

Persistence of Healthcare-Associated (Nosocomial) Infections Due to Inadequate Hand Hygiene: Part 1—Biological and Treatment Factors

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Abstract

The most frequent adverse event in the healthcare delivery system is acquisition of an infection within a healthcare facility. Since infection control measures are known, simple, and low-cost, we examine why the problem of healthcare-associated infections persists. Hundreds of millions of patients each year are affected by a healthcare-associated infection, with negative medical outcome and financial cost. It is a major public health problem even in countries with advanced healthcare systems. This is a bit perplexing, given that hygienic practices have been known and actively promoted. The objective is to address the question: doesn't the use of disinfection, sterilization, handwashing, and alcohol rubs prevent the spread of pathogenic organisms? We conclude that the persistent high prevalence of nosocomial infections despite known hygienic practices is attributable to two categories of factors: biological and inherent shortcomings of some practices (considered in Part 1), and human factors (considered in Part 2). A new approach is presented in Part 3.

Keywords

Infection, Nosocomial, Hospital, Healthcare-Associated, Hygiene, Handwashing

1. Introduction

A healthcare-associated infection (HAI) [1] is an infection that is acquired in a

healthcare setting—*i.e.*, is not the original illness, is not present or incubating at the time of admission to a healthcare facility, and is acquired at the facility. They generally occur within 48 hours following admission to a facility, within three days of discharge from a facility, or within 30 days following a surgical procedure at a facility. Also included are infections that are acquired by the staff that work at a healthcare facility (“occupational” HAIs).

Recognition of the problem of HAI and efforts to address it date back to at least 1825, and governmental agencies and professional organizations have developed, and actively promote, various guidelines, codes, and standards that are directed at eliminating the problem (**Table 1**) [2]. Yet, according to World Health Organization (WHO) estimates, the overall prevalence of HAI is still 5% - 12% in developed countries (e.g., 4.5% in the United States, 7.1% in European countries) and 5% - 19% in developing countries [1]. This translates to hundreds of millions of people worldwide. We sought to examine the question of why the prevalence of HAI remains high, given that the problem is widely-recognized and emphasized in healthcare professional-school curricula and training, and infection control measures are seemingly known, simple, and low-cost.

2. The Magnitude and Seriousness of the Problem

HAIs are the most frequent adverse event associated with healthcare delivery [3].

Table 1. Historical perspective. Some important dates in the recognition and mitigation of health-care-associated infections. Based on summary in Boyce and Pittet (2002) [2].

Years	Event(s)
1825	Labarraque publishes advice that healthcare providers attending patients with contagious diseases would benefit from moistening their hands with a liquid chloride solution.
1843	Oliver Wendell Holmes concludes that puerperal fever is spread by the hands of healthcare personnel.
1847	Semmelweis insists that providers clean their hands with a chlorine solution between each patient; the data show it to be more effective than handwashing with plain soap and water.
1961	U.S. Public Health Service training film about recommended handwashing techniques.
1975, 1985	CDC (Centers for Disease Control and Prevention) publishes formal guidelines for handwashing practices.
1988, 1995	APIC (Association for Professionals in Infection Control) publishes handwashing guidelines; the 1995 version supported wider use of alcohol-based rubs.
1995, 1996	HICPAC (Healthcare Infection Control Practices Advisory Committee) recommends using either an antimicrobial soap or a waterless antiseptic agent when leaving the room of a patient with multidrug-resistant pathogens such as VRE (vancomycin-resistant enterococci) and MRSA (methicillin-resistant <i>Staphylococcus aureus</i>).
2002	CDC publishes “Guideline for Hand Hygiene in Healthcare Settings”.
2009	WHO (World Health Organization) publishes “WHO Guidelines on Hand Hygiene in Health Care”.
2010-	Guideline updates.

Sources of HAI include contact with healthcare personnel and the devices and procedures that are used to treat patients and to help them recover, and the physical equipment of the facility itself. Examples are surgical site infections (SSIs), catheter-associated urinary tract infections (CAUTIs), central line-associated bloodstream infections (CLABSIs), and ventilator-associated pneumonia (VAP), etc. (**Figure 1**) [4].

According to WHO estimates [5], in high-income countries, approximately 30% of ICU (intensive care unit) patients get at least one HAI, and the frequency in middle- and low-income countries is at least 2- to 3-fold higher. European surveys estimate that HCAs cause 16 million extra-days of hospital stay, 37,000 directly-attributable deaths, and an additional 110,000 contributory-deaths annually [6]. Recent data from Belgium estimate that 900,000 bed-days are complicated each year by at least one HAI [7]. Similar figures were reported in the United States, with about 99,000 deaths per year attributed to HAI [8].

The effect of HAIs on mortality in the ICU (intensive care unit) setting (medical and surgical) has shown that survival is significantly worse for HAI-affected patients (**Figure 2**) [9] (**Figure 3**) [9]. In addition, the annual financial losses attributable to HAI in the United States alone are estimated to be nearly \$20 billion in direct hospital costs (**Table 2**), and \$28 - 45 billion overall [10].

3. Normal Skin: Passive and Active Anti-Infective Properties

Hands are the major source of transmission of nosocomial pathogens by healthcare providers, so rigorous compliance to good hand hygiene practices is effective in reducing (but not eliminating) HAIs [11].

The passive and active anti-infective properties of skin have been comprehensively reviewed by Belkaid and Segre [12], and is abridged here. The skin provides structural and physiological barriers to entry of foreign pathogens. It provides protection against invasive infective pathogens and, perhaps surprisingly, supports active populations of symbiotic commensal microbiota [13] [14] [15].

The 10 - 20 μm stratum corneum (outermost and thinnest layer of skin) provides a major barrier to percutaneous absorption, a consequence of the characteristics of its cells (corneocytes, or horny cells). Corneocytes are flat nonnucleated

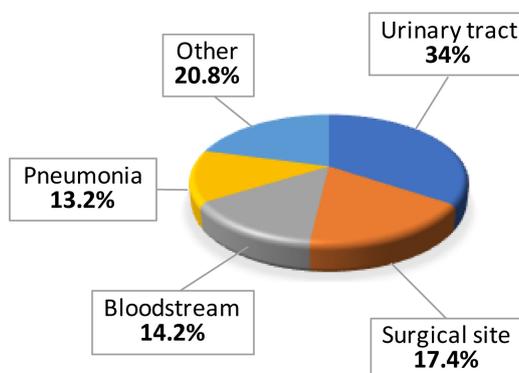


Figure 1. Relative distribution of nosocomial infections. Based on Magill (2014) [4].

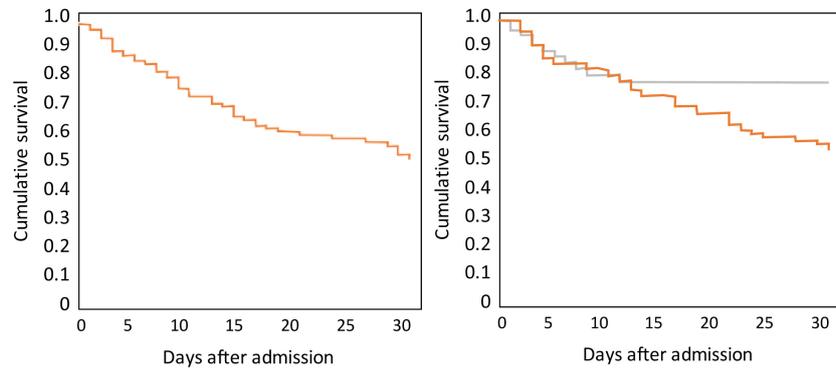


Figure 2. Mortality of SICU (surgical intensive care unit) and MICU (medical intensive care unit) patients with (filled column) and without (open column) nosocomial infections. Based on Toufen *et al.* (2013) [9].

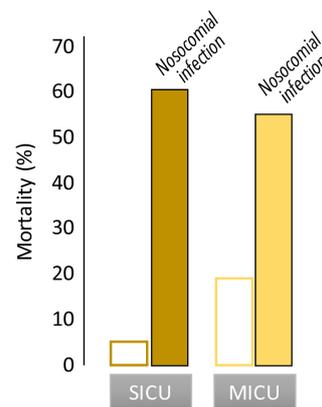


Figure 3. Kaplan-Meier survival curves for patients admitted to (left) a surgical intensive care unit, or (right) a medical intensive care unit with (lower line) or without (upper line) a nosocomial infection. Based on Toufen *et al.* (2013) [9].

Table 2. Annual costs nationally in the United States for four major HAIs. See Stone (2009) [10].

Type	Number	Cost (U.S. dollar)
Bloodstream infections	248,678	\$9.1 billion
Surgical site infections	290,485	\$7.4 billion
Pneumonia	250,205	\$2.5 billion
Urinary tract infections	561,677	\$0.6 billion
TOTAL	1,351,045	\$19.6 billion

cells composed primarily of insoluble fibrous protein keratins that are stabilized by cross-linked proteins, covalently-bound lipids, and polar structures that enhance cohesion of the corneocytes. The intercellular space contains lipid that forms a continuous barrier located directly under the stratum corneum. The stratum corneum is not a static structure, but rather is the net result of a steady state of equal rates of synthesis and loss. Thus, the formation of the skin barrier

is under dynamic homeostatic control, and subject to the influence of endogenous (genetic and metabolic) and exogenous (environmental) influences.

The skin is host to a myriad of communities of microbes located both on the skin and hair surfaces, and in invaginated structures such as sebaceous glands [13] [14] [15]. At about 1 million resident bacteria/cm² skin, there are on the order of 10 billion bacterial cells on the skin surface of the average human [16]. Differences in local environment lead to diversity in type and concentration of resident bacteria: oily (sebaceous) sites such as the forehead are more favorable for more lipophilic bacteria such as *Propionibacterium* species, moist areas preferentially favor *Staphylococcus* and *Corynebacterium* species. Site-preference is also demonstrated by fungi: *Malassezia* at core-body and arm sites, *Aspergillus*, *Cryptococcus*, *Rhodotorula*, *Epicoccum*, and others at foot sites. However, compared to the favorable environment of the gastrointestinal tract, dry skin is less supportive—cool, acidic, desiccated, and nutrient poor (the only nutrients are sebum and stratum corneum peptides and lipids).

Sweat contains salt and antibacterial compounds (free fatty acids and antimicrobial peptides) that disfavors some strains of bacteria, but favors others (e.g., *Staphylococcus*). Sebum secreted from sebaceous glands is lipid-rich and therefore serves as an antibacterial coating against several strains, but provides a favorable environment for others. The exact population (“microbiome”) is a function of age, intrinsic factors such as diet, and extrinsic factors such as temperature, antibiotic use, etc. (the local “biogeography”) [17]. Commensal microbes have coevolved with humans in sometimes symbiotic functions, and appear to provide several postulated advantages, such as inhibition of the colonization and biofilm formation of *S. aureus* (*S. epidermidis*), and protective competition against pathogenic microbes for limited resources (“colonization resistance”) [18] [19] [20].

Cross-talk between skin microbiota and skin immune systems (Figure 4) [12] results in highly sophisticated immune surveillance and response that integrates the innate and adaptive immune systems. Some immune factors are induced by certain microbiota, such as *Propionibacterium* species, expression of components of the complement system is increased, and IL-1 (interleukin-1) levels are modulated. Commensal microbes also modulate the function of local T-cells and increase cytokine production, processes that contribute to limiting the invasion by pathogenic microbes [21].

4. Transmission of Pathogens on Hands

Transmission of healthcare-associated pathogens (from surface to patient, patient to health-care provider, healthcare provider to healthcare provider, health-care provider to patient, visitor to patient, etc.) consists of the following sequence of events: [2]:

- 1) A pathogenic organism must be present at the original site (Table 3) [22].
- 2) The pathogenic organism must remain viable at the original host site until transmission.

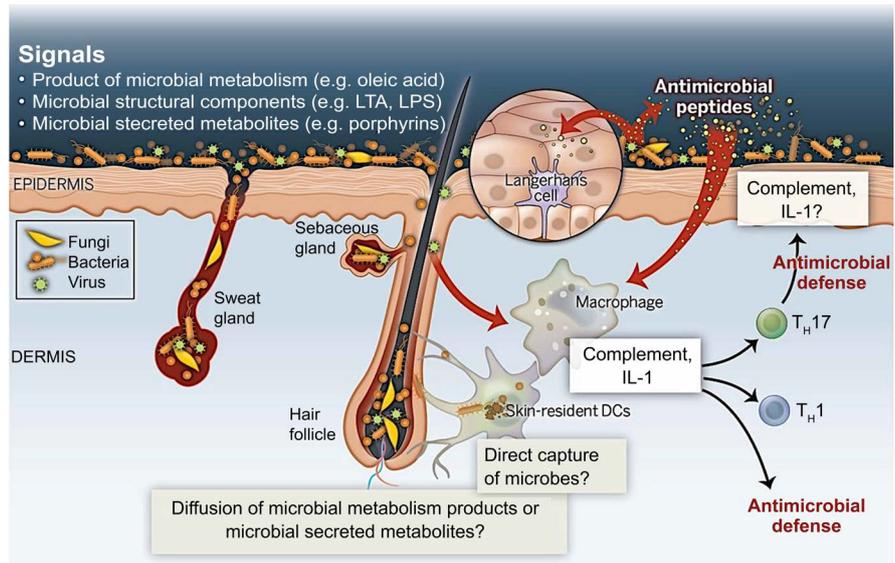


Figure 4. Cross-talk between the microbiota and the skin immune system. From Belkaid and Segre (2014) [12] with permission from the American Association for the Advancement of Science.

Table 3. Bacteria isolates found in cases of nosocomial pneumonia. See Kowalski (2007) [22].

Gram-positive bacteria	Gram-negative bacteria	%
	<i>Staphylococcus aureus</i>	19.0
<i>Pseudomonas aeruginosa</i>		15.5
	<i>Streptococcus</i> sp.	13.75
<i>Klebsiella</i> sp.		8.5
<i>Haemophilus influenzae</i>		8.25
<i>Acinetobacter calcoaceticus</i>		8.0
<i>Proteus</i> sp.		7.5
<i>Peptostreptococcus</i>		7.0
<i>Escherichia coli</i>		7.0
	<i>Peptococcus</i> sp.	5.5
	<i>Fusobacterium</i> sp.	5.0
	<i>Bacteroides melaninogenicus</i>	4.5
<i>Enterobacter</i> sp.		4.25
	<i>Bacteroides fragilis</i>	4.0
<i>Legionella</i> sp.		2.0
<i>Serratia</i> sp.		1.5
<i>Citrobacter</i> sp.		0.75

3) The barrier to transmission must be inadequate or omitted (unfiltered air, non-disinfected surface, incomplete hand washing, antisepsis, or ineffective

hand hygiene agent.

4) The pathogen must be transmitted either directly to recipient or to intermediate host.

Interruption of any of the steps in this process disrupts transmission, failure to interrupt any step in the process will ultimately lead to transmission.

The source of pathogenic organisms is sometimes obvious, such as infected or draining wounds, but not always. For example, a patient's normal intact skin can be colonized with a significant population of an organism such as *S. aureus*, *Proteus mirabilis*, *Klebsiella* spp., or *Acinetobacter* spp. The large volume of skin that is normally shed daily results in the deposition of millions of viable microorganisms being transmitted to surfaces such as gowns, bedding, etc. (particularly staphylococci and enterococci, which are resistant to desiccation) and to healthcare personnel (e.g., *Klebsiella* spp.) while performing even seemingly "clean" activities like lifting a patient, taking vital signs, or therapeutic touch [23]. Studies have documented contamination from activities related to wound care, catheter care, respiratory-tract care, material handling, infant care, and touching inanimate objects (e.g., fabric or furniture) in patient rooms [24].

5. Disinfectants

Any surface within a healthcare facility can become contaminated with an infectious agent. It is most likely to occur on surfaces of medical equipment that come in contact with infected patients or with infective agents transmitted on the hands, gloves, or gowns of healthcare personnel. Such contaminated surfaces can contribute to the spread of healthcare-associated infections. For this reason, the effective use of disinfectants should be a part of a multi-barrier strategy to prevent the transmission of pathogens that contribute to healthcare-associated infections. The use of the right disinfectant(s) can be effective (Table 4) [25].

6. Handwashing

Boyce and Pittet [2] have critically reviewed the pros and cons of various procedures used for hand hygiene, which is summarized here.

6.1. Soap(s) and Water

The cleaning activity of soaps and detergent-based products (which contain esterified fatty acids and sodium or potassium hydroxide) primarily derives from their ability to physically remove contaminated solids such as dirt and organic substances from the hands. This can remove flora that are loosely adherent or transient. Longer wash times are superior to shorter wash times. But plain (non-antimicrobial) soaps have little, if any, antimicrobial activity beyond the physical displacement of the pathogens. Several studies have convincingly shown that handwashing with plain soap fails to remove pathogens from the hands of hospital personnel. For example, in a study conducted by Ehrenkrantz and Alfonso [26], nurses mimicked the process of taking a femoral pulse on patients

Table 4. Chemical disinfectants. Based on summary in Rutala [25].

Chemical Agent(s)	Mechanism(s) of Action
Alcohols	Denaturation of proteins. Ethyl and isopropyl alcohols are most used; methyl alcohol has the weakest bactericidal action of the alcohols, so is seldom used for this application.
Chlorine and chlorine compounds	Unknown, but might involve oxidation of sulfhydryl groups in amino acids (enzymes) → oxidation of respiratory components, depressed DNA synthesis, decreased ATP production, etc.
Formaldehyde	Alkylation of amino acid sulfhydryl groups of proteins and ring <i>N</i> atoms of purine bases.
Glutaraldehyde	Alkylation of sulfhydryl, hydroxyl, carboxyl, and amino groups → alteration of DNA, RNA, and protein synthesis.
Hydrogen peroxide (H ₂ O ₂)	Production of hydroxyl free radicals → attack membrane lipids, DNA, and other essential cell components.
Iodine and iodophors	Iodine penetrates cell walls quickly → disruption of protein and nucleic acid structure and synthesis.
OPA (ortho-phthalaldehyde)	Mechanisms similar to glutaraldehyde; less potent, but greater uptake through outer layers of myco- and gram-negative bacteria.
Peracetic acid	Unknown, but believed to be an oxidizer → denatures proteins, disrupts cell wall permeability, and oxidizes sulfhydryl and sulfur bonds in structural proteins, enzymes, etc.
Phenolics	Low concentration: inactivation of essential enzyme systems and leakage of essential substances from the cell wall. High concentration: protoplasmic poison (penetration and disruption of cell wall, and precipitation of cell proteins).
Quaternary ammonium compounds	Inactivation of energy-producing enzymes, denaturation of essential cell proteins, and disruption of the cell membrane.

heavily colonized with gram-negative bacilli. The nurses then “cleaned” their hands either by washing with soap and water or by using an alcohol hand rinse. The inadequacy of washing with soap and water was demonstrated when the subsequent touching of a piece of urinary catheter transferred the organisms. Furthermore, non-antimicrobial soaps that do not contain emollients can cause skin irritation that is a negative factor for compliance. In the worst case, plain soaps can themselves become contaminated and increase bacterial counts on the skin [27].

6.2. Alcohol-Based Antiseptics (Sanitizing Rinses, Rubs, Gels, Foams)

Alcohols denature proteins by disrupting the intramolecular hydrogen bonding of protein side chains. New hydrogen bonds are formed between the alcohol molecule and the amino acid side chains of the protein [28]. The reactions require the presence of water. Therefore, most commercial products are a mixture of alcohol and water. Alcohols are effective against a wide variety (but not all) gram-positive and gram-negative bacteria, fungi, and viruses (mostly enveloped strains).

Application of alcohols to skin not blocked by dirt or other material is rapidly

germicidal and reduces bacterial counts to a greater extent than does washing with plain or antimicrobial soap. Alcohol is more effective in preventing transfer of HAI. For example, in the study cited above in which handwashing with soap and water was ineffective in transmitting bacilli from a patient to a catheter (92% transfer rate) [26], hand rub using an alcohol-based rinse was significantly more effective (17% transfer rate). Multiple studies under a variety of conditions and settings have demonstrated that the use of alcohol-based products is superior to standard handwashing with plain or antimicrobial soap. If alcohol-impregnated towelettes do not contain enough alcohol, they are no more effective than soap and water [29] [30].

Alcohol-based formulations are generally well tolerated. Frequent use can lead to drying of the skin, which can have a negative influence on compliance. Generally, addition of emollients, humectants, or other skin-conditioning agent reduces the problem of drying, and alcohol-based products containing emollients cause significantly less skin irritation and drying than do plain or antimicrobial soap [31]. One negative aspect of alcohol-based formulations is that they sting upon application to broken skin (cuts, abrasions, etc.).

6.3. Negative Aspects of Hand-Hygiene Products

Frequent and repeated use of handwashing products, particularly soaps and other detergents, but also alcohol, can lead to dry skin, irritation, and even more serious problems, including chronic contact dermatitis. One survey found that almost 9 out of 10 nurses experience skin problems, and estimated that a quarter of all nurses have symptoms or signs of dermatitis involving their hands [32]. The cause of the irritation can either be the antimicrobial agent itself, or one or more component of the formulation. Detergents and alcohols can damage skin by the very mechanism of their antimicrobial action: denaturation of proteins. The degree of irritation can be lessened by adding emollients and humectants to the formulation. Nevertheless, affected healthcare providers experience skin that feels rough, dry, and burning due to erythema, scaling, and fissures. Aside from being unsightly and uncomfortable, damaged skin can host flora such as staphylococci and gram-negative bacilli not normally present to the same extent in healthy skin [33] [34].

Irritant contact dermatitis is also reported with use of iodophors, chlorine compounds, and other products used alone or in combination. The problem is exacerbated by warm water, low relative humidity, failure to use counter measures such as hand lotion or cream, and even the frequent wearing of latex gloves. Allergic reactions have been reported for several antiseptic agents, such as quaternary ammonium compounds, iodine and iodophors, chlorhexidine, and others. Allergic reactions to alcohol-based products might be attributable to the alcohol itself, to an impurity, or to some constituent ingredient of the formulation, such as fragrances, or benzyl-, (iso)stearyl-, or myristyl-alcohol, phenoxyethanol, propylene glycol, parabens, or benzalkonium chloride [35].

7. Resistant Strains

Some of the residual problem of HAIs is attributable to the fact that certain pathogens are resistant to the mechanism of action of hand hygiene products (Figure 5).

7.1. MRSA

Methicillin, a narrow-spectrum β -lactam antibiotic of the penicillin class, was introduced in 1959 in an effort to treat infections caused by *Staphylococcus aureus* that had become resistant to the action of penicillin. Like other β -lactam antibiotics, methicillin acts by inhibiting the synthesis of the cell wall of gram-positive bacteria, specifically by inhibiting transpeptidase enzyme that is required for cross-linking components of the cell wall. Unfortunately, within only a few years there were reports of *S. aureus* isolates that had acquired resistance to methicillin [36], hence the name MRSA (methicillin-resistant *Staphylococcus aureus*). MRSA is now a serious problem worldwide as a major cause of hospital-acquired infections.

The methicillin resistance gene (*mecA*) encodes a methicillin-resistant protein not present in susceptible strains of bacteria. The result is that many MRSA isolates are susceptible only to glycopeptide antibiotics (e.g., vancomycin) or investigational drugs. But some MRSA isolates have now been reported that have decreased susceptibility to even glycopeptides (glycopeptide intermediately susceptible *S. aureus*, GISA) [37].

The effectiveness of hand hygiene on control of nosocomial MRSA has been reviewed by Marimuthu *et al.* [38]. Hand washing with plain or antimicrobial soap alone as a prevention strategy against MRSA is ineffective. The case for alcohol-based handrubs was examined in a systematic review of the literature on the impact of alcohol-based handrub use on MRSA rates [39]. Among the 12 studies included in the review, the use of alcohol-based handrubs was associated with significant reduction in MRSA rates. It remains unclear whether a plateau is reached, at which point hand hygiene does not provide additional benefit.

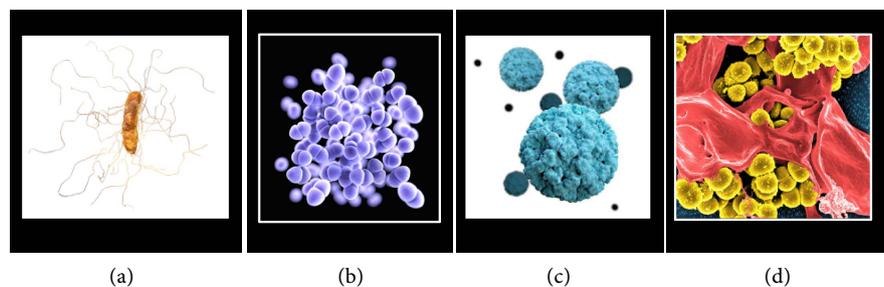


Figure 5. (a) *C. difficile*; (b) VRE (vancomycin-resistant enterococci) (<https://phil.cdc.gov/Details.aspx?pid=16882>); (c) Norovirus (https://upload.wikimedia.org/wikipedia/commons/5/55/Norovirus_virions_white_background_NIH_21348.jpg); and (d) MRSA (methicillin-resistant *Staphylococcus aureus*) (https://upload.wikimedia.org/wikipedia/commons/0/08/MRSA_dead_neutrophil.jpg).

And current hand hygiene practices are not a panacea against MRSA because:

1) hand hygiene improvement efforts involve education and behavior change, which take time—and thus are unlikely to have an immediate effect on MRSA rates,

2) the effectiveness of alcohol-based handrubs on postoperative surgical site infection due to MRSA might be less significant than previously estimated,

3) the incremental benefit of hand hygiene on MRSA after a certain threshold has been reached is unclear, and the general assumption of greater hand hygiene compliance yielding greater benefit is being challenged,

4) it remains unclear whether contact precautions can be stopped in settings with relatively low MRSA prevalence and sufficient hand hygiene compliance [40].

Furthermore, hand hygiene practices may suffer as a result of misuse of gloves with resultant increase in MRSA rates. Therefore, since microbial contamination of healthcare workers' hands can occur despite the use of barrier gloves, regardless of presence of leaks, hand hygiene remains an important component of prevention [41] [42] [43].

7.2. VRE and VRSA

This topic has been comprehensively reviewed by Cetinkaya *et al.* [44] and O'Driscoll & Crank [45], and is abstracted here. Vancomycin is a glycopeptide that works by inhibiting transpeptidation by binding to necessary D-alanyl-D-alanine residue components of the bacterial cell wall. Since this mechanism can kill methicillin-resistant staphylococci and other gram-positive bacteria, vancomycin was widely used for the treatment and prophylaxis against MRSA [46]. It has even been used for the treatment of *Clostridium difficile* enterocolitis. Unfortunately, vancomycin-resistant enterococci (VRE) were reported in England in 1988 [47], then France [48] and the United States soon thereafter [49] [50]. VRE rapidly spread and are now found in hospitals throughout the world [51] [52]. The seriousness of VRE increased dramatically in 2002 when the first patient case of VRE transmitting *vanA* resistance genes to methicillin-resistant MRSA to form a vancomycin-resistant *Staphylococcus aureus* (VRSA) isolate was reported [53]. According to the National Health-care Safety Network (NHSN) 35.5% of enterococcal hospital-associated infections during 2009-2010 were resistant to vancomycin, ranking it as the second most common cause of nosocomial infections in the United States.

Transmission of VRE by healthcare personnel whose hands have become contaminated with the organism while caring for affected patients is now possibly the most common mode of spread of nosocomial pathogens. VRE and other resistant enterococci from cultures of specimens from the hands of healthcare workers show the extent of the problem [54] [55]. Although VRE may also be spread by way of contaminated medical equipment and by disposable cover gowns that are worn by personnel who care for VRE patients [56], transmission

by hands is much more common. Thus, gloves should be removed and disposed of before leaving a patient's room, and hands should be washed immediately with an antiseptic soap or antiseptic agent [29] [57] [58]—plain soap is relatively ineffective in preventing transmission of VRE by hands [30] [55] [59].

7.3. *C. difficile*

C. difficile is a gram-positive bacterium that is such a problem because it can opportunistically repopulate commensal gastrointestinal biota that it is depleted by disease or antibiotic therapy. It causes life-threatening diarrhea because it releases exotoxin A (TcdA, *tcdA*) and B (TcdB, *tcdB*), which destroys epithelial cells of the intestinal lumen. It does this by stimulating the release of pro-inflammatory mediators such as cytokines and chemokines. *C. difficile* was first described by Hall and O'Toole in 1935 and described as “the difficult clostridium” [9] because the bacterium can form spores as a survival mechanism when the bacterium is exposed to hostile conditions [10]. Transmission among humans is mainly *via* contact with fecal matter (fecal-oral route). Ingestion of *C. difficile* spores transforms them in the gastrointestinal tract into an active state [11]. A significant exposure to *C. difficile* is nosocomial, with the most likely transmittal route being healthcare personnel.

Prevention of transmission of *C. difficile* by healthcare personnel presents a challenge. Washing with soap and water physically eliminates contaminated material, but is not antimicrobial. The use of alcohol can only kill the non-spore form of *C. difficile*—not *C. difficile* spores. Healthcare workers should wear gloves and protective gowns when caring for patients with *C. difficile*, and surfaces should be disinfected (but non-chlorine-based cleaning agents can promote formation of *C. difficile* spores). Handwashing reduces spores, and alcohol-based handrubs are effective against non-spore forms—but not the spores—of *C. difficile*.

New hypervirulent strains of *C. difficile* emerged in the early 2000's. *C. difficile* has become one of the most common causes of healthcare-associated infections in United States hospitals. It is the leading cause of gastroenteritis-associated death (an estimated 29,000 in 2011), and costs the healthcare system nearly \$5 billion for acute care facilities alone.

8. Summary and Conclusions

Healthcare-associated infections lead to added suffering, morbidity, mortality, and financial burden to patients and society. Given that HAI is inherently linked to health-care workers' behavior (e.g. sub-optimal hand hygiene practices) and, in some cases, to health-care system gaps (e.g., lack of adequate training or compliance), this problem should be better addressed. Following introduction of recommendations and guidelines for hand-hygiene protocols, HAI incidents dropped from historic high levels to significantly lower current levels despite similar in-patient load on healthcare facilities. However, the HAI incidence level

now appears to have become stuck at the reduced level, suggesting that currently configured protocols might have maxed out. The protocols focus primarily on device and process improvement (such as the use of the right catheter at the right time), and efforts continue to achieve further improvements in both areas. Proper hand hygiene has always been a key part of all protocol recommendations and was heavily emphasised from the start with easy and quick-to-use/easy-to-place alcohol rubs as a central component of improved hand hygiene. Over time however, the biggest challenges to improve hand hygiene have become apparent: 1) rubs do not have a full-kill spectrum and their overuse raises concerns about potentially leading to an increase in drug-resistant pathogens, and 2) despite the convenience of use and easy accessibility of rubs, hand-hygiene compliance has remained persistently low, especially in ICUs. Emphases on having well-defined programs to create greater awareness, provide better training and conduct non-threatening compliance audits have been the primary approach to improve hand hygiene compliance, but they have generally failed to deliver their expected impact. We have highlighted here some of the biological and treatment hurdles that contribute to the failures.

There are also some human-factors, reviewed in Part 2 and addressed in Part 3. The human factors are not optimized, but correspondingly offer the greatest opportunity for significant improvement and better control of health-care-associated infections. One such approach, using human factors engineering, is presented in Part 3.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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