions for hand hygiene has recently been noted (21). Lipids are important components of the epidermis-binding corneocytes that form the skin barrier and that prevent water loss. Moreover, some antimicrobial properties have been attributed to some of these skin lipids (22, 23). The compromise of the skin barrier after lipid removal via alcoholic solutions has not been sufficiently studied; more importantly, the role of these human lipids in the bacterial transmission process has not been explored. In fact, scientific evidence on skin moisture as a relevant factor for bacterial hand transmission can be found (24–26), and this transmission is more efficient when the skin is wet.

Skin microbiota density and composition is strongly conditioned by physical interaction with the environment, where the intensity of the friction of the skin with objects influences its final bacterial density. Friction effects are particularly relevant in specific areas, such as the fingers and palms, which are the most environment-interactive parts of our body. Our epidermis is completely renovated every 4 weeks, and the numerous squamous particles containing dead human cells but also viable bacteria are discharged daily. However, the dynamics of shedding and how it is influenced by the nature of biotic (including other persons) or abiotic contact objects remain poorly studied, as well as the number and type of microorganisms preferentially detached with squamous particles.

Physiological characteristics such as pH, humidity, and temperature influence the microecology and final microbial composition of our skin microbiota (18). Their structure varies by skin localization and depends on the distribution and density of hair follicles; sebaceous, eccrine, and apocrine glands; and scars and anatomic imperfections (27). Differences in the microbiota depending on the skin stratum have been observed, with indigenous bacteria corresponding to deeper skin layers, whereas transient bacteria are located only in the most superficial layers (28).

Significant differences among individuals have been detected in the skin microbiome composition. The intraindividual composition, however, remains relatively stable across time, although it undergoes important daily fluctuations in density, most of them after handwashing or external friction (29, 30). Furthermore, gender differences have also been confirmed; women have significantly higher bacterial diversity in their hands as well as differences in the bacterial composition of the dominant and nondominant hands (29). Age and race effects have not been sufficiently evaluated, although skin microbiota particularities of the Chinese population

(31) and differences related to altitude have recently been reported (32).

THE HAND'S MICROBIOME

As occurs in other human microbial-associated ecosystems, new molecular tools based on 16S rRNA massive sequencing have revealed a more diverse skin microbiota than those found by traditional microbiological cultures (33). Most of the microorganisms inhabiting human skin belong to the *Corynebacterium*, *Propionibacterium*, and *Staphylococcus* genera, with a median bacterial load (population size) of $\sim 1 \times 10^7$ bacteria per cm^2 (34). More than 150 bacterial species have been found in the palms, most belonging to the *Actinobacteria*, *Firmicutes*, and *Proteobacteria* phyla (29).

It is of relevance to differentiate between autochthonous resident microbiota and transitory microbiota that we can acquire after physical interactions with contaminated surfaces (35). Furthermore, transitory microbiota might have a commensal or a pathogenic behavior, depending on their interaction with the immune system. As occurs in other parts of our body, the skin microbiota have a continuous dialogue with the immune system, which recognizes and destroys the external (alien) pathogens. In a healthy state, the resident microbiota do not represent an insult to the innate immune system, although they could occasionally activate it, particularly when reaching a high population density. In this sense, the immune system could be implicated in the regulation of the microbial skin ecosystem, which also maintains resilience properties that allow it to recover its composition and structure after attacks (36). In general, the skin constitutes a defensive barrier against the external microbial world. Not only shedding, but physical (pH, low humidity), chemical (skin antimicrobial fatty acids), biological (local enzymes, such as serine proteases, and constitutively produced cationic antimicrobial peptides, such as β-defensins and cathelicidins), and innate immunity effectors (inflammatory cytokines, such as interleukin-1, interleukin-17, and epidermal Toll-like receptors) contribute in an inducible, coordinated, and overlapping way to maintain a limitation on the density of microbial skin populations, and thus the interhuman transmission ability (37–41). Some skin structural features are critical to maintaining skin microbial homeostasis; in particular, the role of filaggrin (filament aggregating protein) ensures binding to keratin fibers in epithelial cells, which results in lipid barrier integrity and water retention and finally skin hydration (42).

HAND CONTAMINATION BY NONRESIDENT ORGANISMS

Alien bacterial organisms are those not represented in the normal skin microbiome, and consequently include those that are incorporated into the hand's surface by occasional environmental contamination. The acquisition of external bacteria by hand exposure to contaminated fomites or surfaces is a critical source of nosocomial infection, particularly for health workers (43). However, bacterial interchange events between the environment and hands occur daily on countless occasions during routine actions such as eating (44), paying with cash (45, 46), or touching mobile phones (47). Undoubtedly, a major source of external bacterial contamination is the microbiota from other places on our own body (for instance, nostril-to-finger transmission), and also from family or friends. External bacteria rarely reach high populations, however, and often do not trigger a response from the innate immune system (e.g., by antimicrobial peptides), which reveals the inoffensiveness of these quotidian contaminations (40).

In the hand transmission process, environmentally tolerant microorganisms have more opportunities to be successfully transmitted to the hand. In fact, each type of bacterial organism, including pathogens, has a particular transmission efficiency rate that is influenced by its initial inoculum at the source as well as its capability to adhere to new surfaces. *Staphylococcus saprophyticus*, *Pseudomonas aeruginosa*, and *Serratia* spp. were transferred in greater numbers than was *Escherichia coli* from a contaminated to a clean piece of fabric after hand contact (48).

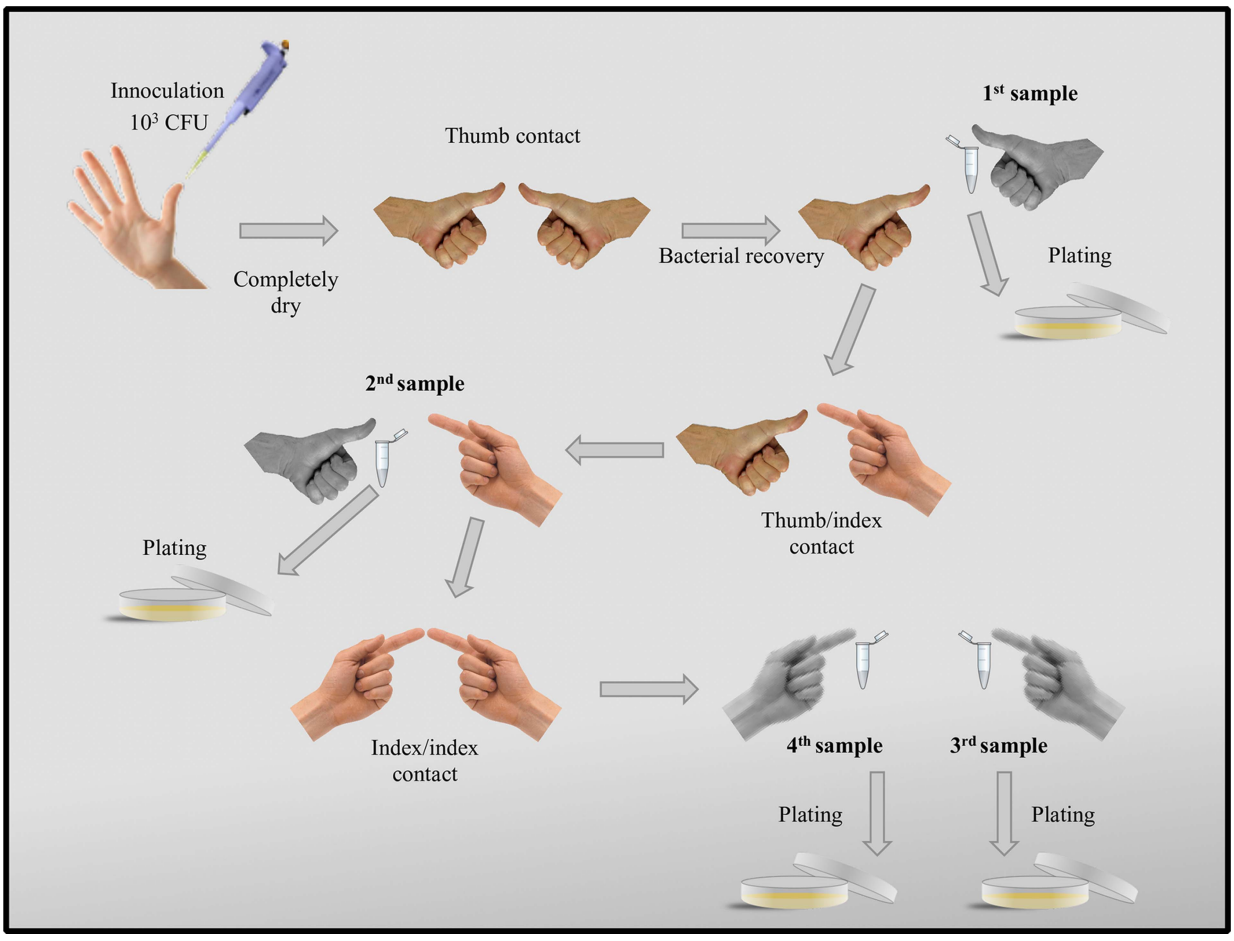
Curiously, in the bacterial hand transmission process, the transmission efficiency of human-to-human exchanges has scarcely been evaluated (49), and intrapersonal particularities have not yet been explored. In the next sections, we share recent data obtained by our group on the human role in hand-to-hand bacterial transmission, particularly in terms of interindividual differences.

DESIGN OF A MODEL FOR TESTING INTRAINDIVIDUAL FINGER-TO-FINGER TRANSMISSION EFFICIENCY

In a recent publication by our group, experimental results regarding intraindividual bacterial hand transmission efficiency of 30 healthy volunteers (20 women and 10 men) with four different *Enterococcus faecium* clones were presented (50). We designed a new test to explore the finger-to-finger bacterial transmission of the

volunteers, as shown in Fig. 1. Each finger was put in close static contact (ensuring full surface contact, but with minimal pressure and without twists or wipes) for ~10 sec. Interestingly, this simple experiment provided consistently significant differences in host finger-to-finger transmission among individuals and bacterial isolates. The 30 individuals were classified into three transmission efficiency categories: poor, medium, and high finger-to-finger bacterial transmitters. An interesting result not previously described is that the 10 male volunteers were classified as poor or high transmitters, whereas almost all 20 of the women were grouped in the medium category. As was mentioned earlier, men and women have significant differences in their skin composition. Men usually have lower pH values in their skin, but there are also differences in sweat and sebum production, skin moisture, skin thickness, and hormone levels (51). Possible interindividual differences in the lipid composition of the human skin might also be considered. Chemical and physical interactions between bacterial and human lipids might determine the final adherence of the bacteria to the superficial skin layer. However, for a microorganism to colonize a new environment, such as a receptor hand, the lipid interactions of the invasive bacteria with the human lipids or the external lipids of the resident skin microbiota can be decisive. In addition, the physical attraction or repulsion forces between lipids can determine the permanence of a microorganism. Although the bacterial hand transmission process has considerable clinical repercussions in terms of human infections, particularly those associated with health care centers, the microecological determination of transmission has not been sufficiently explored.

FIGURE 1 Schematic representation of the intraindividual finger-to-finger transmission efficiency test, which employs a total of four fingers of the same individual. The remaining bacteria on the finger surface are recovered after the contact between fingers and immediately plated on M-*Enterococcus* agar plates, which are counted after 24 to 48 h.



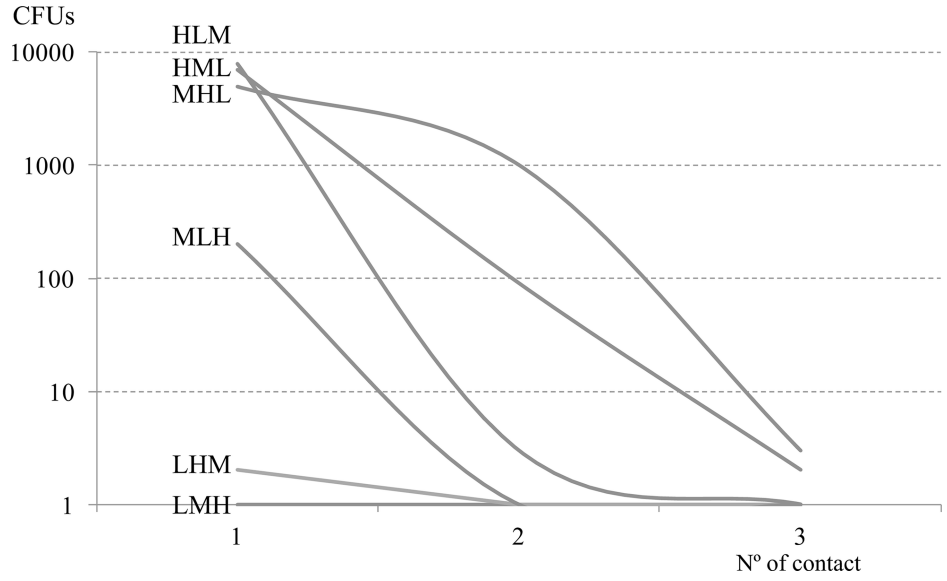
TESTING THE FINGER-TO-FINGER INTERINDIVIDUAL TRANSMISSION CHAIN

In the last section, we discussed the possibility of differences between individuals in their own finger-to-finger transmission potential. The best transmitters are typically those who more effectively release the bacterial population and/or those who more completely bind to the released bacteria from the donor finger. In any case, we can hypothesize that the best transmitters from their own fingers are also good transmitters for other individuals. We evaluated this hypothesis by constructing a finger-to-finger transmission chain with various individuals. For this purpose, we selected three volunteers to represent each category (high, medium, and poor transmitters), and we chose the foodborne *E. faecium* L50 strain as the most transmissible. The scheme used for this purpose was similar to that described previously, but with finger contact among the three volunteers: the first individual received a bacterial load of 10^7 CFU of *E. faecium* L50 on the thumb, which was put in contact for 10 sec with the thumb of the second volunteer, when it was completely dry, and this thumb was put in contact with the thumb of the third volunteer. The remaining bacterial load after the transmission of the three implicated fingers was recovered with an Eppendorf tube (see Fig. 1) and seeded onto M-*Enterococcus* agar for colony counting. All possible combinations of the chain were explored: high-medium-poor, high-poor-medium, medium-high-poor, medium-poor-high, poor-medium-high, and poor-high-medium. The results of this experiment are shown in Fig. 2, demonstrating a good reproduction of the transmission pattern that we observed in the individual experiments. The success of the transmission chain depends on the position of the poor transmitter. In fact, the poor-transmitter volunteers had the ability to cut off the transmission chain independently of their position.

TRANSMISSION EFFICIENCY OF DIFFERENT BACTERIAL SPECIES AND CLONES

Finger-to-finger transmission efficiency is conditioned by the particular characteristics of both the human and the bacterial organisms. In fact, there appears to be differences even among clones in a single species. To explore this possibility, we examined the intraindividual transmission of five bacterial species using the same scheme described in Fig. 1, but only involving two fingers. The selected species were (i) ST18-CC17 *E. faecium* isolated from a blood culture and responsible for a nosocomial outbreak, (ii) ST5-CC5 methicillin-resistant *Staphylococcus aureus* from a blood culture, (iii) VIM-1-producing *Klebsiella pneumoniae* colonizing the gut of an admitted patient, (iv) ST175 *P. aeruginosa* from a blood culture, and (v) ST10-CC10 *E. coli* from a blood culture. The transmission ability of each isolate was tested in three volunteers each one representing a transmission category. These experiments were conducted

FIGURE 2 The transmission chain process was explored using three volunteers—high, medium, and poor transmitters—and the foodborne *E. faecium* L50 clone. All six possible combinations of the three volunteers were assayed.



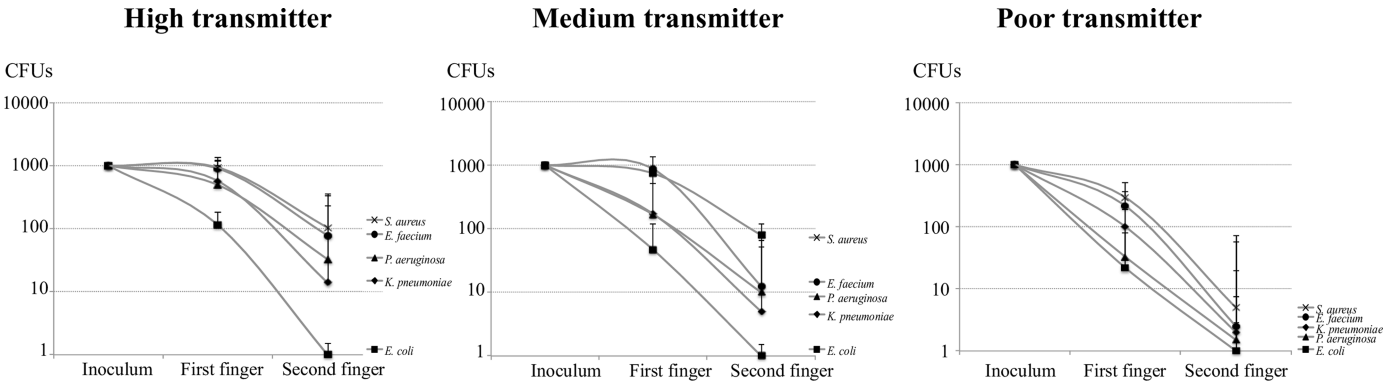


FIGURE 3 Differences in the transmission efficiency of five bacterial species using one volunteer per transmission category. The transmission pattern was repeated for the three individuals.

in triplicate per clone and volunteer, and the results are expressed by the median value of the CFU count (Fig. 3). Although the final colony count on the second fingers varied as a function of the volunteer category, the same transmission pattern was observed in the three volunteers. The Gram-positive organisms, *E. faecium* and *S. aureus*, exhibited the highest transmission efficiency, whereas the Gram-negative organisms were less efficient. Unexpectedly, *E. coli*, which is one of the most universal and ubiquitous bacteria, had the lowest transmission rate. The nosocomial character of the species was the selection criterion employed for our experiment, but these data could be completed with other species/clones and volunteers to better understand the transmission differences between bacteria and humans (38, 39).

FUTURE PROSPECTS IN BASIC BIOLOGY OF HAND TRANSMISSION: DIGGING INTO SKIN MICROENVIRONMENTS

The biology of hand transmission requires a much more detailed characterization of hand surface microenvironments, their variability among humans, and possibly circadian changes within each host. We need to know the hands' skin microecological conditions, including basic physicochemical traits such as temperature, water content, osmolality, pH, ions, iron, proteins (including enzymes), peptides, sugars, short-chain fatty acids, and bacterial microbiota profile—and ultimately antibody screening arrays, molecule-oriented antibodies or full-sample mass spectrometry (matrix-assisted laser desorption ionization–time of flight mass spectrometry) profiles—to obtain a full-environment fingerprint. Compact telemetry devices could be developed to obtain all these data. The final aim of such an approach is the bioinformatic (phylogenetic-like) construction of "microenvironment trees," thus closing the circle of the microbe-environment evolutionary unit (52). Whether the structure of particular "individual-specific skin microenvironments" favoring bacterial survival and transmission correlates with particular human genotypes (as suggested by studies in atopic dermatitis) remains an interesting topic of research. These studies might indeed reveal whether some individuals (or human populations) are genetically prone to be better at human-to-human transmission of organisms causing infectious diseases (53), certainly a hot topic for preventive measures and targeted interventions.

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