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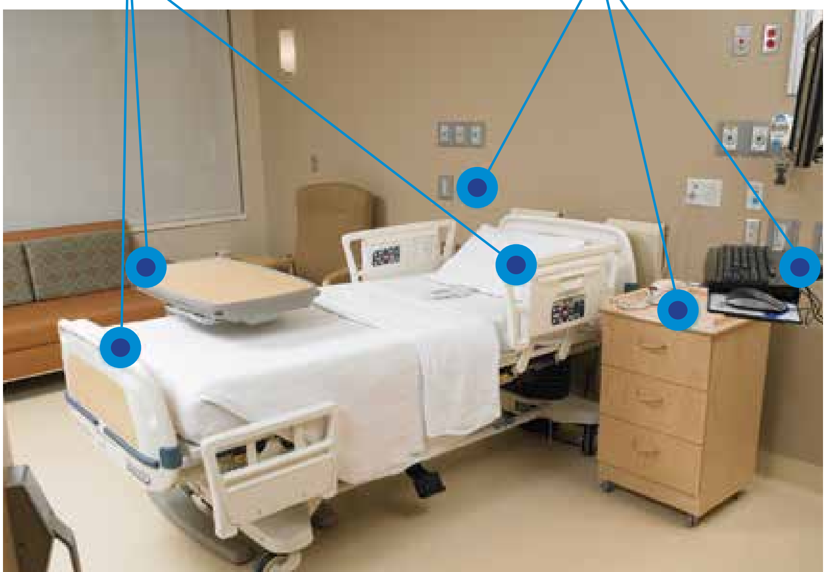

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REVIEW ARTICLE

Antibiotic resistance: Evolution and alternatives

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ABSTRACT

Globally, infection control has been challenged by the rapid advent and dissemination of antibiotic resistant microorganisms. The 70-odd years' history of post antibiotic era has shown that despite the fitness cost, microorganisms will continue to evolve and we now face a never-ending battle of bacterial resistance against the antibiotics of last resort that we have at our disposal. In this article, we give a brief overview of the discovery of antibiotics, the emergence of antibiotic resistance, and the alternative strategies that can be sought for the treatment of infections caused by multidrug resistant bacteria.

KEY WORDS

Antibiotic resistance, evolution, treatment and alternatives

INTRODUCTION

Antibiotics have revolutionized medicine in many respects; their discovery was a turning point in human history. Regrettably, the development of specific mechanisms of resistance following the introduction of these drugs has plagued their therapeutic use (1). Now, it is clear that the success of antibiotics might only have been temporary and medical practitioners as well as scientists around the world expect a long-term and perhaps never-ending challenge to find new therapies to combat antibiotic-resistant bacteria (2). Hence, broader approach to address bacterial infection is needed. In this article, we discuss the holistic overview of antibiotic resistance development, its increasing trend that has led to urgency towards the development of some alternatives to antibiotics which can be probable candidates in the treatment of infections caused by multidrug resistant bacteria in future.

HISTORY OF ANTIBIOTIC USE AND RESISTANCE

More than 60 years ago, even before the first clinical use of antibiotics; resistant organisms had been isolated (3). The potential problem of the widespread distribution of antibiotic resistant bacteria was recognized by scientists and healthcare specialists from the initial use of these drugs (3). Once the antibiotic was used widely, resistant strains capable of inactivating the drug became prevalent.

In 1930, seven years before the introduction of Sulfonamides (the first effective group of antibiotics) a resistance mechanism was reported for the wonder drug, and paradoxically, the same mechanisms operate some 70 years later (4). Following these drugs was the introduction of another therapeutic agent, streptomycin, introduced in 1944 for the treatment of tuberculosis. Paradoxically, mutant strains of *Mycobacterium tuberculosis* resistant to therapeutic concentrations of the antibiotic were found to arise during patient treatment (5). As other antibiotics have been discovered and introduced into clinical practice, a similar course of events has ensued. The latest example has been the first ever reporting of plasmid-mediated colistin resistance in *Escherichia coli* isolated from animals, food, and patients in China by Yi-Yun Liu and colleagues in November 2015 (6). Following their report in *The Lancet Infectious*

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Conflicts of interest

None.

Diseases, plasmid mediated resistance of colisitn has been reported from several other parts of globe including Vietnam, Denmark, Germany, Switzerland, and several other countries (7,8).

Environmental bacteria, which predate the modern antibiotic era by billions of years, have been reported to carry genes encoding resistance to antibiotics that have become critically important in modern medicine (9). An instance of which has been the culture of viable multidrug-resistant bacteria from the Lechuguilla Cave in New Mexico, which had remained totally isolated for >4 million years (10). Likewise, DNA extracted from 30,000-year-old Beringian permafrost contained genes coding for resistance to ß-lactams, tetracyclines, and glycopeptides, confirming that resistance predates antibiotic use in medicine and agriculture (9). Furthermore, major ß-lactamase classes predate the existence of humans. Class A ß-lactamases evolved approximately 2.4 billion years ago, and were horizontally transferred into the gram-positive bacteria about 800 million years ago. The family of genes, including the progenitors of CTX-Ms, diverged 200-300 million years ago (11).

MECHANISM AND EVOLUTION OF ANTIBIOTIC RESISTANCE

Antibiotic resistance has been defined as the temporary or permanent ability of an organism and its progeny to remain viable and/or multiply in presence of specific concentration of an antibiotic that would otherwise destroy or inhibit other members of the strain. Bacteria may be defined as resistant when they are not susceptible to a concentration of antibiotic used in practice (12). Distinct gene transfer mechanisms have been proposed for a variety of commensals and pathogens leading to the wide dissemination of resistance gene in microbial kingdom (13-15). A few of the resistance types that illustrate the difficulties in maintaining effective antibiotic activity are mentioned in this review.

Resistome

Antibiotic resistance is a dynamic phenomenon for the natural environment itself is the ultimate source of putative resistance gene. The ability of microorganisms to overcome a myriad of chemical and environmental challenges, including those chemicals toxic to bacteria-"antibiotics" is not a modern day's trait. Over the millennia, microorganisms have evolved evasion strategies to overcome those challenges. Soil bacteria may contain antibiotic resistance genes responsible for different mechanisms that permit them to overcome the natural antibiotics present in the environment (16-18). This gene pool has been recently named the "resistome", and its components can be mobilized into the microbial community affecting humans because of the participation of genetic platforms that efficiently facilitate the mobilization and maintenance of these resistance genes (3,19). The natural history of antibiotic resistance genes can be revealed through the phylogenetic reconstruction and this kind of analysis suggests the long-term presence of genes conferring resistance to several classes of antibiotics in nature well before the antibiotic era (20,21). Structure-based phylogeny of serine and metallo-ß-lactamases, for example, established that these ancient enzymes originated more than two billion years ago, with some serine ß-lactamases being present on plasmids for millions of years (11). Phylogeny of the ß-lactamase and housekeeping genes is highly congruent in *Klebsiella oxytoca* implying that these genes have been evolving for over 100 million years in this host (22). The similar phylogenetic analysis of ß-lactamases in the metagenomic clones derived from the 10,000 years old "cold-seep" sediments indicated that most of the diversity of these enzymes is not the result of recent evolution, but is that of ancient evolution (23).

Intrinsic resistance

Intrinsic resistance refers to the pre-existence of bacterial genomes in certain genera, species and strains that could generate a resistance phenotype. It is the ensemble of chromosomal genes that are involved in intrinsic resistance and whose presence in strains of a bacterial species is independent of previous antibiotic exposure and is not due horizontal gene transfer (24). For example, many enteric bacterial species including *Pseudomona saeruginosa*, exhibit a very low susceptibility to hydrophobic antibiotics like macrolides, because hydrophobic antibiotics have difficulties penetrating the outer membrane of these organisms (25). Intrinsic resistance mechanism has been recently established for some of the problematic bacteria causing nosocomial infections in hospital settings (26,27). Ironically, the most prominent intrinsically resistant bacteria have an environmental (non-clinical) origin, in habitats that are much less likely than clinical settings to present intense antibiotic selective pressure (28).

Acquired resistance

Acquired resistance refers to the resistance of bacteria to previously susceptible antibiotics. In contrast to the intrinsic resistance mechanism resident in bacteria since antiquity, acquired resistance is a recent phenomenon developed in bacteria primarily aided by the anthropogenic activities such as use of antibiotics for other purposes besides the treatment of infection like, growth promotion in animals, prophylactic use in aquaculture, pest control, use as biocides as well as excessive use of antibiotics by human as a selective force for the process (16,24,29). This trait is gained by bacteria either by mutation or by horizontal gene transfer. Environmental bacteria are the one that can serve as the vectors for transmission of resistance gene to commensals (3,19). Ultimately, these commensal bacteria undergo certain mutations induced by commonly used antibiotics, so as to ascertain its survival in the host and serve as the source of resistance gene to the pathogenic bacteria (30-32). Environmental bacteria contain a large number of genes capable of conferring antibiotic resistance to human pathogens upon transfer through horizontal mechanism (3,33,34).

ALTERNATIVES TO ANTIBIOTICS

Antibiotics are among the most important tools in medicine, but their efficacy is threatened by the evolution of resistance. Since the earliest days of antibiotics, resistance has been observed and recognized as a threat; today, many first-generation drugs are all but ineffective (35). The emergence of resistance to antibacterial agents is a pressing concern for human health. New drugs to combat this problem are therefore in great demand (36,37), but as past experience indicates, the time for resistance to new drugs to develop is often short and the resistance thus acquired is stable (38,39). So far scientists if not have completely avoided, at least made attempts to postpone the ultimate crisis of antibiotic resistance apocalypse through the continued modification of existing compounds and the discovery of new antibiotic classes. However, it is apparent that the quest for an invincible antibiotic, "the magic bullet" that would withstand bacterial resistance, is a race against time. Thus an alternate approach to address bacterial infection is needed (2). Here, we focus primarily on some of the alternatives approaches to antibiotics that target bacteria or the host cells without any impairment in the normal body functions and would potentially deliver therapies of clinical use thereby, relieving the host of infection.

PROBIOTICS

Probiotics are live microorganisms which, when administered to a host in adequate amount confers a health benefit. Basic research towards the implication of probiotics as a therapeutic agent so far have identified utility of probiotics in treatment of oral inflammation and dental caries (40), treatment of antibiotic-associated diarrhea (41) and potential of probiotics in several other conditions are being sought. Defined mixtures of bacteria or the use of non-toxigenic spores of *Clostridium difficile* will probably provide therapeutic and prophylactic therapies that will improve current clinical practice for the treatment of *C. difficile*-associated diarrhea and antibiotic-associated diarrhea (42). The action of probiotics in the host is exerted by three mechanisms: modulation of the content of gut microbiota; maintenance of the integrity of the gut barrier and prevention of bacterial translocation; and modulation of the local immune response by the gut-associated immune system. Regarding their role for the prevention and treatment of infectious diseases, adequate evidence coming from randomized clinical trials (RCTs) is available for antibiotic-associated diarrhea (AAD), *Clostridium difficile* infection (CDI), acute gastroenteritis and infectious complications following admission to the Intensive Care Unit (ICU). Existing evidences support their role for decreasing the incidence of AAD and CDI when administered in parallel symptoms among pediatric populations with acute gastroenteritis, particularly of rotavirus etiology (43).

PHAGE THERAPY

Biological control is a terminology used to refer the application of organisms or their products to environment including plants and animals in order to reduce the numbers of other biological agents and undesirable organisms. This can include the targeting of undesired microorganisms by other microorganisms. Several approaches have so far been studied for assisting in biological control in medical science as a potential therapeutic tool (44). Bacteriophages, the viruses that infect bacteria, have for decades been successfully used to combat antibiotic-resistant, chronic bacterial infections. Phage therapy has been proposed as a promising alternative to antibiotics (45). Phage therapy has been studied in recent years as a probable candidate for treatment of MDR bacterial strain, specifically against biofilm-producing bacteria (44,46).

Bacteriophages can be used as a therapeutic option in several different ways. Its application in treatment can be made either using the phage in its wild form or it can be genetically engineered so as to assign new properties to a wild-type phage to suit the desired treatment. Bacteriophage can be used in small doses because they replicate when their host bacterium is present. During treatment of an infection they might also evolve to infect the strains causing the disease. This replication and evolution makes them unique in pharmaceutical product development. More product than was dosed will be present in the patient and that product can change over time; what is sampled after dosing is not exactly what was given to the patient. Besides, these phage lysins (bacteriophage-derived enzymes) can be used to target specific organisms. Lysin CF-301 is being developed to treat *Staphylococcus aureus* because of its potent, specific, and rapid bacteriolytic effects (47).

IMMUNE MODULATION

Immune modulatory therapies can be another promising approach; a new paradigms for anti-infective therapy. Under this therapy the natural mechanism in the host are exploited to enhance the treatment benefit against the infection. The objective is to initiate or enhance protective antimicrobial immunity while limiting inflammation-induced tissue injury. A range of potential immune modulators have been proposed, including innate defense regulator peptides and agonists of innate immune components such as Toll-like receptors and NOD-like receptors (48,49). Immune modulation therapy is a wide option which may include stimulation of immune system as well as suppression of the immune system depending upon the disease condition and cause of infection.

ANTIBODIES

An important tool as an alternate option in the treatment of drug resistant bacterial infection can be antibodies, an effective armament in the "arsenal" of today's clinician. Typically monoclonal or polyclonal antibodies are administered in large doses, either directly or indirectly into the circulation, via a systemic route which is well suited for disseminated ailments and have been successfully testified in treatment against *Staphylococcus aureus* (50,51). Antibodies that bind to and inactivate a pathogen, its virulence factors, or its toxins are widely considered one of the alternative approaches most likely to have major clinical impact and have been reportedly used in treatment against carbapenem resistant Enterobacteriacae (52). Antibodies are considered a low-risk area with strong science basis, history of safe use, and a high degree of technical feasibility (2).

VACCINES

Vaccines constitute one of the greatest success stories within the health sector. They form part of a multi-faceted public health response to the emergence of pandemics. The physiological mechanisms behind vaccination are well established and the positive public health impact of prophylactic vaccines remains medically undisputed (53). Vaccination activates the immune system and induces both innate and adaptive immune responses, thus leading to the production of antibodies, in the case of a humoral response, or to the generation of memory cells that will recognize the same antigen, if there is a later exposure (54). Periodic and repeated injections can improve the efficacy and effectiveness of inoculations (55,56). Traditional vaccines are generally classified into live-attenuated and inactivated/killed vaccines. Bacterin is a suspension of killed or weakened bacteria used as a vaccine. Live-attenuated bacteria, replicating transiently in the host, are capable of expressing a full repertoire of antigens (57). Utilizing these properties of vaccine several treatment strategies have already been adopted for infection control due to invasive bacterial diseases caused by *Streptococcus penumonae, Hemophilus influenza, Neisseria meningitis and Mycobacterium tuberculosis* (58-62).

ANTIMICROBIAL PEPTIDES

Antimicrobial peptides (AMPs) are an essential part of innate immunity that evolved in most living organisms over 2.6 billion years to combat microbial challenge (63). These small cationic peptides are multifunctional as effectors of innate immunity on skin and mucosal surfaces and have demonstrated direct antimicrobial activity against various bacteria, viruses, fungi, and parasites (64). Novel biologic effects of AMPs have been recently documented such as endotoxin neutralization, chemotactic and immunomodulating activities, induction of angiogenesis and wound repair. Thus these ancestral molecules are crucial components of the innate immune system and attractive candidates for novel therapeutic approaches. Many reports of protective effects of antimicrobial peptides in human against bacterial infection have been reported earlier (65). Although scientific literature and clinical trial have not yet led to a therapeutic breakthrough for the systemic use of these peptides, further research and development in this field can lead to reduction of toxicity through use of non-natural amino acids, improve formulation and design.

LIPOSOMES

Bacteria use an array of virulence factors to establish infection in the host (66). Targeting one of these virulence factors can prevent the infection. Gram-positive bacteria like *Staphylococcus* and *Streptococcus* secrete cytotoxic pore-forming toxin as an important virulence factor to cause a substantial burden of disease. Antitoxins strategies indeed are among the most intensively pursued anti-infective strategies. The strategies, however, have clear limitations. Even if they target toxins associated with virulence, they do not address the broad heterogeneity in bacterial virulence factors. Hence, neutralization of these toxins using a broad spectrum anti-infective weapon or preventing these toxins to act upon specific receptors on host can be a novel approach to treat MRSA strains of *S. aureus* and other MDR strains of gram-positive bacteria (67). Liposomes, which can be synthesized from natural lipids are nearly spherical vesicular structures made up of one or more lipid bilayers (unilamellar or multilamellar liposomes, respectively), and possess limited intrinsic toxicity. Liposomes (engineered) can be tailored to effectively compete with host cells for toxin binding. Liposome-bound toxins are unable to lyse mammalian cells in vitro. These artificial liposomes act as decoy targets to sequester bacterial toxins that are produced during active infection in vivo and hence prevent the damage to mammalian cells and inflammation (68). These liposomes have the potential to suppress chronic infections. Indeed, all constituents of the formulation have already been used in other pharmaceutical formulations and multiple administration has proven to be non-toxic in humans (69).

BIOFILM AND QUORUM SENSING INHIBITON

Biofilm-producing bacteria are one of the most problematic etiological agents causing hospital-acquired infection of implantable medical devices such as orthopaedic prostheses and intravascular catheter. Within biofilms, bacteria are significantly less susceptible to antibiotics and host defenses, making biofilm infections difficult to diagnose and treat, and often necessitating removal of the infected implant (70). Quorum sensing (QS) allows communication between bacteria, synchronizing alteration in genetic expression of the whole bacterial population, thus coordinating activities such as biofilm formation and the production of virulence factors (71). Inhibition of quorum sensing and biofilm formation can be an effective measure to combat infections caused by these problematic organisms. Inhibitors targeting QS can block the functions of QS system and therefore prevent bacterial virulence regulated by QS system. QS inhibitors (QSIs) are classified into three groups including non-peptide small molecule, peptide (mainly AIPs, i.e., auto inducing peptides homolog), and protein QSIs. Non-peptide QSIs mainly interfere with the synthesis of QS signal molecules or the binding to the receptors (72). Protein

Return to TABLE OF CONTENTS

synthesis inhibitors (e.g., oxazolidinones and tetracyclines), cell membrane and wall-active antibiotics (e.g., lipopeptides and glycopeptides) and inhibitors for DNA and RNA synthesis (e.g., rifampin) have been successfully used for treating staphylococcal biofilm (73). Methane-thiosulfonate and mercurial p-hydroxymercuribenzoic acid could target sortases, a membrane enzyme catalyzing the covalent anchoring of surface proteins to peptidoglycans, which are involved in bacteria adhesion (74).

CONCLUDING PERSPECTIVE

The optimism of the early period of antimicrobial discovery has been tempered by the emergence of bacterial strains with resistance to these therapeutics. Today, clinically important bacteria are characterized not only by single drug resistance but also by multiple antibiotic resistance – the legacy of past decades of antimicrobial use and misuse. Drug resistance presents an ever-increasing global public health threat that involves all major microbial pathogens and antimicrobial drugs. Hence, the situation demands some alternative approaches capable of broadly addressing the bacterial infection. However, there is still a considerable gap between antibiotic alternatives and antibiotics concerning the effectiveness of disease prevention and growth promotion. Meanwhile, the alternatives that we currently have at our disposals to tackle the situations as mentioned in this article can be prioritized and investments in such projects need to be increased. Antimicrobial resistance has to become a major international science program to provide the solutions needed now by society. At the same time, we must not forget that "it's better to prevent than cure". Thus, we must strengthen the supervision and enforcement of laws in order to control antibiotic resistance through approaches such as antimicrobial stewardship in clinical settings and similar approaches to reduce their use and residues from the food chain within established safe levels.

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REVIEW ARTICLE

A global threat of antimicrobial resistance: A narrative review

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KEY WORDS
antimicrobial resistance; microbes; antibiotics; pathogen; drug resistance; antibiotic-resistant; bacteria; transmission; human; animal; model; causal; relation

INTRODUCTION

Antimicrobial Resistance (AMR) is the ability of microbes to resist the effects of drugs that normally inhibit their growth or kill them. Infections by these organisms that are resistant to multiple antimicrobials are difficult to treat. It increases length of hospital stay, morbidity, and mortality. More than 70% of bacteria that cause hospital-acquired infections are resistant to first-line antibiotics, which results in treatment of these infections with second- and third-line drugs that are more expensive and more toxic to the patient (1). AMR is linked to antibiotic use since the discovery of penicillin (2). Alexander Fleming warned against overuse of penicillin. Over time, resistance to all classes of antimicrobials has emerged. In the recent past, there has been a rise of several resistant pathogens that include bacteria, viruses, fungi, and parasites. Multiple studies published over the last 60 years, describe the genetics, biochemistry, origins, evolution, and mechanisms of AMR (2).

A major breakthrough in 1929 was the discovery of penicillin. In World War II (1939-1945), penicillin played a major role in treatment of war wounds. The success of penicillin led to discovery of other antibiotics such as streptomycin followed by many more, targeting various bacteria that cause numerous illnesses (1). Antibiotics have revolutionized medicine. Beyond doubt, antibiotics are one of the most successful drugs developed to treat infections marred by the fact that the very same microbes they are supposed to kill can also become resistant to them, consequently rendering them ineffective. Increasing AMR in recent years became the most pressing public health priority.

Discovery of novel antibiotics has slowed down recently, while their use has tremendously increased. The Federal Drug Administration (FDA) approved 16 antibiotics between 1983 and 1987; only two were approved between 2008 and 2012 (2). Understanding the evolution of resistance will help develop plans and policies to mitigate resistance to antibiotics. Mechanisms by which pathogens develop AMR include (1) inactivation of antibiotics by ß-lactamase enzyme (2) modification of target drug binding proteins (3) impaired penetration ofdrug into the target of bacterial cell wall (4) presence of efflux pumps in cell wall, which pump out antibiotics (3). The Center for Disease Control and Prevention (CDC) estimates that in the United States, antibiotic-resistant infections sicken more than two million people every year of which at least 23,000 die (4). AMR also poses a serious economic threat in terms of direct healthcare costs and lost productivity due to sick days each year (4). Antimicrobial overuse and misuse in both humans and animals has led us down this path of antimicrobial resistance in microbes.

METHODS

Search strategy

Literature search included studies that addressed antibiotic resistance in relation to antibiotic use in humans, animals, and agriculture. Search engines such as Google Scholar, Embase, and PubMed were used to find published literature using the key terms antibiotic resistance, anti-microbial resistance, strategy, agriculture, antibiotics, abuse, misuse, overuse, recommendation, guideline, threat, and public health with reference lists of relevant articles searched by hand. The search included systematic reviews, evidence-based medicine, consensus development conferences, and guidelines. Recommendations and guidelines were searched from Center for Disease Control and Prevention, Society for Healthcare Epidemiology of America (SHEA), National Institute of Health, World Health Organization, Public Health Agency of Canada, Infection Prevention and Control Canada, and US Food and Drug Administration. Searches were restricted to the English language.

Study selection

The focus of this review is to bring attention to the growing global menace of antimicrobial resistance, causes behind its rise, and potential ways to mitigate the crisis. To this effect, abstracts of searched articles and their content were examined for relevance. No limits were placed on articles' publication date and study methodology (observational or experimental) study setting (hospital, urgent care, community center, etc.) and study region (country) were ignored. Articles with strategies to minimize antimicrobial resistance in humans and animals were selected. Guidelines and recommendations of national and world health organizations and action plans adopted by governments were also reviewed.

Model of causation

Post literature review, a model of causation was developed that describes the dynamics of how resistant pathogens spread among humans and animals. It highlights the risk factors that increase AMR and the chain of transmission (spread of AMR pathogens) among humans and animals through food chain. The model illustrates a pathway for zoonotic transmission of pathogens via consumption of contaminated meat. It also shows that resistant pathogens can transmit to humans by consuming crops that were treated with fertilizer containing feces (manure) of animals colonized with resistant pathogens. Additionally, it also lists several factors to mitigate AMR.

RESULTS

Risk factors

Antibiotic resistance in microbes is an adaptive trait acquired after antibiotic exposuredue to use, overuse, and misuse in both medical and agriculture community. Use of antibiotics in food-producing animals plays an important role in developing microbial resistance. The model of causal relationship (Figure 1) describes the chain of transmission of antimicrobial resistant bacteria between humans, animals and the environment. It highlights the risk and mitigating factors for antimicrobial resistance.

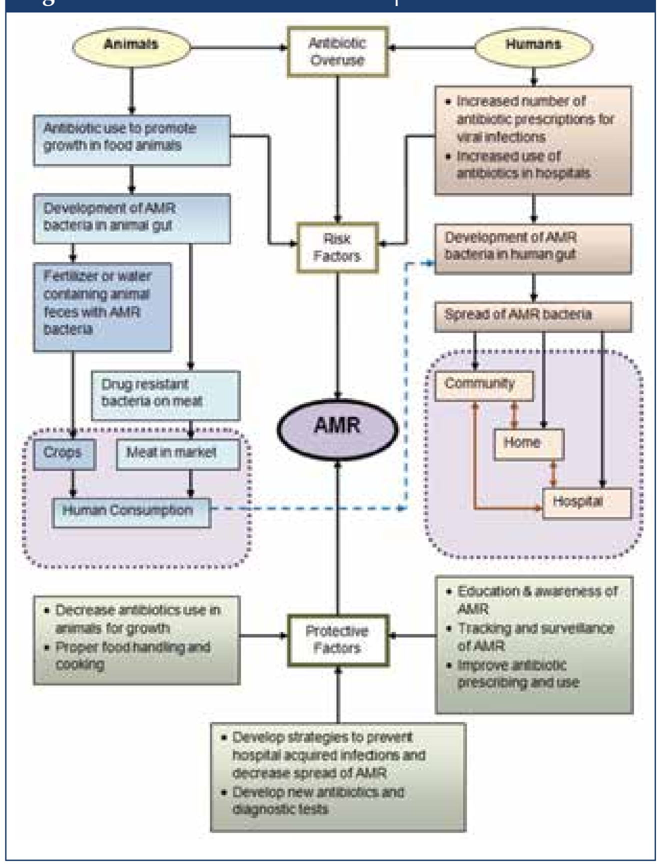
Humans

Antibiotic use is the single most important factor leading to antibiotic resistance around the world. According to CDC, antimicrobial drug use creates selective evolutionary pressure that enables antimicrobial resistant bacteria to survive and increase in numbers (4). Half of the 100 million antibiotic prescriptions written annually in office-based healthcare settings in the United States are for upper respiratory infections, which are viral in origin. This practice of overuse of antibiotics is because of patient demand, physician time constraints, and diagnostic uncertainty (1). The past two decades have seen a rise of many resistant pathogens. One of many examples includes rise of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB), now identified in 92 countries. In 2012, World Health Organization (WHO) observed that there were about 450,000 new cases of MDR-TB (5).

Several drug-resistant pathogens that have emerged due to increased or improper use of antimicrobials cause increase in morbidity and mortality (6). Some of these pathogens include methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus (VRE), penicillin-resistant Streptococcus pneumoniae, and antimalarial-resistant Plasmodiumfalciparum. People colonized or infected with the resistant pathogens are the source of spread of bacteria in healthcare settings such as acute care hospitals and nursing homes. Pathogens also spread among family members and members of the community. For example, skin and soft tissue infections with MRSA are seen in clusters of people of the same household or from the same community (7).

Prevalence of multi-drug resistant organisms varies temporally, geographically, and by healthcare setting. For example, VRE emerged in the eastern United States in the early 1990s, but did not appear in the western United States until several years later (8). Cluster outbreaks of these resistant pathogens are now occurring more frequently than ever. Globalization has contributed to the spread of these resistant pathogens across all nations ofthe world. A research published by Globalization and Health studied the resistance patterns of several most common bacteria in three geographically separated and culturally and economically distinct countries – China, Kuwait and the United States. The study found that China has the highest level of antibiotic resistance, followed by Kuwait and the U.S. (9). International travel also has allowed free movement of medications, including antimicrobials, across borders. Travelers purchase antibiotics over the counter in various countries, with questionable potency. These individuals then self-diagnose and self-medicate without the supervision of a healthcare provider; this improper use and misuse ofantibiotics can lead to not just adverse effects of drugs, but also increase in AMR bacteria (1).

Figure 1: Model of causal relationship



Animals

The global increase in antimicrobial resistance is not just due to use of antibiotics in humans. About 70% of the antibiotics administered to food animals are for non-therapeutic purposes such as growth promotion (10). The use of antibiotics in food producing animals for rapid growth and disease prevention also promotes emergence of antibiotic resistant bacteria in animals, which reaches humans via the food supply (11). Data published by Food and Drug Administration (FDA) reports nearly three-fourths of antibiotic use in United States is in food-producing animals. This report noted that these animals serve as carriers and spread antibiotic-resistant bacteria to the consumer (12). In a report about antibiotic resistance as a worldwide problem, CDC documents that drug-resistant bacteria have been isolated on meat from food-producing animals, fertilizer, or water containing animal feces, and crops on which these fertilizers are used. Global trade has extended this problem beyond borders (4).

McEwen and Fedorka report that prevalence of antimicrobial-resistant organisms in food animals varies. Evidence suggests that antimicrobial use selects for emergence of antimicrobial resistance in zoonotic enteropathogens (e.g., Salmonella spp., Campylobacter spp.), commensal bacteria (e.g., Escherichia coli, Enterococci), and bacterial pathogens of animals (e.g., Pasteurella, Actinobacillus spp.) (13).

Antibiotic use has also increased in aquaculture with rapid growth in production of aquatic species (like fish, shellfish, shrimp and molluscs) to keep up with the global demand. Many MDR fish pathogenic bacteria are found in fish farms, and multi-drug resistant plasmids from these MDR fish pathogens can be transferred to human pathogens (14).

DISCUSSION: Strategies to mitigate AMR

Humans

A concentrated effort of all members of the society is required to address the problem of antibiotic resistance. Awareness and education regarding the threat of increasing AMR is required for both healthcare providers and the public (14). CDC has directed several efforts towards decreasing risk factors for AMR by improving prescribing habits of providers and decreasing improper and misuse of antibiotics (4). One such effort is "Get Smart for Healthcare", a national campaign by CDC. Alongside CDC, WHO has put tremendous efforts in combating this global public health crisis. Various programs have been developed for tracking AMR. One such example is The National Antimicrobial Resistance Monitoring System for enteric bacteria established in 1996. This program facilitates data collection and trend-analysis for identification of emerging resistance (1). CDC gathers data on antibiotic-resistant infections and evaluates the causes and risk factors to help providers develop strategies to prevent those infections. The Study for Monitoring Antimicrobial Resistance Trends (SMART) is a global surveillance system on antimicrobial resistance of microbes. Data on resistant pathogens from various SMART studies is used to study the diversity and increasing trends of AMR globally (10).

The Canadian Nosocomial Infection Surveillance Program (CNISP) was established in 1994 as a collaborative effort of the Canadian Hospital Epidemiology Committee (CHEC), a subcommittee of the Association of Medical Microbiology and Infectious Disease (AMMI) Canada and the Centre for Communicable Diseases and Infection Control (CCDIC) of the Public Health Agency of Canada (PHAC) (15). The CNISP provides rates and trends of healthcare-associated infections at Canadian healthcare facilities. Surveillance as such provides data to develop national guidelines and monitor progress in curbing AMR. However, there are limitations to how surveillance data is interpreted, i.e., participating hospitals do not represent the healthcare system in its entirety, and the trend of AMR infections in a hospital setting is not representative of an emergency department or an outpatient clinic (16).

National Healthcare Safety Network (NHSN) in US is a CDC platform that collects and provides data on infections and drug resistance in healthcare settings. The Society of Healthcare Epidemiology and CDC published guidelines and tools for infection preventionists will help develop strategies to prevent hospital-acquired infections and to prevent the spread of resistant pathogens in healthcare settings. Hand hygiene and disinfection is important in the management of microbes in hospital and community settings (17). MDR pathogens that cause hospital-acquired infections require expensive and even toxic antibiotics and lengthen hospital stay (14). Most common transmission of healthcare-associated pathogens is through the hands of healthcare workers, hence hand hygiene plays an important role. Several studies demonstrate that increase in handwashing compliance significantly decreases nosocomial infections (14).

Animals

Controlled use of antibiotics in animals for promoting growth is another cornerstone among efforts to reduce AMR (14). The use of antibiotics for growth promotion is banned in Europe and a similar ban is being contemplated in the United States (10). The government of Canada also remains committed to taking action on antimicrobial resistance (AMR) and antimicrobial use (AMU) activities. The Federal Action Plan on Antimicrobial Resistance and Use in Canada, released in October 2014, aims to respond to the threat of AMR in three areas: surveillance, stewardship, and innovation (18). Drug-resistant bacteria are found on meat that comes from food animals and on crops on which fertilizer and water containing animal feces is used. Proper food handling and cooking of meat and vegetables is important to prevent spread of antibiotic resistant bacteria (19). Optimal use of existing vaccines, using probiotics and prebiotics to improve health of animals are alternatives to antibiotics. Reducing antibiotic use in agriculture, especially in food animals, is important. A solution to the problem of antibiotic resistance in humans requires a strategy to prevent the transfer of resistance genes into human microbiome through food intake or contact with environment. Another is to develop standard protocols on the appropriate use of antibiotics in animal husbandry that are acceptable globally by all nations should be developed. Also, monitor the global emergence of multi-drug resistant (MDR) bacteria in animals internationally via surveillance programs (14).

One of several programs by the CDC to improve antibiotic use is Get Smart: Know When Antibiotics Work on the Farm. This educational campaign promotes appropriate antibiotic use in veterinary medicine and animal agriculture. Additionally, CDC also funds and assists several state-based efforts to educate veterinarians and food producers including those in dairy and beef industries (20).

The US Department of Agriculture (USDA) reports that organic food accounts for 1%-2% of total US food sales and projected an increase of 20%-30% annually. The USDA rules stipulate against administering anyantimicrobials to animals raised organically and removal of sick animals from organic operation (13).

The framework for action to prevent, limit and control the emergence and spread of AMR and AMU committed to by the government of Canada maps out a coordinated and collaborative approach. Response to the threat will be a collaboration of the federal government with all jurisdictions and stakeholders with the goal of proper delivery of healthcare, approval of antimicrobials for medical coverage, and regulation of antimicrobial use (AMU) in agriculture and veterinary medicine (21). Public Health Agency of Canada (PHAC), collaborates with other agencies such as Health Canada (HC), the Canadian Food Inspection Agency (CFIA), the Canadian Institutes of Health Research (CIHR), Agriculture and Agri-Food Canada (AAFC), the National Research Council (NRC), and Industry Canada (IC) to develop and support strategies to combat AMR. These federal departments lead by the PHAC work with human health, animal health, agri-food and industry stakeholders at federal, provincial, and territorial (F/P/T) levels. Under the banner of Global Health Security Agenda (GHSA), this group of departments works with international partners to develop and implement a Global Action Plan on AMR (target completion in 2019) that spans human, animal, agricultural, food, and environmental sectors (21).

Given the clear need for action on this issue in the US, President Barack Obama signed an executive order on September 26, 2014 launching federal efforts to combat the rise in antibiotic-resistant bacteria. National Strategy on Combating Antibiotic-Resistant Bacteria outlines steps that US government will take to improve prevention, detection, and control of resistant pathogens. In order to protect the health of public, the president's 2016 budget proposed an investment of $1.2 billion to fund projects for research and innovation, improve public health, develop strategies to improve antibiotic stewardship, strengthen antibiotic resistance risk assessment and surveillance, and reporting capabilities (22).

Antimicrobial stewardship

As of 2013, Accreditation Canada requires an Antimicrobial Stewardship Program (ASP) in all acute care facilities (23). A team of infectious disease physician(s), pharmacist(s), microbiologist(s), epidemiologist(s), etc. are a part of an ASP. Stewards in an ASP seek to optimize safe use of high-risk medications (like antimicrobials) for optimum results in patients as per the guidelines in the Required Organizational Practices (ROP). The ROP guidelines advocate patient safety while mitigating risk of infections and healthcare costs. Accreditation Canada reports that effective ASPs along with comprehensive infection control has been successful in lowering (emergence and transmission) of AMR bacteria. Using the ROP guidelines, ASPs may be customized by each organization to match its size, environment, and patient population (24).

Public Health Ontario (PHO) promotes and supports antimicrobial stewardship program. PHO provides at least 32 different strategies to assist healthcare institutions with building and enhancing a stewardship program (22). Similarly, a more comprehensive antimicrobial stewardship toolkit compiled by the American Hospital Association (AHA) in partnership with Association of Professionals in Infection Control and Epidemiology (APIC) includes resources for healthcare systems to assist with starting a stewardship program anew or enhance an existing one, resources (like webinars, guides, etc.) for clinicians, and resources for patients (Q&As, handouts, best practices, etc.)(25).

The National Collaborating Centre for Infectious Diseases (NCCID), funded by the Public Health Agency of Canada, has taken on the role of a public health knowledge broker for infectious diseases; it facilitates appropriate stewardship and surveillance and builds bridges between practitioners and patients with a mandate to work across jurisdictions to address national priorities. One of the focuses of the NCCID is to raise awareness of antimicrobial resistance (AMR), antimicrobial use (AMU) and antimicrobial-resistant organisms (ARO) in the Canadian population, especially the underserved (26).

Numerous studies suggest that ASPs can improve antimicrobial prescribing and microbial outcomes. Kaung et al. conducted a study in a setting where ESBL-producing Enterobacteriaceae are endemic. In this study, per guidelines of an ASP, patients received carbapenem de-escalation. After a safety evaluation and clinical outcomes, it was concluded that de-escalation of carbapenems resulted in fewer adverse effects (drug reactions, *Clostridium difficile* associated diarrhea) and decreased incidence of AMR (27).

Chang et al., after an ASP guided three-year cohort study of culture-guided de-escalation of antibiotics, reported a reduction in mortality, patient length of stay, defined daily dosage, AMR rate, and healthcare cost. They concluded with a high recommendation for similar implementation of ASP in hospitals (28).

Haley and colleagues studied the impact of audit and feedback in an ASP for three years at a Veterans Affairs medical center. Although statistically insignificant in the short-term in the study setting, they recognized the potential of audit and feedback in improving antimicrobial use and outcomes, in reducing the use of broad-spectrum antimicrobials consequently decreased length of stay, cost, and adverse events (29).

In 2016, a multidisciplinary expert panel of IDSA and SHEA published new and updated guidelines to implement and measure antibiotic stewardship interventions. These evidence-based guidelines are recommendations and best practices that may be adopted/customized by antibiotic stewardship progam(s) to promote optimal use of antibiotics (30).

CONCLUSION

AMR is a global concern; it challenges care and control of infectious diseases and greatly increases cost of healthcare. With not many new antibiotics on the horizon to combat this problem, AMR threatens a return to pre-antibiotic era and jeopardizes healthcare gains for individuals and society. It compromises health security and damages trade and economy. A global approach is needed to contain AMR pathogens. With the knowledge that AMR is a natural phenomenon that is unstoppable and its progress can only be slowed, efforts by WHO and CDC promote research to develop new antimicrobials to combat resistant pathogens and new diagnostic tests for early diagnosis and to track developing resistance (4).

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Return to **TABLE OF CONTENTS**

ORIGINAL ARTICLE

The risk factors of healthcare-associated bloodstream infections among older adults in intensive care units

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ABSTRACT

Background: The advancements in medicine have brought about a greater increase in aging population. In Taiwan, one in 10 people is elderly. Being elderly is the greatest risk factor for bloodstream infections in the intensive care units (ICU). It has been associated with increased length of stay in the ICU and increased mortality.

Methods: This retrospective case-control study was conducted to identify the risk factors and pathogens associated with bloodstream infections (BSIs) among elderly ICU patients. We collected data from 132 ICU patients above 65 years old that were matched with 132 controls in ICUs in Taiwan from 2006 to 2011.

Results: The risk factors associated with bloodstream infections in this population were central venous catheter placement (OR, 7.219; 95%CI, 0.843~61.842),central venous catheter replacement (OR, 6.278; 95%CI, 2.054~19.190), hemodialysis (OR, 6.010; 95%CI, 1.516~23.833), blood transfusion (OR,3.171; 95%CI, 1.161~8.659), and other infections (OR,9.440; 95%CI, 1.075~82.897). The most common pathogens were *Candida species* (22.7%), *Klebsiella pneumoniae* (10.6%), *Acinetobacter baumannii complex* (9.9%), and *Staphylococcus aureus* (9.9%).

Conclusion: Our study supports the need for care bundle procedures during the implementation of intravascular catheterization, during catheter use, replacement of catheter equipment, and quality of catheter care, to prevent bloodstream infections among elderly patients in ICUs.

INTRODUCTION

Taiwan's Ministry of Health and Welfare declared Taiwan as having an aging population explosion in 1993 (1). The proportion of people over 65 years old has continued to rise in Taiwan since then, and as of 2011, this population made up 28.7% of all hospitalizations (1). The elderly are at increased risk for infection, particularly those who are hospitalized in intensive care units (ICUs) (1). According to a recent survey conducted by the United States Centers for Disease Control and Prevention (CDC), the rate of healthcare-associated infections (HAIs)

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(nosocomial infections) in the United States alone was 4.0% in 2011. The most common HAIs were pneumonia and surgical-site infection (tied at 22%), followed by gastrointestinal infection (18%), urinary tract infection, (13%) and primary bloodstream infection (10%). Analysis indicated that being older, having a longer length of stay, having a central catheter in place, or being in an ICU increased the risk for HAIs. Forty-three percent of the HAIs occurred among those > 65 years of age (2). In Taiwan, the rate of HAIs was around 1.6 % in 2013 (3). Among the elderly, the most common HAIs were urinary, respiratory, and bloodstream infections (BSIs), the latter being most prevalent in ICUs. Reviewing the data obtained from the HAI survey system at one medical center in southern Taiwan, we found that bloodstream infections accounted for 36.9% of all such infections and these infections originated in medical ICUs where 60.4% of the infections occurred in elderly patients. Therefore, it would be helpful to identify the risk factors for bloodstream infections in elderly patients in ICUs to plan early interventions aimed at reducing the risk in this vulnerable population.

METHODS

Setting

We retrospectively reviewed six years of medical records from one 1678-bed medical center in southern Taiwan. It has two intensive care units with 28 beds in total.

Sample

Patients were included if they were 65 years old and over, were admitted to the medical ICU from 2006 to 2011, and stayed in that unit for more than 48 hours. Patients were excluded if they were younger then 65 years old or their stays in the ICU were less than 48 hours. Cases were defined as any patient admitted to an ICU between 2006 and 2011 who had a record of a healthcare-associated bloodstream infection (HABSI) as defined by the Taiwan CDC (4). The definition of HABSI in Taiwan is the isolation of a pathogen from ≥ 1 set of blood cultures, or ≥ 2 sets of blood cultures drawn after 48 hours hospital admission. The requirement to diagnose a HABSI with *coagulase-negative staphylococci* or *Bacillus, Corynebacterium,* or *Propionibacterium* species is that two sets of blood samples from separate venipuncture sites at the separate timing for bacterial cultures. In adittion to the above, the patient has at least one of the following signs or symptoms: fever(>38°C), chills, or hypotension.

Matching procedure

Controls were defined as elderly ICU patients 65 years old and over admitted to an ICU from 2006 to 2011, stayed in that unit for more than 48 hours, and there was no record of a HABSI. Controls were matched with cases for medical ICU, gender, and age within five years.

In addition to basic demographic data from the patient files: gender, age, date of hospital admission and discharge. Other information was collected, as follows: in-dwelling intravenous catheter, underlying diseases, acute physiology and chronic health evaluation (APACHE) II score, laboratory tests, and received mechanical and pharmaceutical interventions.

Data analysis

The T test and chi-square test were used to test differences in continuous variables or categorical variables between the case and control subjects. Stepwise logistic regression model was used in our multivariate regression analysis. A p value of <0.05 indicated significance. All statistical operations were performed using SPSS statistical package (version 14.0).

RESULTS

In total, we analyzed the data from 132 cases and 132 controls (ratio 1:1). The average age was 78.10, SD±7.72 and 78.19 SD±7.90, respectively (Table 1). There was no difference between cases and controls with respect to age, gender, and ICU. The average rate of HAIs in the selected ICUs from 2006 to 2011 was 10.3‰. Among those HAIs, the rate of BSIs in the selected ICU was 3.8‰. Among participants with BSIs, 61.8% were elderly people. The most common pathogens for HAI-BSIs were *Candida species* (22.73%), *Klebsiella pneumonia* (10.61%), *Acinetobacter baumannii* (9.85%), and *Staphylococcus aureus* (9.85%). Several factors have found significant differences between case group and control group, as can be seen in Table 2.

Stepwise multivariate logistic regression (Table 3) revealed that patients with HABSI had received significantly central venous catheter placements (OR 33.3; p value =0.039), central venous catheter replacements (OR 6.3; p value =0.001), hemodialysis (OR 6; p=0.011), and blood transfusions (OR 3.2; p=0.024) and had a significantly greater number of nosocominal infections (OR 9.4; p=0.043).

TABLE 1: Comparison of demographic variables between cases and controls

		Case group			Control group				
Variables		N	mean	SD	N	mean	SD	t	p
Age		132	78.10	7.72	132	78.19	7.90	0.095	0.925
		N	%		n	%		Chi-square	p
Sex	Male	74	50		74	50		0.000	1
	Female	58	50		58	50			
ICU	I	58	50		58	50		0.000	1
	II	74	50		74	50			

TABLE 2: Clinical findings between cases and controls

Variables		Case group (n=132) mean	SD	Control group (n=132) mean	SD	Value	p
Length of stay		24.57	46.34	7.54	5.59	-4.2a	<0.001
APACHE II		24.11	8.00	21.55	7.43	-2.4a	0.020
Albumin		2.31	0.52	2.78	0.96	4.6a	<0.001
Hb		8.31	1.55	9.82	2.25	6.3a	<0.001
CRP		95.09	74.57	68.99	73.38	-2.7a	0.007
BUN		63.66	45.02	42.88	34.47	-4.1a	<0.001
Numbers of admission diagnoses		6.13	3.02	5.70	2.71	-1.2a	0.231
Numbers of ICU diagnosis		6.96	3.43	6.33	2.77	-1.7a	0.099
				N	%	N	%
Chronic disease	yes	131	99.2	121	91.7	8.7c	0.003
	no	1	0.8	11	8.3		
Interventions							
Central venous catheter placement	yes	130	98.5	95	72	36.9c	<0.001
	no	2	1.5	37	28		
Central venous catheter replacement	yes	69	52.3	11	8.3	60.3b	<0.001
	no	63	47.7	121	91.7		
Hemodialysis	yes	45	34.1	15	11.4	19.4b	<0.001
	no	87	65.9	117	88.6		
Blood transfusion	yes	95	72	40	30.3	45.9 b	<0.001
	no	37	28	92	69.7		
Intravenous nutrition infusion	yes	26	19.7	2	1.5	23.0 c	<0.001
	no	106	80.3	130	98.5		
Other catheters	yes	119	90.2	97	73.5	12.3b	<0.001
	no	13	9.8	35	26.5		
Surgery	yes	9	6.8	3	2.3	3.1b	0.076
	no	123	93.2	129	97.7		
Other nosocomial infection	yes	33	25	7	5.3	19.9b	<0.001
	no	99	75	125	94.7		
Steroids use	yes	104	78.8	81	61.4	9.6b	0.002
	no	28	21.2	51	38.6		
Antibiotics use	yes	132	100	120	90.9	12.6c	<0.001
	no	0	0	12	9.1		

a. Student t-test; b. Chi-square test; c. Fisher's exact test

DISCUSSION

This study was the first to specifically examine HABSI in elderly patients hospitalized in ICUs in Taiwan. The findings indicated BSIs in association with longer ICU length of stay and more central venous catheter placements, central venous catheter replacements, hemodialysis, and blood transfusions as well as having other nosocomial infections. In a study by Reunes et al., the main risk factors associated with BSI among hospitalized elderly patients were intravenous catheterization and being bedridden (5).

Goto and Al-Hassan estimated that BSI ranked among the top seven causes of death in North America and Europe (6). Like other studies (7-10) we found a significant association between hospital-associated BSI and length of stay in an ICU. According to a study by Venkatram et al., the central venous catheter accounted for 4-14% central venous catheter-related bloodstream infections, which lead to increased use of antibiotics and high mortality rate of 22.9% (11).

Studies reported by Provost et al. (12) and Galpem et al. (13) found that the use of central line aseptic "bundle procedures" resulted in a significant decrease in central line-associated BSI. These procedures included such measures as maximum sterile barrier precautions, hand washing, skin cleansing with an appropriate antiseptic, care of injection site, catheter care, and dressing selection. The authors concluded that attention to these details reduced catheter-related BSI. Attention to these details should improve patient safety and quality of care.

In 2011, the United States CDC updated its guidelines for the prevention of central venous catheter-associated BSI.

TABLE 3: Stepwise multivariate logistic regression analysis of BSI risk				n=264		
Variables	r	SE	df	p	Odd ratio	95%CI
Central venous catheter placement	1.977	1.096	1.000	0.039*	7.219	0.843~61.842
Central venous catheter replacement	1.837	0.570	1.000	0.001*	6.278	2.054~19.190
Hemodialysis	1.793	0.703	1.000	0.011*	6.010	1.516~23.833
Blood transfusion	1.154	0.513	1.000	0.024*	3.171	1.161~8.659
Other nosocomial infection	2.245	1.109	1.000	0.043*	9.440	1.075~82.897
*P<0.05						

These guidelines include a checklist or "bundle" to ensure proper catheter placement and education for the medical staff (14). Studies of central line catheter care bundles have shown to decrease the rate of BSI (11,15). The recent ICU bloodstream infection guidelines implemented by the Taiwan CDC that incorporate care bundle procedures to prevent BSI should, therefore, reduce the number of catheter-related BSI. We found that the rate of central venous catheter (CVC) insertion decreased from 56.7% in 2013 to 51.2% in 2014. The rate of catheter-related bloodstream infections (CRBSI) also decreased from 4.32% to 1.68% during the same period. In addition, there were 21 months free of CRBSI from January 2013 to September 2014 (16).

According to Magill et al., a multistate CDC-conducted survey found the rate of primary bloodstream infections ranked fifth among HAIs at 10% in 2011. According to their estimates, 15,600 catheter-associated BSI occurred in the United States in 2011 (2). The current study also found that the odds ratio of occurrence of healthcare-related bloodstream infections for patients with other HAIs to be 9.4. We found no related research that explored the relationship between blood transfusion and healthcare-related BSI. However, in our study, the odds ratio of occurrence of healthcare-related BSI for the patients receiving blood transfusion was 3.2. This may possibly be because the concentration and viscosity of blood products are high, infusion time is long, or the intravenous set was not replaced often enough, resulting in the growth of pathogenic microorganisms.

The species identification for healthcare-related BSI in our study were similar to other studies (5,8,17). The most common species in our study were *Candida species, Klebsiella pneumoniae, Acinetobacter baumannii,* and *Staphylococcus aureus*. Both *Candida species* and *Staphylococcus aureus* were related to catheter placement and replacement, the cleaning of skin, and disinfection procedures. According to the Taiwan Nosocomial Infection Surveillance (TNIS) report (3), *A. baumannii* was among the top three species identified in healthcare-related BSI in the ICU from 2003 to 2012 in Taiwan.

During a nine-year study in Taiwan, Jang & Lee et al. identified *A. baumannii* as the causative microorganisms in 96 healthcare-related BSI. Analysis showed that CVC use and respiratory ventilation, and prior *A. baumannii* colonization were significantly associated with BSI among ICU patients (8). A large retrospective matched case-control study conducted between 2006 and 2009 in a large U.S. medical center found risk factors for A. baumannii BSI among the cases were severity of illness, prior hospitalization, prior antibiotic exposure, ICU admission, and CVC placement (17). In addition, our study was conducted in Taiwan and the results cannot be generalized to other countries. This study has several limitations. One limitation is that is a retrospective study, and some medical charts may not contain complete information. Another limitation is that it is a single hospital study, and may not be representative of the whole country.

CONCLUSION

Our data found that healthcare associated BSI in elderly ICU patients were significantly associated with longer ICU length of stay, more CVC placements and replacements, hemodialysis, blood transfusions, and the presence of other HAIs. Intravascular catheter care bundle procedures have been found to contribute the most to the prevention of BSI. Therefore, the use of care bundles for CVC placement is recommended for all patients in ICUs. It also is highly recommended that patients with other infections, including those of the respiratory and urinary tracts, be carefully monitored for possible bloodstream infections.

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QI IN IPAC

Addition of bacitracin and cranberry to standard Foley care reduces catheter-associated urinary tract infections

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ABSTRACT

Background: Catheter-associated urinary tract infections (CAUTIs) represent over 30% of hospital-acquired infections with an annual incidence of 560,000 CAUTIs per year in the United States. An estimated 13,000 deaths are attributable to CAUTIs annually. Standard prevention strategies frequently fail to eliminate CAUTI in intensive care units. The effectiveness of a hospital-based program of cranberry products (CP) and meatal antimicrobials to prevent CAUTI in a heterogeneous ICU population has not been evaluated.

Methods: Data of Foley days and incidence of CAUTI in the Critical Care Unit (CCU) and the general wards (GW) in a single 245-bed suburban medical center were collected as a part of routine infection control surveillance. Standard CAUTI prevention bundles were applied throughout the hospital in 2009. In May 2012 an intervention of applying Bacitracin ointment to the urinary meatus-Foley junction and oral cranberry juice or tablets was started only in the CCU. A retrospective review of the data collected before and after the intervention in both the GW and CCU was completed.

Results: Prior to the QI intervention in May 2012, average CAUTI rates were 2.8 CAUTIs per 1000 catheter days (CI 0.26-1.89) in the CCU and 1.6 CAUTIs per 1000 catheter days (CI 0.71-4.97) on the GW ($p = 0.28$). After the intervention, the average number of CAUTIs/1000 days in the CCU was 0, which was significantly different from the average of 1.52 CAUTIs/1000 days (CI 0.78-2.26) on the GW ($p < 0.001$).

Conclusion: Our data indicate that the addition of cranberry-containing products and antimicrobial meatal care may further reduce incidence of CAUTI when added to standard recommendations. Further research will be necessary to determine if these interventions could be effective in a wider population.

KEY WORDS

Catheter Associated Urinary Tract Infection, Intensive Care Unit, Hospital Acquired Infections, Cranberry, Quality Improvement, BacitracinAbstract

INTRODUCTION

Urinary catheters, employed in 15-25% of hospitalized patients, are used to closely monitor urine output, treat urinary obstruction, and avoid contamination of perineal soft-tissue infections (1,2). Catheter-associated urinary tract infections (CAUTIs) are symptomatic urinary tract infections in patients with an indwelling urinary catheter for at least 48 hours. There are more than 560,000 CAUTIs annually, which represent approximately 30% of all hospital-acquired infections (3). The scope of the problem is of enormous importance to patient care and medical costs as there are an estimated 13,000 CAUTI-attributable deaths annually and the cost of each CAUTI is roughly $500-1000. It is estimated that a large proportion of CAUTIs may be preventable (4).

The Centers for Disease Control (CDC) currently recommends addressing the risks and benefits of indwelling catheters prior to use and discontinuing catheters as soon as possible. Additionally, aseptic insertion and maintenance of a closed drainage system are recommended without robust evidence. Indwelling catheters should be properly secured and maintained below the bladder with unobstructed flow (5).

Cranberry (Vaccinum Macrocarpon) is thought to decrease the incidence of urinary tract infections through many bioactive compounds. These include Type-A Proanthocyanins (PACs) and fructose (known to decrease adhesions of fimbriated E-Coli to the bladder epithelium) (6) (7), ascorbic acid, hydroxybenzoic acid and flavonols which is known to exert antioxidant effects (8) (9), and inulin a prebiotic that enhances the growth of commensal E-Coli in the rectum (10). Vitamin C and Hippuric acid in the urine decreases urine pH and may act as a bacteriostatic agent, although its effectiveness is thought to be minimal (12). Bacitracin ointment though active only against Gram-positive bacteria, may serve to prevent ascending infection which plays an important role in the pathogenesis of recurrent UTI (12).

To date, the effectiveness of a hospital-based program of cranberry products (CP) and application of topical antimicrobials to the urinary meatus to prevent CAUTI in a heterogeneous ICU population has not been evaluated.

METHODS

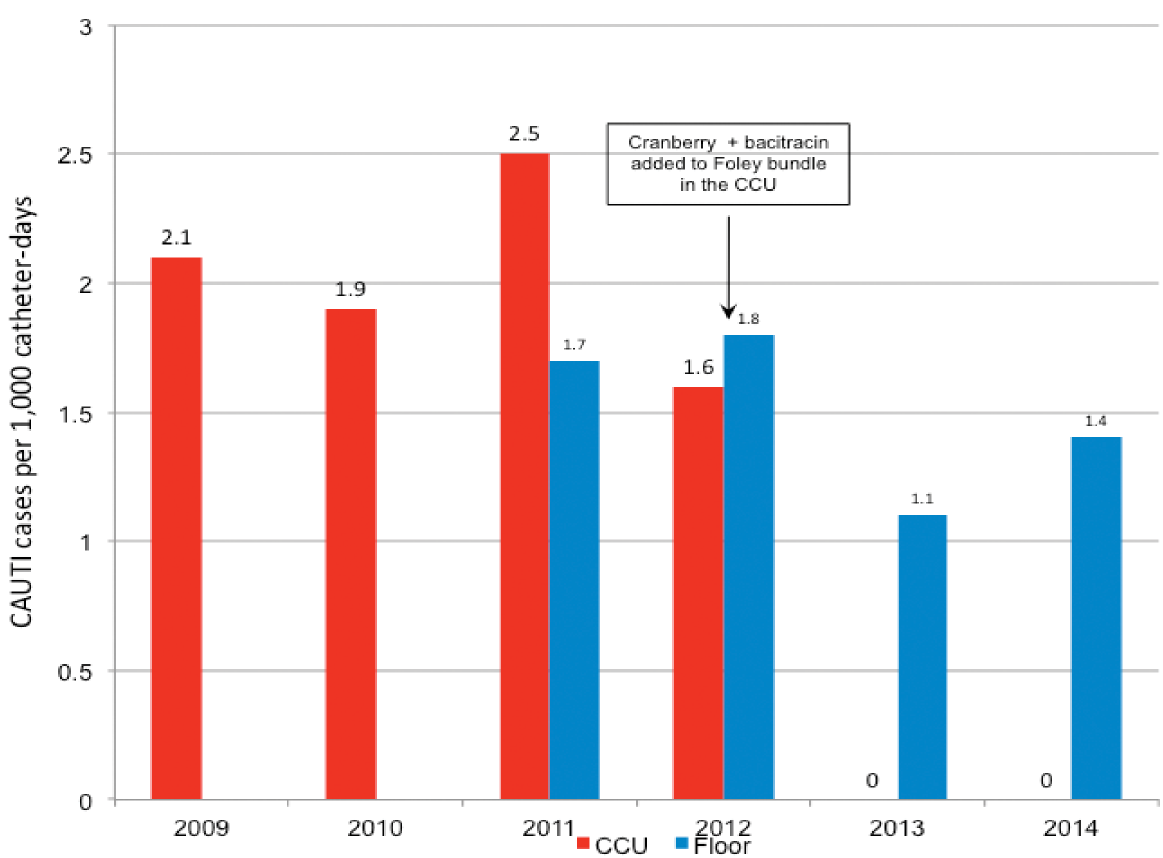
This was a retrospective study of patients presenting to a 245-bed suburban community hospital with a 16-bed Critical Care Unit. The approval to collect the data for the study was obtained from the Institutional Review Board. Urinary catheter utilization and CAUTI cases (CDC's National Healthcare Safety Network definition) were recorded and are reported as CAUTI/1000 catheter days per month in both the CCU and general wards (GW). Data were also available from January 2009 to 2015 in the CCU, and May 2011 to March 2015 on the GW. No demographic or patient data were collected. The definition of CAUTI was the NHSN definition of CAUTI. The individuals determining the whether the patient met criteria for CAUTI or not was a member of the infection control department. These decisions were reviewed throughout the hospital by the chief of the infection control department. These results were reported to NHSN and are subject to random audits by the CDC.

In May 2009, a quality bundle to prevent CAUTI was implemented in the CCU. In March 2011, the quality bundle was applied on the GW. The bundle aiming at reducing CAUTI included: (1) adherence to sterile technique during Foley catheter insertion, (2) use of the leg tape as a securement device, (3) maintenance of unobstructed urine flow, (4) emptying the Foley bag in a sterile fashion, (5) keeping the urometer below the level of the bladder at all times, (6) in-service education of nurses on Foley care every year, (7) reviewing all cases of CAUTI in a timely fashion, and (8) daily assessment of Foley by both physician and nursing staff for each patient.

In May 2012, the critical care unit (CCU) implemented the following measures: (1) the use of a CP given enterally for all patients with Foley catheters; and (2) application of bacitracin ointment to the catheter-urinary meatus junction twice daily. Of note, CP fluctuated from cranberry tablets 450mg enterally

FIGURE 1: Rates of CAUTI from 2009 to 2014.

Legend: Rate of CAUTI in the CCU and on the GW per 1000 days of Foley use.
Cranberry and Bacitracin were added in May of 2012 to the standard Foley care bundle.
No patient had adverse reactions to the treatment. This was collected through the QI process of incident reports, pharmacy collection of medication side effects and Critical Care committee collection of patient injuries.



three times daily from May 2012 until October 2012 to 120 milliliters of sugar-free 7% cranberry juice enterally three times daily from November 2012 until September 2014 and finally 120 milliliters of 23% cranberry juice enterally three times daily from September 2014 until September 2015. The change from oral tablets to juice was due to institutional change of policy prohibiting the use of non-FDA regulated medications in the hospital. The first juice choice was the diet one for fear of hyperglycemia. A search and discussion regarding the percentage of cranberry in the diet juice continued and finally it was decided that giving more cranberry in the non-diet form is to be done and hyperglycemia was to be dealt with relative ease.

No CP or meatal care was provided on the GW. The rate of CAUTI on the GW was used as a control for this analysis.

Data were normally distributed and described using means and 95% confidence intervals. Comparisons within groups pre- and post-intervention as well as between groups were done with student's t-test. All statistical calculations were done using STATA v13.1 (College Station, TX: StataCorp LP). All hypothesis tests were two-sided, with a significance level of $p \le 0.05$.

RESULTS

Prior to the CP/Bacitracin intervention in May 2012, average CAUTI rates were 2.8 CAUTIs per 1000 catheter days (CI 0.26-1.89) in the CCU and 1.6 CAUTIs per 1000 catheter days (CI 0.71-4.97) on the GW ($p = 0.28$). After the initiation of CP and meatal care, the average number of CAUTIs/1000 days in the CCU was 0, which was significantly different from the average of 1.52 CAUTIs/1000 days (CI 0.78-2.26) on the GW ($p < 0.001$) (Figure 1). There was no significant change in average Foley days per month pre- and post-intervention on either the GW (227 to 227 Foley-days, $p= 0.98$) or in the CCU (198 to 182 Foley-days, $p=0.24$).

DISCUSSION

Catheter-associated UTIs represent a major source of hospital-acquired infection, and lead to significant costs, morbidity, and mortality. Our retrospective, observational data suggest that the addition of CP and bacitracin meatal care to the CDC CAUTI prevention bundle are associated with a reduction in CAUTI incidence.

CP have previously demonstrated promise in reducing UTI incidence. Two meta-analyses have evaluated CP in preventing non-catheter associated UTI with mixed results (13,14). With respect to CAUTI, use of CP in a single randomized controlled trial resulted in a reduction in CAUTI in women following gynecological surgery (15). Topical antibiotics seem to have an intuitive mechanism but have been scarcely studied, and prior evidence has not supported routine use (16). Currently, the use of cranberry and topical bacitracin are not approved by the FDA for use in preventing urinary tract infections.

This work has several limitations. The single site nature of this work makes it possible that idiosyncratic factors may be responsible for reduced CAUTI. Furthermore, as we did not collect demographic data, there may be unknown clinical confounders to influence the results. However, the magnitude of the reduction and the temporal relationship of the CP and meatal care intervention to the CAUTI reduction add credence to a causal relationship. Another limitation is the simultaneous initiation of CP and meatal care which limits our ability to determine independent effectiveness of these interventions. While no adverse events were recorded, ICUs are a critical area of intervention for hospital acquired infections. The data for prevention of CAUTIs is relatively scant, but our data indicate that the addition of cranberry containing products and antimicrobial meatal care may further reduce incidence of CAUTI when added to recommendations already made by the CDC. Further research will be necessary to determine if these interventions could be effective in a wider population.

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EMERGING TECHNOLOGIES

The first dual-sterilant low-temperature sterilization system

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ABSTRACT

A new low-temperature sterilizer is described which uses both hydrogen peroxide and ozone in a multiphase process. The primary sterilant, vaporized hydrogen peroxide, is introduced into a chamber until a differential pressure of 19 torr is reached. By keeping the differential pressure constant, both the sterilant dose and exposure time are allowed to vary, which allows for a single cycle to be used to sterilize a wide variety of loads with differing size, material, and geometry. Lethality is achieved due to the effect of hydrogen peroxide in both the vapour and micro-condensation phases. Ozone is subsequently added to the chamber to decompose residual hydrogen peroxide and further increase lethality. Device performance has been validated by half-cycle, simulated-use, and in-use testing.

KEY WORDS

sterilization, hydrogen peroxide, ozone

INTRODUCTION

The STERIZONE® VP4 (VP4) Sterilizer is the first new low-temperature sterilization technology cleared by the U.S Food and Drug Administration (FDA) since introduction of the hydrogen peroxide gas plasma sterilizer in 1993 and the ozone sterilizer in 2003. The VP4 is also the first dual-sterilant device cleared by FDA for terminal sterilization of cleaned, rinsed, and dried metal and non-metal reusable medical devices.

The VP4 uses both vaporized hydrogen peroxide (VHP) and ozone in a multiphase process, providing a minimum Sterility Assurance Level of 10-6 (1). The sterilization cycle is compatible with a variety of materials and device geometries including general instruments, single channel flexible endoscopes, and rigid channel devices. The device can also sterilize up to 75 pounds of medical instruments in a single load (2). Device performance has been validated by not only half-cycle testing, but also simulated-use and in-use (within a hospital) testing.

Although both hydrogen peroxide (H2O2) and ozone are well-known sterilants, the process by which both are introduced, controlled, and combined within the VP4 sterilization chamber is unique. This results in different process parameters and chemistries, in comparison with first-generation sterilization processes. This paper describes the critical parameters, chemistry, and enhanced lethality found with the VP4 Sterilizer.

Sterilizer cycle description

The STERIZONE® VP4 Sterilizer is a self-contained stand-alone device, using VHP and ozone in a multiphase process. Unlike other low-temperature sterilizers, which require use of various cycles for different types of devices, the VP4 offers a single sterilization cycle ("Cycle 1") intended for all allowed substrates and geometries, including general instruments, single channel flexible endoscopes, and rigid channel devices. The process pressure and time profile for Cycle 1 is provided in Figure 1.

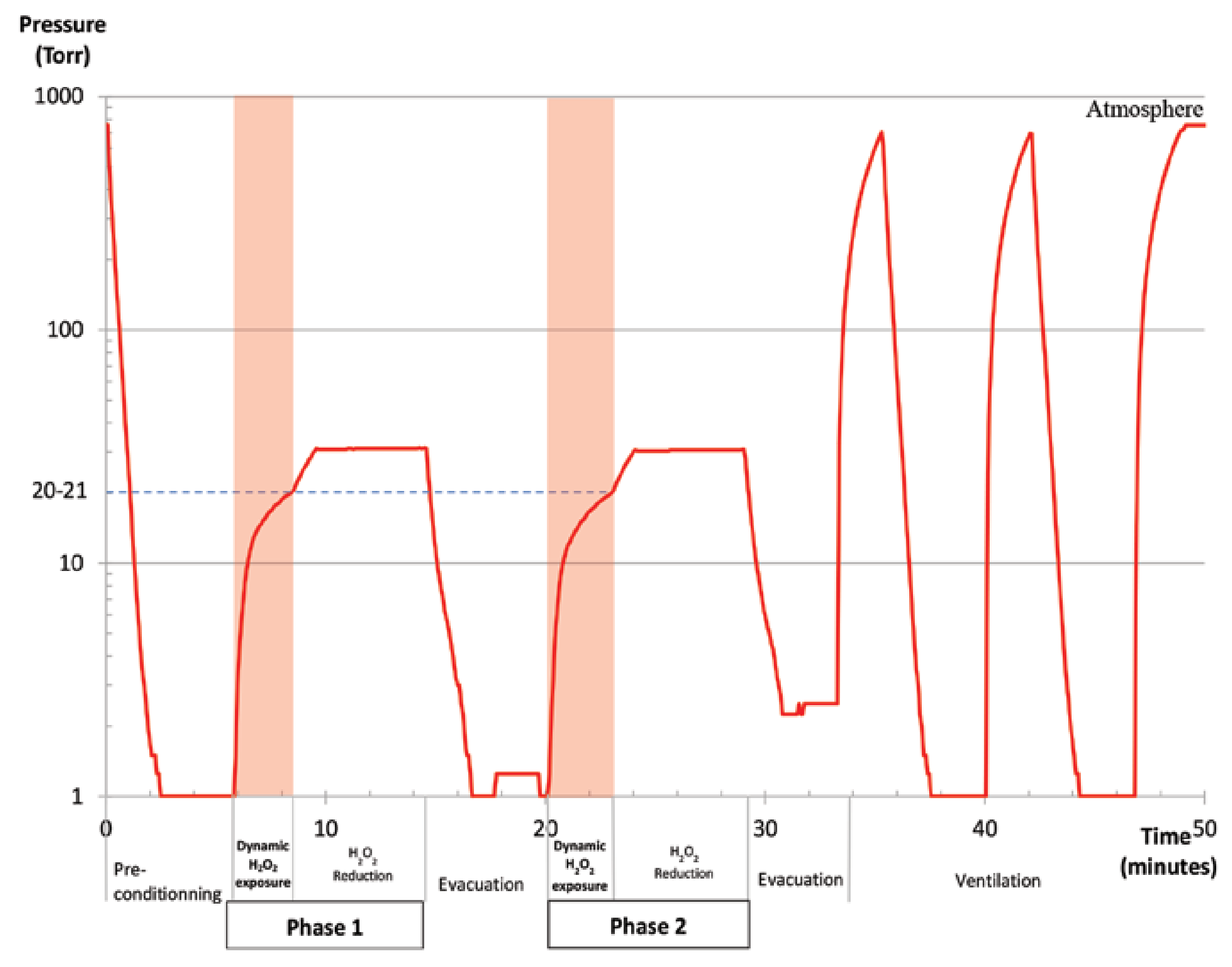
Upon loading medical devices into the sterilization chamber and closure of the door, the chamber is subjected to a vacuum of 1 torr (referred to as Pre-conditioning step). The Pre-conditioning step has a total maximum duration of 10 minutes, and is reconfirmed immediately following the degassing period.

The first cycle phase (Phase 1) is initiated with the Dynamic H2O2 exposure step. During this step, a 50 weight-percent H2O2 solution is injected in vapour form into the sterilization chamber until a differential pressure set point of 19 torr is reached (i.e., the actual chamber pressure is 20 torr, less the initial vacuum of 1 torr, which is equivalent to a "differential pressure" or "DP" of 19 torr).

Hydrogen peroxide vapour is generated within the VP4 by flash vaporization, meaning that the mixture of H2O2 and water vapour injected into the sterilization chamber is substantially the same weight percent composition as the multi-component liquid. Flash vaporization is achieved at elevated temperatures, which accounts for the respective boiling points of the components (H2O = 100°C; H2O2 = 150.2°C; 50% aqueous solution of H2O2 = 114°C).

The VP4 incorporates a "Dynamic Sterilant Delivery System™", which provides continuous exposure to hydrogen peroxide through multiple small-pulsed injections of the sterilant (≈ 40 mg/pulse), with one pulse injected per second.

Figure 1: Cycle process pressure profile for Cycle 1 of the STERIZONE® VP4 Sterilizer.



The amount of sterilant introduced into the sterilization chamber is dependent upon reaching the set differential chamber pressure of 19 torr. This in turn means that both the total dose and time of sterilant exposure vary depending on the weight and composition of the load, and the load temperature (i.e., variables that effect differential pressure). This differs from first generation VHP devices, which employ static dose and time parameters (but variable chamber pressure). By keeping the differential pressure within the sterilization chamber constant at 19 torr, while allowing the dose and exposure time to vary, a single cycle can be used to sterilize a wide variety of loads with differing size, material, and geometry.

The second step of the cycle phase is the H2O2 reduction step. During this step, 2 mg/L of ozone is injected into the chamber, followed by a five-minute dwell time. This step is intended to reduce residual hydrogen peroxide, which may have been preferentially absorbed by certain polymers. This step also enhances microbicidal efficacy via the formation of hydroxyl radicals. However, a 6-log spore reduction is consistently achieved for all reusable devices that fall within the sterilization claims after exposure to only the first Dynamic H2O2 exposure.

During the second cycle phase (Phase 2), the same sequence is repeated, including the Dynamic H2O2 exposure and H2O2 reduction steps. The full cycle is then completed with an evacuation and ventilation, through a catalytic converter, which decomposes excess hydrogen peroxide vapour into water and oxygen. Since the sterilization chamber remains sealed during all process steps, there is no occupational or environmental exposure to sterilants.

Because differential pressure is the critical process parameter for the VP4 Sterilizer, and not dwell time or sterilant dose, both are allowed to vary depending on the load size, temperature and composition. This in turn allows for total cycle time to vary between 46-60 minutes, reflecting a variable Dynamic H2O2 exposure time of between 210-600 seconds (per half-cycle).

Micro-condensation of hydrogen peroxide vapour
VHP is, by definition, a gas when introduced into a chamber, reflecting the same weight percent composition as found in the prevaporized liquid solution. At typical room temperatures and atmospheric pressure, both water and H2O2 are predominantly liquid, with the headspace air within a closed container having a small amount of gas phase H2O2/H2O that is in equilibrium with the liquid.

When VHP is initially injected into a chamber under vacuum, both H2O2 and H2O remain in the gas phase. However, as the H2O2/H2O gas concentration increases, coupled with encountering the cooler temperatures of the sterilization load, the H2O2/H2O vapour will begin to condense into a microscopic layer, also known as the "micro-condensation" layer (3). The exact temperature required to condense moist, H2O2-laden gas is called the dew point (4). In a fixed temperature environment, dew point may also be expressed in terms of the pressure (or concentration) of H2O2-laden gas required for condensation (i.e., "dew pressure"). The relationship between dew point and condensation in a sterilization chamber is identical to the formation of fog in a moist environment (i.e., the dew point is the temperature at which the air becomes 100% saturated with water vapour, which condenses into water droplets, which we see as fog).

Once the dew pressure has been reached for a given temperature and weight fraction of H2O2, a micro-condensation layer (measured in micrometers, and thus not visible to the human eye) forms on the surface of the sterilization load, which is in equilibrium with the H2O2/H2O vapour. However, because hydrogen peroxide has a lower equilibrium vapour pressure (i.e., lower dew pressure) versus water, it will preferentially condense into the micro-condensation layer. This in turn means that once the dew pressure has been reached, the equilibrium concentrations of H2O2 will be much higher in the liquid phase (>70%) versus the vapour phase (<10%), even for low weight-percent H2O2 solutions (5). The high concentration of H2O2 in the liquid phase is believed to be responsible for very rapid kill, which is greater than the corresponding gas-phase lethality, particularly for a low-temperature environment (6).

The extent of condensation for a given H2O2/H2O weight percent depends on, among other things, temperature (both chamber and load). Figure 2 presents the theoretical dew pressure curves of a 50 weight-percent H2O2 solution at three different temperatures: 20°C, 30°C, and 40°C. As expected, the higher the temperature, the higher the dew pressure (i.e., the pressure required for the first condensate to form). Thus, at 20°C, the dew pressure is only 3.5 torr whereas at 40°C, the dew pressure is 13 torr.

Below the dew pressure, H2O2/H2O is in the vapour phase. Above the dew pressure, a micro-condensation layer is formed on any exposed surface, with an equilibrium established between the gas and liquid phases.

Figure 2: H2O2/H2O system theoretical dew pressure curves at 20°C, 30°C and 40°C (7).

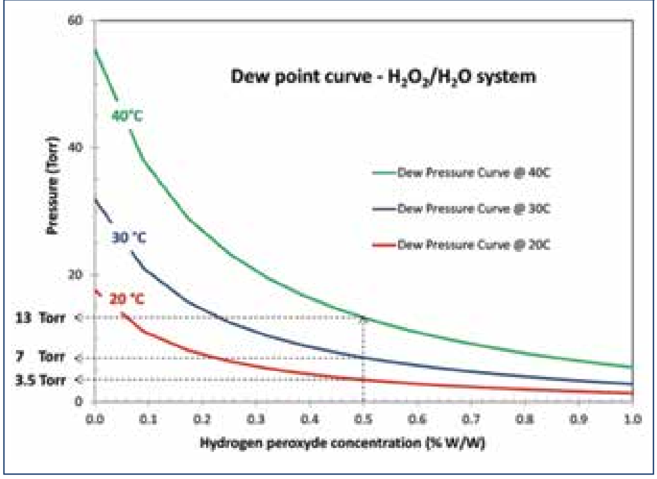
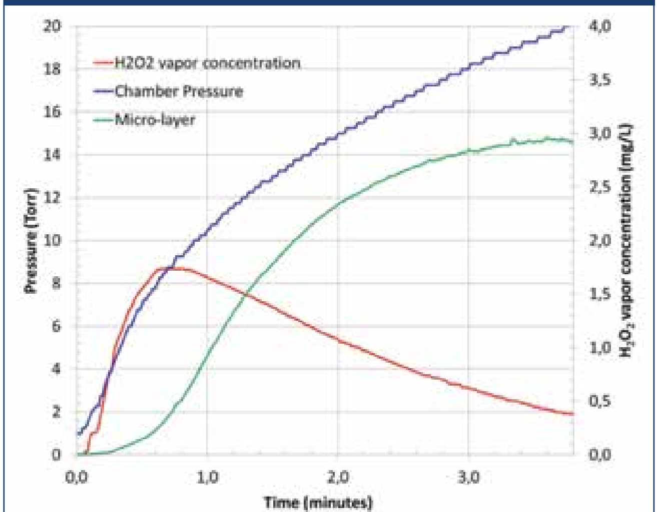


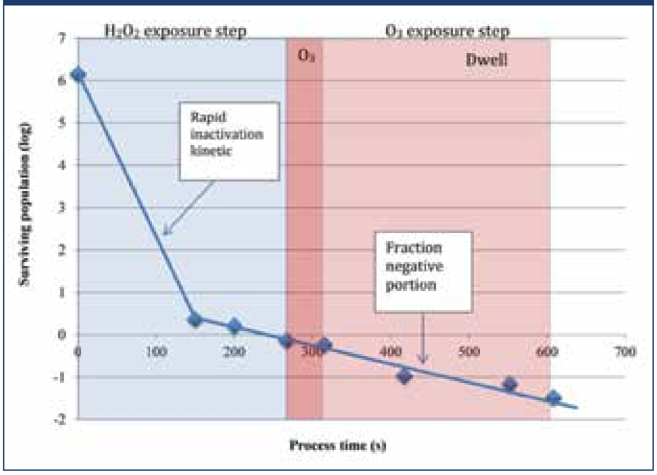
Figure 3: Condensation of the 125-280 Solution™ during the Dynamic H2O2 exposure step for a 50 lb load at 26°C.



In other words, as the pressure of vaporized H2O2/H2O increases within a chamber, lethality is achieved due to the effect of both H2O2 in the vapour and micro-condensation phases.

Empirical data confirms the formation of a micro-condensation layer in the VP4, as detailed in Figure 3. Three variables were measured in the sterilization chamber during a standard hydrogen peroxide injection: chamber pressure (blue curve, expressed in torr), H2O2 vapour concentration (red curve, expressed in mg/L), and thickness of the micro-condensation layer (green curve, expressed in kÅ). Hydrogen peroxide vapour concentration was measured using UV spectroscopy whereas the thickness of the microlayer was measured using a crystal microbalance. The experiment was conducted at the upper end of the recommended load temperature for the VP4, namely 26°C, which is less likely to form micro-condensation.

Figure 4: Inactivation of the Test Pack on the rack only at 23°C ± 2°C, in the H2O2 exposure step followed by the O3 exposure step (O3 injection + dwell).



In the early phase of H2O2 injection, chamber pressure increases (blue curve), and H2O2 vapour concentration increases (red curve), without any meaningful change in the thickness of the micro-condensation layer (green curve). However, at approximately 30-40 seconds, the rate of change in micro-condensation layer increases, corresponding to an approximate peak in H2O2 vapour concentration. This point also corresponds to a chamber pressure (or dew pressure) of approximately 7-8 torr, which as discussed in Figure 2, is the pressure at which condensation begins to form. Thus, the experimental dew pressure is consistent with the theoretical dew pressure.

Once micro-condensation begins to form in the chamber, H2O2 vapour concentration drops in spite of the fact that H2O2 injection continues until the chamber pressure reaches 20 torr. The fact that the H2O2 vapour concentration decreases while the micro-condensation layer increases, confirms that micro-condensation is occurring within the chamber. If the injected VHP remained in the gas phase, the H2O2 vapour concentration would continue to increase over the complete injection cycle (corresponding to the increase in VHP over time), reaching the same concentration as the initial solution. Furthermore, the micro-condensation layer would remain minimal.

Thus, the VP4 achieves sterilization efficacy by use of vaporized hydrogen peroxide, which exhibits lethality in both the vapour and micro-condensation phases. By maintaining a constant differential pressure of 19 torr, a minimum micro-condensation layer is formed on all surfaces, which ensures lethality. Although the role of micro-condensation in conventional VHP sterilizers remains controversial (some manufacturers of conventional VHP sterilizers claim that the sterilant is always in the vapour phase), it is likely that all VHP devices form micro-condensation layers, particularly with sterilization loads processed at room temperature (8, 9). However, it is also likely that they are uneven and uncontrolled, meaning that biocidal activity is primarily due only to hydrogen peroxide vapour, which is less efficient than microcondensation (10).

Differential pressure as a primary process parameter

The critical process parameters for controlling the formation of micro-condensation within a sterilization chamber include the differential pressure and load temperature. Both thermodynamic calculations and experimental data confirm that increasing the injection of H2O2/H2O vapour beyond the dew point pressure (at a given temperature) will result in micro-condensate formation. However, increasing the DP to a specific target beyond the dew point pressure, is a function of the volume of H2O2/H2O vapour injected into the system, the size and surface area of the sterilization load, and load temperature.

Experimental data confirms that a differential pressure of 19 torr will consistently sterilize the most challenging instruments/loads, at the highest allowed temperatures. This has been validated in half-cycle, simulated-use (where the most resistant microorganism to the sterilization process is mixed with organic and inorganic soils and inoculated onto devices) and in-use testing (medical devices soiled during actual hospital procedures are tested for sterility).

The size of the load (defined as weight and/or surface area) can influence the time required to reach the differential pressure since large loads allow for more micro-condensation. When H2O2/H2O vapour is being condensed on large surface areas, a greater volume of vapour is required in order to maintain or increase the overall vapour pressure. Thus, the time required to reach a DP=19 torr in a large load will be longer than in a small load, since the Dynamic H2O2 delivery system operates at a fixed injection rate.

In addition to DP, experimental data has been generated to confirm that the load temperature should be between 20-26°C. As previously discussed, temperature plays an important role in determining the dew pressure, with increasing temperatures resulting in higher dew pressures. Although load temperatures above 26°C form a micro-condensation layer, experimental data shows that for certain types of instruments, sterilization efficacy is reduced above 26°C. This in turn is attributed to lower condensation levels and lower H2O2 exposure times (i.e., for a given load, the time required to reach a DP=19 torr is shorter at high temperatures). Since the VP4 uses continuous small-pulsed injections of H2O2 vapour until the differential pressure is reached, the total sterilant exposure time is limited to the time required to reach the differential pressure. If less time is required to reach differential pressure due to less condensation, the load has a lower exposure time to the sterilant.

Load temperature should not be confused with chamber wall temperature, which is set at 41°C in

Return to TABLE OF CONTENTS

the VP4. First generation VHP devices also set chamber wall temperatures at relatively high levels (±50°C), which discourages formation of micro-condensation on chamber walls. However, since sterilization loads are usually conditioned at room temperature (±23°C), load temperatures are much lower than chamber wall temperatures. This in turn has a direct effect on the formation of micro-condensation layers. Nonetheless, existing VHP devices do not provide load temperature restrictions, even though load temperature is crucial to maintaining a "dry" process (8, 9).

As noted above, load temperature and injection time are correlated in the VP4. This is because the device continuously injects H2O2/H2O vapour into the sterilization chamber until the differential pressure of 19 torr is reached. However, at high temperatures (> 26°C), it takes less time to reach 19 torr, particularly for small loads. Thus, by restricting the range of injection times, one can effectively account for load temperatures outside the range of optimum efficacy. Specifically, experimental data confirms that when the injection time is limited to between 210-600 seconds, "worst-case" sterilization loads warmer than 26°C are aborted (i.e., the minimum injection time of 210 seconds is not reached). Likewise, "cold" loads (under 20°C) are also aborted, since they exceed the upper limit of allowed injection time.

The foregoing discussion highlights a difference between the VP4 and first generation VHP devices. Whereas the VP4 maintains a constant differential pressure of 19 torr, with a variable dose and exposure time, conventional VHP devices allow for DP to vary, although dose and exposure time are kept constant. In addition, VHP devices do not control or address the issue of load temperatures, even though chamber and load temperatures are in practice very different. Finally, the VHP devices address the static nature of their process by incorporating multiple cycles into a single device, each targeting different loads, with differing VHP exposure times and dose.

Role of ozone

Within each cycle phase, after achieving a differential pressure of 19 torr, 2 mg/L of ozone is injected into the sterilization chamber followed by a five-minute dwell time. After injection of ozone, chamber pressure increases to 27-30 torr.

The primary purpose for this step is to reduce residual hydrogen peroxide, which may be preferentially absorbed by certain polymers (e.g., polyoxymethylene and polyurethane) (11). Residual hydrogen peroxide can render a material cytotoxic unless removed by secondary reaction or extended aeration.

Adding ozone to hydrogen peroxide also enhances overall microbicidal efficacy. The chemical reaction between ozone and hydrogen peroxide is known as the "peroxone oxidation" (12). In a typical application (e.g., water treatment facility), gaseous ozone is injected into a liquid containing hydrogen peroxide with various contaminants. Contaminants are oxidized near the gas-liquid interface.

Experimental data confirms that ozone reduces residual hydrogen peroxide concentration in polymers with a high propensity towards absorbing VHP. For example, polyurethane has a 17% reduction in residual H2O2 when exposed to the H2O2 reduction step. Both in vitro and in vivo biocompatibility testing on material samples processed with the VP4 confirm that all common metallic and polymeric materials are non-toxic and safe for use.

Although a 6-log spore reduction is consistently achieved during the first Dynamic H2O2 exposure step, data confirms that the addition of ozone results in additional lethality. Using a specially designed Test Pack (which FDA required to have equivalent or greater resistance than worst-case devices and loads), the inactivation potential of the H2O2 reduction step was measured using process time (i.e., the only common variable between the hydrogen peroxide step as controlled by differential pressure, and ozone injection controlled by dose and dwell time). As shown in Figure 4, the inactivation profile is biphasic with the Dynamic H2O2 exposure step adding up to 1.8 log lethality, beyond the 6-log half-cycle reduction achieved from exposure to only VHP. Replacing ozone with oxygen resulted in minimal additional lethality, confirming that the reaction of ozone with H2O2 is responsible for the additional microbial potential.

Preliminary studies have confirmed that this additional lethality can be used to sterilize very challenging devices such as flexible colonoscopes, which currently are reprocessed using only high-level disinfection.

Finally, material compatibility is not compromised by the addition of ozone, which is known to be highly corrosive to certain materials used in medical devices (13). Because ozone preferentially reacts with residual hydrogen peroxide, it does not directly oxidize material surfaces. Thus, overall material compatibility of the VP4 process is comparable to conventional VHP sterilizers, in spite of the addition of ozone.

SUMMARY/CONCLUSIONS

The STERIZONE® VP4 (VP4) Sterilizer is the first new low-temperature sterilizer to be controlled by differential chamber pressure. Unlike conventional VHP devices, which maintain a constant dose and exposure time, but allow chamber pressure to vary, the VP4 maintains a constant chamber pressure, while allowing dose and time to vary depending on the load size and composition. This results in a single sterilization cycle able to process widely differing devices and weight without the need to select a preferred cycle.

Like first-generation low-temperature sterilizers, the VP4 achieves sterilization by use of vaporized hydrogen peroxide, which is an oxidizing agent known for its bactericidal, virucidal, sporicidal and fungicidal properties. However, lethality is based on both the vapour and micro-condensation forms of hydrogen peroxide, with the latter being recognized as having superior microbial kill rates.

A hydrogen peroxide reduction step has been added to Cycle 1 to reduce residual H2O2 preferentially adsorbed by certain polymers. Experimental data has been generated to prove that ozone reduces residuals in select polymers, but also results in additional lethality.

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CONCISE REPORT

Epidemiologic and molecular characteristics of methicillin-resistant *Staphylococci* environmental contamination in outpatient settings of a Chinese megalopolis

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ABSTRACT

Background: Severe outcomes of methicillin-resistant Staphylococcus aureus (MRSA) infection and rare studies regarding characteristics of Staphylococci in environment of hospitals all over the world. The aim of this study was to perform a cross-sectional study to elucidate the epidemiologic and molecular characteristics of Staphylococci isolates of tertiary hospitals in Guangzhou, China.

Methods: 400 surface samples were collected from the waiting halls of four Guangzhou tertiary hospitals and sent to laboratory for isolation and identification of Staphylococci isolates, antibiotic resistance testing, and gene detections including mecA gene, qac gene, Panton-valentine leukocidin (PVL) genes, the staphylococcal cassette chromosome mec (SCCmec) typing and multilocus sequence typing (MLST).

Results: 66.25% of 400 samples were detected with Staphylococci, including five methicillin-resistant Staphylococcus aureus (MRSA) isolates. 83.77% of the Staphylococci isolates were classified as multidrug resistant (MDR) isolates. Five isolates of MRSA carried a range of SCCmec types, including four NT (non-typeable) and one IVa. Staphylococcus aureus isolates were classified into several ST (sequence typing) types. Only one MRSA isolate was positive for the qac gene, and two MRSA isolate were positive for the PVL genes. None methicillin-susceptible Staphylococci aureus (MSSA) isolate was positive for the qac gene, and three MSSA isolates were positive for the PVL genes.

Conclusion: In conclusion, the current study reveals multiclonal transmission and suggests that the outpatient departments of Guangzhou tertiary hospitals were likely cross-contaminated from multiple sources.

KEY WORDS

methicillin-resistant *Staphylococcus aureus*; hospitals; prevalence; molecular typing; drug susceptible profile.

Staphylococcus aureus (*S. aureus*) is one of the common pathogenic bacteria. Methicillin-resistant *Staphylococcus aureus* (MRSA) was first found in UK in 1961, subsequently quickly spreading to China and many other countries and regions (1,2). Its emergence and spread has not only limited the selections of clinical medication, but also prolonged hospitalization, increased the mortality and economic burden of patients (3,4). Moreover, it has become significant challenge to clinical treatment and infection control.

However, most current studies focused on patients and medical staff in hospitals. There are rare studies regarding environment of hospitals. Thus, it is essential to perform a cross-sectional study to elucidate the prevalence, antimicrobial susceptibilities, and molecular characteristics of *Staphylococci* isolates contaminating environment of outpatient departments in Guangzhou, China.

METHODS

Guangzhou, as the third megalopolis in China, can provide convenience for *S. aureus* transmitting from public places to humans due to its crowded places and dense population. So we conducted surface sampling in outpatient departments of tertiary hospitals between March and April of 2014 in Guangzhou. Four tertiary hospitals, including Guangdong General Hospital, Guangdong No.2 Provincial People's Hospital, the First Affiliated Hospital of Guangdong Pharmaceutical University, and the First Affiliated Hospital of Guangzhou Medical University were randomly selected. Five locations, including escalator buttons, seats, registration desks, toilet faucets and banisters were selected because of their frequently touched by the patients. Samples were collected on

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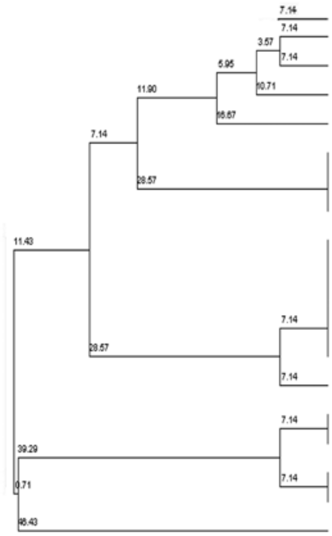
Conflicts of interest
None.

Figure 1: Clonal dendrogram and detailed information on *Staphylococcus aureus* isolates.



Isolate Number	ST Type	Time	Hospital[a]	Location	SCC*mec* Type	PVL	qac	MDR
MRSA-226	125	Weekday	H1	Registration desk	NT	+	-	+
MRSA-283	5	Weekday	H2	Toilet faucet	NT	+	-	+
MSSA-282	221	Weekday	H2	Toilet faucet		-	-	-
MSSA-307	6	Weekday	H4	Registration desk		-	-	-
MSSA-1	72	Weekend	H1	Escalator button		+	-	-
MSSA-90	72	Weekend	H2	Toilet faucet		-	-	+
MSSA-12	72	Weekend	H1	Seats		-	-	+
MSSA-74	188	Weekend	H2	Registration desk		-	-	-
MSSA-155	188	Weekend	H4	Toilet faucet		-	-	+
MSSA-281	188	Weekday	H2	Toilet faucet		-	-	+
MSSA-309	188	Weekday	H4	Toilet faucet		-	-	-
MSSA-382	188	Weekday	H3	Toilet faucet		+	-	+
MSSA-383	1462	Weekday	H3	Escalator button		+	-	+
MRSA-42	398	Weekend	H1	Banisters	IVa	-	-	+
MRSA-359	398	Weekday	H3	Escalator button	NT	-	-	+
MSSA-26	2140	Weekend	H1	Registration desk		-	-	+
MSSA-47	2140	Weekend	H1	Banisters		-	-	+
MRSA-352	808	Weekday	H3	Seats	NT	-	+	+

[a] H1, Guangdong No.2 Provincial People's Hospital; H2, The First Affiliated Hospital of Guangdong Pharmaceutical University; H3, The First Affiliated Hospital of Guangzhou Medical University; H4, Guangdong General Hospital.

weekday and weekend, respectively. Swabs moistened with saline were used to sample surfaces. The samples were then transported to the laboratory immediately.

Samples were detected to identify *Staphylococci, S. aureus*, MRSA, methicillin-susceptible *S. aureus* (MSSA), coagulase-negative *Staphylococci* (CoNS), methicillin-resistant coagulase-negative *Staphylococci* (MRCoNS), and methicillin-susceptible coagulase-negative *Staphylococci* (MSCoNS).

All *Staphylococci* isolates were detected antibiotic resistance using the Kirby-Bauer disk diffusion method for 11 antimicrobial agents (cefoxitin, clindamycin, rifampicin, moxifloxacin, tobramycin, trimethoprim, penicillin, linezolid, teicoplanin, erythromycin, and gentamicin) and were classified as multidrug resistant (MDR) if they were non-susceptible to ≥3 antibiotic classes.

All *S. aureus* isolates were tested for the presence of the *qac* gene, the Panton-Valentine leukocidin (*PVL*) genes, and the multilocus sequence typing (MLST). All MRSA were used to confirm and type the staphylococcal cassette chromosome *mec* (SCC*mec*) gene. More details can be found in our previous study (5).

Data were analyzed using descriptive statistics and χ^2 tests. A *P* value <0.05 was considered statistically significant. All statistics were conducted using Stata 14.1 (College Station, Texas, USA).

RESULTS

Identification of Staphylococci isolates

We collected 200 samples on weekday and 200 samples on weekend, including five MRSA isolates, 13 MSSA isolates, 21 MRCoNS isolates, 226 MSCoNS isolates, and 135 *Staphylococci*-negative isolates. Detailed information can be found in Table 1.

Antibiotic resistance of Staphylococci isolates

There were 265 *Staphylococci* isolates, in which the most resistant was to penicillin (252), followed by erythromycin (241), clindamycin (170), rifampicin (148), trimethoprim (107), gentamicin (82), moxifloxicin (66), tobramycin (41), cefoxitin (26), teicoplanin (8), and linezolid (4). 83.77% of *Staphylococci* were detected as MDR. 100% of MRSA isolates, 100% of MRCoNS isolates, 83.19% of MSCoNS isolates, and 61.54% of MSSA isolates were tested as MDR.

Molecular characteristics of S. aureus isolates

40.00% of the MRSA isolates carried the *PVL* genes, and 20.00% of them carried the *qac* gene. Unlike the MRSA isolates, 23.08% of the MSSA isolates were positive for *PVL* genes, and none of the MSSA isolate was positive for the *qac* gene. With regard to ST type, the most predominant ST type among the five MRSA isolates was ST398 (40.00%). And among 13 MSSA isolates, ST 188 was the most prevalent ST type (38.46%). As for SCC*mec* type, one MRSA isolate was classified as SCC*mec* type IVa and the remaining four MRSA isolates were NT. Detailed information can be found in Figure 1.

DISCUSSION

The current study is the first one to systematicaly report the prevalence, antibiotic resistance, and molecular characteristics of *Staphylococci* isolates from environmental surfaces in outpatient departments in China. The proportion of *S. aureus* isolation in the current study was similar to that from an Iranian study conducted on hospital wards (4.50% vs 7.10%) (6). However, considerably

TABLE 1: Distribution of isolates among different sample locations, hospitals and time [n (%)]

Factors	*S. aureus*		CoNS		χ^{2*}	*P**	*Staphylococci*(-)	Total	χ^{2**}	*P***
	MRSA	MSSA	MRCoNS	MSCoNS						
Locations					4.22	0.380			15.65	0.004
Escalator button	1 (1.25)	2 (2.50)	7 (8.75)	47 (58.75)			3 (28.75)	80 (20.00)		
Seat	1 (1.25)	1 (1.25)	2 (2.50)	41 (51.25)			35 (43.75)	80 (20.00)		
Registration desk	1 (1.25)	3 (3.75)	5 (6.25)	34 (42.50)			37 (46.25)	80 (20.00)		
Toilet faucet	1 (1.25)	6 (7.50)	4 (5.00)	50 (62.50)			19 (23.75)	80 (20.00)		
Banister	1 (1.25)	1 (1.25)	3 (3.75)	54 (67.50)			21 (26.25)	80 (20.00)		
Hospitals					1.23	0.746			3.52	0.318
H1[a]	2 (2.00)	4 (4.00)	6 (6.00)	59 (59.00)			29 (29.00)	100 (25.00)		
H2[a]	1 (1.25)	4 (4.00)	3 (3.00)	51 (51.00)			41 (41.00)	100 (25.00)		
H3[a]	2 (2.00)	2 (2.00)	4 (4.00)	60 (60.00)			32 (32.00)	100 (25.00)		
H4[a]	0 (0.00)	3 (3.00)	8 (8.00)	56 (56.00)			33 (33.00)	100 (25.00)		
Time					0.04	0.850			18.80	0.000
Weekend	1 (0.50)	7 (3.50)	7 (3.50)	97 (48.50)			88 (44.00)	200 (50.00)		
Weekday	4 (2.00)	6 (3.00)	14 (7.00)	127(63.50)			47 (23.50)	200 (50.00)		
Total n (%)	5 (1.25)	13 (3.25)	21 (5.25)	226(56.50)			135(33.75)	400 (100.00)		

* The calculation on χ^2 and *P* value was based on the distribution of *S. aureus*.
** The calculation on χ^2 and *P* value was based on the distribution of *Staphylococci*.
[a] H1, Guangdong No.2 Provincial People's Hospital; H2, The First Affiliated Hospital of Guangdong Pharmaceutical University; H3, The First Affiliated Hospital of Guangzhou Medical University; H4, Guangdong General Hospital.

higher MRSA detection levels were noted in several previous studies. The considerable differences in the reported value for MRSA prevalence could be affected by factors such as limited sampling locations, varying sampling techniques, and different regional hygiene measures (5).

Antibiotic resistance in the current study showed that the outcomes of resistance to penicillin, erythromycin, clindamycin and rifampicin are relatively severe. However, there were some isolates resistant to teicoplanin and linezolid, which are final effective antibiotics in treating *Staphylococci* infections. There was no significant difference between *S. aureus* and CoNS, which was consistent with a recent Chinese study (7). The proportion of antibiotic resistance among MRSA isolates was significantly higher than that of MSSA isolates.

Molecular characteristics of *S. aureus* showed that the anti-disinfectant *qac* gene was discovered in one MRSA isolate in the current study. With regard to the results of MLST, ST188 was the most predominant ST type of MSSA and has been reported that it can be widely disseminated between communities and hospital settings. The appearance of these clones in an urban environment is rarely reported and, thus, we cannot rule out the possibility that those two ST398 isolates were transmitted by people who have close contacts with animals or meats (5). As for the outcomes of SCC*mec*, 80% the MRSA isolates were detected as SCC*mec* NT, which indicated that genetic mutation has occurred in the process of MRSA transmission. This phenomenon was almost the same as the findings of University of Washington studying group (8,9).

In conclusion, the current study reveals multiclonal transmission and suggests that the outpatient departments of Guangzhou tertiary hospitals were likely cross-contaminated from multiple sources.

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CONCISE REPORT

Antimicrobial susceptibility in a tertiary care hospital in Pakistan

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ABSTRACT

Background: This study examined antimicrobial susceptibility trends among hospitalised patients in the North West General Hospital and Research Centre in Peshawar, Pakistan.

Methods: Retrospective analysis of blood culture reports of inpatients (N=101), admitted in different wards, from January 7, 2015 and August 15, 2015.

Results: There were 43 (43%) females and 58 (57%) males with median age of 58 years. Sepsis was the major diagnosis (18.8%), whereas, diabetes mellitus and chronic kidney disease were observed to be the two main comorbid conditions (10.9%). Among Gram-positive pathogens methicillin resistant S. aureus (MRSA) (38.7%) and methicillin sensitive S. aureus (25.8%) were the most common, whereas, cephalosporinase-producing E. coli (28.8%) and extended-spectrum beta-lactamase (ESBL) E. coli (25.8%) were the most common among Gram-negative microorganisms. In total, 23 different antimicrobials were tested for susceptibility. MRSA and S. aureus were found 100% sensitive to vancomycin and linezolid. Higher resistance trend was observed in most of the checked cases against trimethoprim (86%), sulfamethoxazole + trimethoprim (83%), amoxicillin plus clavulanate (78%) and cefotaxime (95%).

Conclusion: Susceptibility data of the presented study may serve in designing a useful protocol for empirical therapy selection of patients with systemic infections.

KEY WORDS
antimicrobial susceptibility; resistant pathogens; Pakistan, MRSA

INTRODUCTION

During the past few decades, antimicrobial resistance has emerged as a major threat around the globe, and has significantly contributed to mortality and morbidity through infectious diseases. It leads to therapeutic ineffectiveness, higher medical cost, disease prolongation and longer hospital stay. Microbial resistance limits the treatment of choice and has a negative impact on patient outcomes. In 2013 microbial resistance led to about 2 million infections, approximately 23,000 deaths, financial losses of 20 billion USD with a productivity loss of 35 billion USD (Centres for Disease Control and Prevention) (1). Irrational use of antimicrobials is one of the major contributing factors to drug resistance. In the presence of microbial resistance, the chances of post-operative infection may increase by 40-50%. Self-medication, inappropriate drug use, and poor health infrastructure are the main factors for drug resistance (2, 3).

Although the pattern of microbial drug resistance varies geographically, some pathogens including MRSA, vancomycin-resistant enterococci (VRE), and extended-spectrum beta-lactamase-producing (ESBL) E. coli and K. pneumoniae, are posing threat to the developing and developed countries (4, 5). The findings of Khan et al. show the rapidly developing microbial resistance between 2001 and 2007 against ceftriaxone in Pakistan. Resistance towards nalidixic acid, chloramphenicol, cotrimoxazole and ofloxacin has also been significantly increased (6).

This study explores the patterns of microbial susceptibility to commonly prescribed antimicrobials in a tertiary care hospital of Peshawar, Pakistan.

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FIGURE 1: Growth of gram negative microorganisms in blood samples n=66

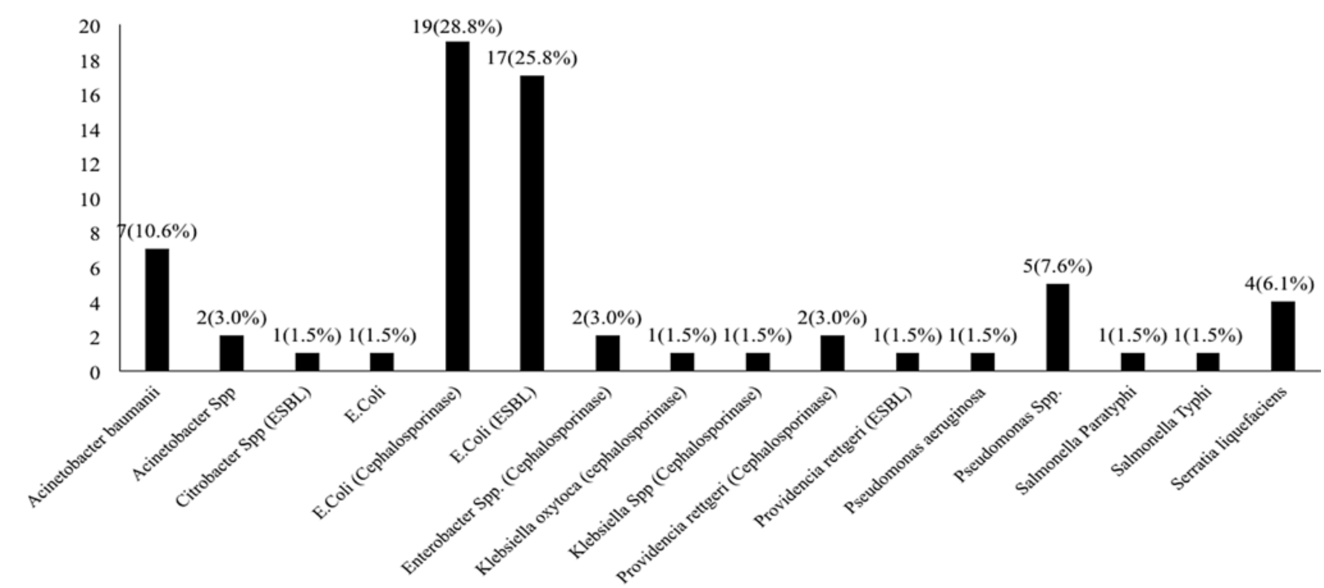
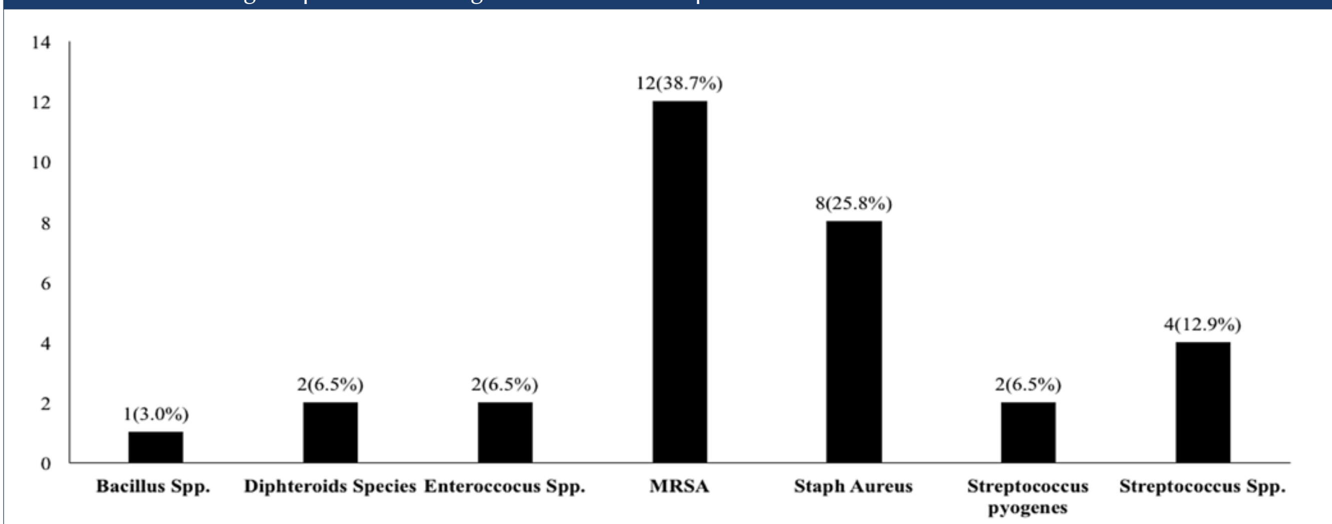


FIGURE 2: Growth of gram positive microorganisms in blood samples n=31



METHODS

The study involved retrospective analysis of blood culture records of inpatients from both genders and with different age groups, from a clinical microbiology laboratory of the North West General Hospital and Research Centre in Peshawar, Pakistan, from January 7, 2015 and August 15, 2015.

Microbial testing

The blood samples were tested for minimum inhibitory concentration (MIC) of different classes of antimicrobials, namely penicillins, cephalosporins, carbapenems, quinolones, aminoglycosides, macrolides, glycopeptides, sulfonamides, polymyxins, and anti-tuberculosis agents. To check susceptibility of the microorganisms, MacConkey agar and chocolate agar were used, whereas for the microbial sensitivity, Müller-Hinton agar and nutrient agar were used. The MIC of antimicrobials was used to categorize the microorganisms as susceptible, intermediate or resistant. Duplicate blood samples from the same patients were omitted. Intermediate susceptibility was counted as susceptible in this study.

Ethical approval and data analysis

The study protocol was approved by the Research Ethics Committee of the North West General Hospital and Research Centre in Peshawar. A descriptive statistical analysis of the data were performed using SPSS version 22.0 for Windows (Statistical Package for Social Sciences, Chicago IL, USA).

Results

The antimicrobial susceptibility reports of 101 patients from different age groups and units were collected. There were 43 females (43%) and 58 males (57%) with age ranging from

1 to 95 years old (median = 58). Majority of the samples were collected from patients diagnosed with sepsis/septicaemia (N=19, 18.8%), followed by urosepsis (N=9, 8.9%), pneumonia/chest infections (N=9, 8.9%), and urinary tract infections (N=6, 5.9%). Diabetes mellitus and chronic kidney disease were observed to be the two main comorbid conditions among the patients (N=11, 10.9%). Among the Gram-negative microorganisms cephalosporinase-producing E. coli was the most frequent (N=19, 28.8%), followed by ESBL E.coli (N=17, 25.8%) and A. baumannii (N=7, 10.6%), as shown in Figure 1. MRSA was the most common (N=12, 38.7%) Gram-positive pathogen of the studied population, followed by S. aureus (N=8, 25.8%), and Streptococcus spp. (N=4, 12.9%), as shown in Figure 2.

Pattern of antimicrobial susceptibility

Pathogens isolated from blood culture samples were checked for their susceptibility against 23 different antimicrobials. The classes of antimicrobials administered are shown in Table 1 below, alongside the pattern of antimicrobial susceptibility.

TABLE 1: Microbial susceptibility

Antimicrobial tested	N	Resistant	Sensitive	% Resistance
Penicillin G	30	24	6	80%
Clindamycin	24	15	9	63%
Sulfamethoxazole + trimethoprim	78	65	13	83%
Amoxicillin plus clavulanate	85	66	19	78%
Trimethoprim	83	71	12	86%
Doxycycline	30	1	29	3%
Fusidic Acid	22	6	16	27%
Gentamycin	90	52	38	58%
Erythromycin	29	18	11	62%
Fluxocillin	22	14	8	64%
Rifampicin	22	4	18	18%
Linezolid	23	0	23	0%
Vancomycin	23	0	23	0%
Ciprofloxacin	62	53	9	85%
Piperacillin and tazobactam	62	59	3	95%
Cefotaxime	56	53	3	95%
Amikacin	62	10	52	16%
Meropenem	62	13	49	21%
Ceftazidime	61	55	6	90%
Imipenem	62	13	49	21%
Tigecycline	4	3	1	75%
Amoxicillin	1	1	0	100%
Cefoperazone plus Sulbactam	6	6	0	100%

DISCUSSION

Microbial resistance has been recognized since the beginning of the antibiotic era, but within the past two decades the development of deadly resistant strains occurred with an aggravating consistency. This escalating evolution of resistance, linked with a diminished antibiotic pipeline, has driven some to claim that a post-antibiotic era is imminent (7). Rational drug therapy and susceptibility profiles should be kept in consideration while selecting the antimicrobials. Sensitivity of antimicrobials toward specific microorganisms assists in treatment choice and use of empiric antibiotic therapy. However, during the selection of antibiotics, site of infection and source should be considered, as well as individual, patient-specific factors (8). Empiric antibiotic treatment initiation can be a leading factor in higher mortality rate among patients. Those patients receiving appropriate antimicrobial therapy are at lower risk of mortality than those receiving inappropriate empiric therapy (8). A lower mortality rate, shorter hospitalization, and reduction in medical costs can be easily achieved by administration of appropriate antibiotics for serious infections.

Our study results are in line with a study in Pakistan, where the percentage of bacterial growth was 49% S. aureus, 18.2% P. aeruginosa and 9.1% E. coli. Among these, 54.1% were gram positive while 45.9% were gram negative (9).

The sensitivity of MRSA to antimicrobial in our study is similar to results from other studies performed in Pakistan (10-12). Furthermore, the resistance of MRSA to gentamycin and sulfamethoxazole + trimethoprim in our study is slightly higher as compared to a study performed in Pakistan, in which the resistance to gentamycin is 76.35% and for sulfamethoxazole + trimethoprim is 86.48% (13).

Our study results reveal Staphylococcus aureus growth of 25.8%, with almost 100% sensitivity to the amoxicillin plus clavulanic acid, doxycycline, flucoxacillin, rifampicin, linezolid vancomycin, and clindamycin. A similar trend of S. aureus susceptibilities were observed by Bukhari et al. (14). Cephalosporinase-producing E. coli and ESBL E. coli exhibited 100% resistance to ciprofloxacin, piperacillin and tazobactam, cefotaxime, amikacin, and meropenem in the blood samples in our study. A similar study in Pakistan by Fayyaz et al. on E. coli spp. growth and susceptibility to antimicrobials reported 55% growth and different resistance pattern to our results, with higher susceptibility to amikacin and imipenem (15).

LIMITATIONS TO THE STUDY

This study was retrospective; therefore it was challenging for the authors to get actual MIC data that assist in determining the zone of inhibition and in classifying the intermediate antibiotics.

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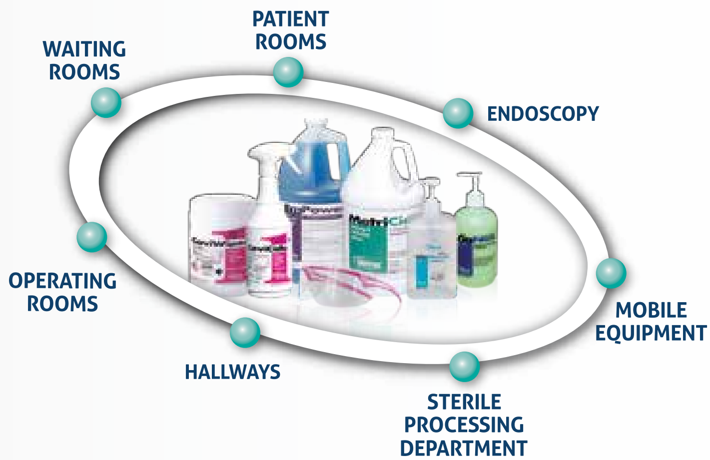

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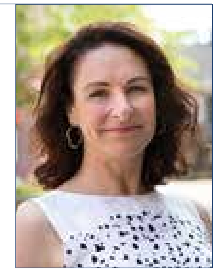


The importance of **continuing education**

Suzanne Rhodenizer Rose, RN, BScN, MHS, CIC
President, IPAC Canada

In previous president's messages, I have mentioned the numerous supports and mentors I've had along the way. My workplaces have been useful venues to connect with other healthcare providers; however, there is nothing quite the same as learning and networking with your peers at national and provincial conferences and workshops in the field of infection prevention and control. Many infection prevention and control professionals work in isolation or pairs, and therefore the exposure to new ideas from like-minded professionals is limited. It is through these magnificent forums that I have gotten some of my best ideas, foundational elements for key initiatives, and professional contacts that have been germane to me achieving successful outcomes.

As the dog days of summer wane, committee work ramps up with frenetic fervor, new projects are on the docket, and the fall conference offerings are in full swing. Herein lies the rub – so many exceptional opportunities to learn, so many networks to leverage and build, so many people to mine ideas from, and so little funding or support to attend. Continued professional development is one of my core professional values. Like many, I have slogged through countless texts and journal articles and written a gazillion papers through my academic endeavors. I have done my absolute best to promote the importance of continuing education and to support the teams that I work with to do the same.

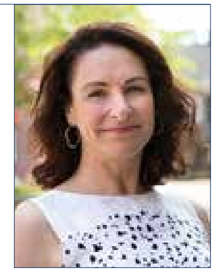
The Institute of Medicine (2010) conducted an interesting literature review that examined the correlation between continuing professional education and quality of healthcare. Albeit challenging to define reliable outcome measures, the authors cited that there is evidence that continuing professional education improves one's knowledge base and skill level (not shockingly), can change healthcare provider behaviours and attitudes, and can improve clinical outcomes. Is this not the goal of every healthcare organization in Canada? Is evidence-based practice not a foundational element of healthcare delivery? Then why is professional development and continuous learning all too susceptible to budget cuts in the times of fiscal constraint? Is it seen as a *perk* rather than a professional necessity. It would seem that this is low-hanging fruit, a fairly cost-effective method to improve patient outcomes with, I might add, the added bonus of improved job satisfaction. Many institutions do not provide the time and/or the money professionals need to attend continuing education opportunities. I do believe that as professionals, we also need to invest in our *own* personal commitment to continuing education as part of our professional responsibility; however, organizational commitment is essential to sustain a professional's lifelong learning endeavors.

Florence Nightingale's *Notes on Nursing* addresses the fact that nurses must learn constantly, through observation and experience (which we do every day at work) as well as through actively seeking *new* knowledge and *new* evidence. A commitment to continued learning is a professional and an organizational responsibility *if* the highest degree of high-quality healthcare is to be achieved. True Story. Even today.

Institute of Medicine. *Redesigning continuing education in the health professions*. 2010. Retrieved from http://www.nap.edu/openbook.php?record_id=12704.

Nightingale F. Notes On nursing: What it is and what it is not. Harrison, London; 1859. Retrieved from http://www.nursingplanet.com/Nightingale/conclusion_appendix.html.

L'importance de la **formation continue**



Suzanne Rhodenizer Rose, IA, B.Sc.Inf., MHS, PCI
Présidente, PCI Canada

J'ai déjà évoqué ici toutes les personnes qui m'ont soutenue et guidée au fil de ma carrière. Les postes que j'ai occupés à ce jour ont mis sur mes pas d'autres fournisseurs de soins, mais rien ne vaut l'apprentissage et le réseautage avec des pairs à l'occasion des congrès et ateliers nationaux et provinciaux sur la prévention et le contrôle des infections. Nombre de professionnels du domaine travaillent seuls ou en tandems et sont donc peu exposés aux idées nouvelles de professionnels attachés aux mêmes principes qu'eux. Pour ma part, c'est lors ces formidables forums que j'ai trouvé certaines de mes meilleures idées, les éléments de base d'initiatives clés et des relations professionnelles qui sont à l'origine de mes meilleurs résultats.

Tandis que la canicule s'apaise, les comités se réactivent avec ferveur, voire avec frénésie, de nouveaux projets emplissent les ordres du jour et les congrès d'automne comblent les agendas. Et voici le hic : il y a tant d'occasions exceptionnelles d'apprendre, tant de réseaux à joindre et à créer, tant de collègues riches d'idées à faire fructifier, mais si peu d'argent ou d'autres formes de soutien pour faciliter la participation. Le perfectionnement professionnel est au cœur de mes valeurs professionnelles. Comme beaucoup d'autres, j'ai avalé d'innombrables textes et articles savants et j'ai écrit des kilomètres de papiers pendant mes années universitaires. J'ai fait de mon mieux pour convaincre de l'importance de la formation continue et pour encourager les équipes dont j'étais membre à faire de même.

En 2010, l'Institute of Medicine a fait un intéressant recensement de la littérature sur la corrélation entre la formation continue et la qualité des soins de santé. Bien qu'il soit difficile de définir une mesure fiable des résultats, les auteurs relèvent des signes probants du fait que la formation continue élargit la base de connaissances et relève le niveau des compétences du sujet (voilà qui ne surprend guère), qu'elle influe sur le comportement et l'attitude des fournisseurs de soin et qu'elle peut améliorer les résultats cliniques. N'est-ce pas précisément l'objectif de toute organisation de soins de santé au Canada? La pratique inspirée de données probantes n'est-elle pas un élément fondamental de la prestation des soins? Pourquoi, alors, le perfectionnement professionnel et la formation continue sont-ils si exposés aux compressions budgétaires? Sont-ils considérés comme des à-côtés plutôt que comme une nécessité professionnelle? Ce sont pourtant des objectifs aisément accessibles et un moyen relativement économique d'améliorer la santé des patients qui se doublent, j'oserais dire, de l'amélioration de la satisfaction au travail. Or, beaucoup d'établissements ne réservent ni le temps ni le budget nécessaires à la formation continue de leur personnel. Certes, nous devons, à titre de praticiens, nous mobiliser *personnellement* et faire de la formation continue une responsabilité professionnelle, mais l'engagement des organisations est également essentiel à une formation soutenue, tout au long de la vie professionnelle du personnel.

Dans *Notes on Nursing*, Florence Nightingale soutient que les infirmières doivent apprendre constamment, par l'observation et l'expérience (ce que nous faisons tous les jours au travail), mais également rechercher activement des connaissances *nouvelles* et des indices *nouveaux*. Pour fournir les soins les plus efficaces, de la meilleure qualité qui soit, soignants et organisations doivent s'investir dans la formation continue. Une opinion qui reste très vraie aujourd'hui.

Institute of Medicine. Redesigning continuing education in the health professions, 2010, consultable [en anglais] à l'adresse http://www.nap.edu/openbook.php?record_id=12704.

Nightingale Florence. Notes On nursing: What it is and what it is not, Harrison, Londres, 1859, consultable [en anglais] à l'adresse http://www.nursingplanet.com/Nightingale/conclusion_appendix.html.

Learning Object Repository – **say what?**

Gerry Hansen, BA
Executive Director, IPAC Canada

So…what is this new thing that IPAC Canada has created with the funny name? Think of it as a free library of excellent tools that have been shared by your peers in infection prevention and control. It is sort of like the little neighborhood book library that people use to share books, only better. Have you ever created an education tool for work that you were really proud of and would like to share with your peers across Canada, but you were unsure how to do this?

A few years ago an excellent educational video was submitted to the IPAC Canada board with a request to share it with the membership. At that time, there was no means of reviewing and posting tools that were contributed.

We now have a dedicated virtual sharing space where all submitted tools are reviewed by the Learning Object Repository (LOR) Committee and posted for use as appropriate. Once posted, the tool will remain available for two years. Then the author will be asked to review and update the tool and re-submit it if they would like. Everyone who uses an LOR tool can provide feedback to the author using a feedback form on the site. If you have ever been part of a project that goes from good to great or great to amazing because of feedback, this is what we hope the LOR will do. Have a look at the LOR site and please share your creations.

We would like to acknowledge several IPAC Canada members who have a significant amount of their time and expertise in development of the LOR. The vision for the LOR was that of Dr. Donna Moralejo, former Education Director of IPAC Canada. Site developers and review committee are:

- Anne Bialachowski, RN, BN, MS, CIC, Chair
- Melody Cordoviz, RN, BSc, BScN, CIC, LOR Administrator
- Natalie Bruce, RN, MScN, CIC
- Sandra Callery, RN, MHSc, CIC
- Felicia Laing, BSc, MSc

Many thanks also to Shirley McDonald, ART, CIC, Webmaster; and Pamela Chalmers, Web Designer, for their expert support.

The next deadline for submission is April 1, 2017.

(With thanks to Anne Bialachowski, Chair, Learning Object Repository Committee).

"Think of it as a free library of excellent tools that have been shared by your peers in infection prevention and control."

Important Role for Standalone Indoor Air Purification Systems

INTRODUCTION

Most people pay little attention to their indoor air quality, despite the fact that US EPA states that 68% of human diseases are spread through indoor air. [1] Why is this the case? People believe that their heating, ventilation, and air conditioning (HVAC) systems are taking care of 'cleaning' their indoor air. But HVAC systems are primarily designed to maintain the indoor air temperature at comfortable levels. Even when HVAC systems have filtration components they are not always as effective as they need to be in cleaning the air, especially when it comes to infection control.

HEALTH CARE FACILITY INDOOR AIR QUALITY

Many areas in health-care facilities can benefit from special air purification including: examination rooms used by high-risk patients, rooms for isolation of patients with infections, and lab environments.

SOURCES OF INFECTIOUS PARTICULATE IN INDOOR AIR

Humans are a key source of airborne agents which infect people. Measles, influenza viruses and the tuberculosis bacteria are known to be transmitted by means of shared air between people.

Laser plumes and surgical smoke can be a source of airborne contaminant as they release a plume that includes particles, gases, tissue debris, and offensive smells. Some viruses and bacteria (e.g., human papillomavirus HPV, HIV) have been detected in laser plumes. [2]

Increased concentrations of airborne red blood cell pathogens lead to acute lung infection and, conversely, increased rates of mortality and morbidity. [3]

In addition to infectious bioaerosols, non-infectious particulate must also be addressed by health-care facilities including sensitizing and allergenic agents (e.g., ethylene oxide, glutaraldehyde, formaldehyde, hexachlorophene, and latex allergens). Asthma and dermatologic and systemic reactions often result from exposure to these chemicals. Anesthetic gases and aerosolized medications (e.g., ribavirin, pentamidine) can be hazardous to health-care workers.

CLEANING INDOOR AIR IN HEALTH CARE FACILITIES

Containment of the hazardous aerosol at the source is a key first level of control. The combination of filtration equipment and airflow rates are often underappreciated for the effect they have on the concentration of infectious agents. If the filter efficiency and/or air change rate is high enough, a larger number of infectious agents can effectively be removed before they spread and affect people.

THE ROLE FOR STANDALONE AIR PURIFICATION SYSTEMS IN HEALTH CARE FACILITIES

There are two transmission patterns: (i) within-room exposure, and (ii) transmissions beyond a room through corridors, and through the HVAC system which recirculates air throughout the building. Standalone air purification systems have been used as an effective first level control solution with respect to both transmission pattern types. Specifically when a solution is needed to: (i) temporarily recirculate air in rooms with no general ventilation, ii) augment systems with inadequate airflow, and iii) provide increased effectiveness in airflow.

CHOOSING A STANDALONE AIR PURIFICATION SOLUTION

Standalone air purifier effectiveness is dependent on the: i) filtration system, ii) air handling capacity, and iii) operating sound level. Portable units should be capable of recirculating air through medical grade filters, and the units should be designed to achieve the equivalent of 12 air cleanings/hour (ACH). [2] These systems must also be capable of operating at noise levels that do not inhibit occupants from performing their necessary tasks, otherwise they will be 'turned down' which can negate their full efficacy. One example of a highly effective system is the Cascade White (6000C) from Surgically Clean Air.

SUMMARY

Today, more and more well-known hospitals, health care institutions, and medical labs have taken proactive steps to take care of their indoor air quality and established a new school of thought on the use of standalone medical grade air purifiers in managing infectious and non-infectious airborne particulate.

REFERENCES

[1] U.S. Environmental Protection Agency 'Indoor Air Quality' www.epa.gov/indoor-air-quality-iaq

[2] U.S. Department of Health & Human Services Centers for Disease Control & Prevention (CDC) Atlanta, GA

[3] Babaev A, Pozzi F, Hare G, Zhang H (2014) Storage of Red Blood Cells and Transfusion-Related Acute Lung Injury. Anesth Crit Care Open Access 1(1): 00002. DOI: 10.15406/jaccoa.2014.01.00002

CIC® Graduates

New and certified CIC®s from a variety of healthcare settings have spent hours studying, digesting facts, and reading current literature. This information and life experience, along with a successful completion of the CIC® examination, ensure infection prevention and control professionals deserve to place a CIC® after their names. Congratulations to the following April-June list of graduates.

New Certificants

Alexander S. Chapman, CIC

Jessa Craig, BSc, BScN, RN, CIC

Annic J. Deguire, RN, CIC

Eric Devine, BASc, MPH, CPHI(C),CIC

Iman Hassan, MD, CIC

Jenean A. Johnson, RDH, CIC

Maureen E. Kano, RN, BN, CIC

Kate Mombourquette, RN, BScN, CIC

Sandra Paton, RN, CIC

Sindhu Pillai, CIC

Michele Terfry, CIC

Courtney C. Trombley, RN, BSN, CIC

Recertified

Sherri D. Beckner, CIC

Tanya J. Denich, CIC

Alison M. Devine, CIC

Dana L. Finnegan-Yee, CIC

Renee Freeman, CIC

Sherri D. Gurini, CIC

Janice Lee McIntyre, CIC

T. Christine Moore, CIC

Deborah M. Paton, CIC

Barbara Schmidt, RN, BScN, CIC

Denise H. Sorel, CIC

Tracey Spencer, CIC

Angela Thomas, CIC

Karen D. Valentine, RN, BScN, CIC

Bring in a **New Member!**

Membership has its benefits – education, collaboration and representation. The IPAC Canada website (*www.ipac-canada.org*) has so much information on the benefits of being a member. The annual member resource guide for finding other IPAC Canada members, links to infection control sites, audit tools, the audit tool app, upcoming mentor program, Learning Object Repository...the list is extensive. Tell another Infection Prevention and Control Professional (ICP), tell an infection control or ID physician, tell your Medical Laboratory Technologist, tell Environmental Services, tell EMS, tell your designate, and tell your director about the benefits of joining our national organization.

If that person joins IPAC Canada by March 1, 2017, both you and the new IPAC Canada member will be eligible to win a complimentary 2017 conference registration (Monday-Wednesday, value $650). You are eligible for the draw with every new IPAC Canada member that you get to sign up from June 1, 2016 to April 30, 2017 inclusive. Should the winning members have already paid their 2017 conference registration, a refund will be made to the person or the institution which has paid the fee. The New Member Contest form is available from *www.ipac-canada.org* or by contacting the IPAC Canada office. An announcement of the winners of this offer will be made by March 15, 2017. Membership applications can be found at *http://www.ipac-canada.org/about_join.php*.

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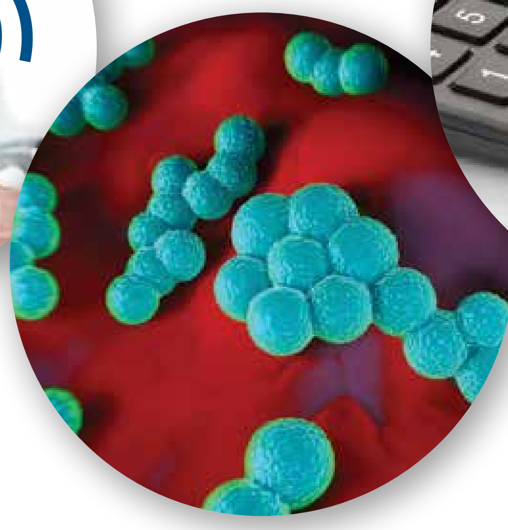

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* Statistically significant

Reference: 1. Kelly, J. W., MD, Blackhurst, D., DrPH, McAtee, W., BS, & Steed, C., MSN, RN, CIC. (2016, June 23). Electronic hand hygiene monitoring as a tool for reducing health care–associated methicillin- resistant Staphylococcus aureus infection. *American Journal of Infection Control.*

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Distance Education Graduates

IPAC Canada congratulates the graduates of the 2015-2016 Distance Education Online Novice Infection Prevention and Control Course. The following group of graduates has successfully completed the course. This course also provides IPAC Canada members with the opportunity to share their expertise in the roles of coordinators, instructors, and discussion facilitators. Many thanks go to the faculty of the course and to the families and colleagues of the students for making it all possible for students to strengthen their knowledge and skills. We know that they are ready and eager to apply them to practice.

Congratulations and best wishes to:

Nicole Anderson, BHSc, BSc

Ruxshin Amooyan, CPHI(C)

Erica Bainbridge, RN, BN

Christopher Bell, MPH

Katrina Chia, BAsc, CPHI

Jocelyn Coehoorn, BSc

Kerry Deibert, RN

Renee de Leon, BScN, RN

Shawna Ferenc, RN, BN

Tara Ferguson, BScN, RN

Andrea Feys, RPN

Melanie Fidyk, RN

Kim Flannery, RN, BN, BSc

Rhonda Garland, RN

Wendy Garrison, MLT

Justyna Giczewska, RPN

Sarah Haromy, ASCP, BSc

Jeremy Jamilano, BSc BEH, CPHI(C)

Zaheeda Jessani, RN, BN

Robin Johnson, MLT

Melanie Kearly, RN, BN

Nathan Kenny, B.Comm

Annie Lord-Stephens, RN

Bonnie MacKenzie, RN

Kerry Manzuik, RN

Kelly Maxwell, BScN

Jim Moore, BSc, Btech, CPHI(C)

Toni Moran, BSc. BAsc, CPHI(C)

William Morell, RN, BScN

Connie Newton, RN, BScN

Helen Popson, RN

Kristal Prevost, RB, BScN

Robert Rockbrune, BSc

Kaethel Sauerborn, BHSc

Helga Sellin, MLT

Katelynn Smith, MLT, BSc

Karen Stoopnikof, BSN, MSN

Lori Stuber, BSc, MSc, BScN

Amanda Sturgeon, BASc(EH), CPHI(C)

Ruth Sutherland, RN

Melissa Swetch, RN, BScN, MN

Kim Treller, LPN

Erica Zylak, RN, BScN

2015-2016 Faculty

- **Heather Candon**, BSc, MSc, CIC
  Course Coordinator/Instructor
- **Jane Van Toen**, MLT, BSc, CIC
  Course Coordinator/Instructor
- **Jill Richmond**, BA, RN, BN, CIC
  Practicum Coordinator/Facilitator
- **Laura Fraser**, RN, BScN, CIC
  Instructor
- **Leila Kipke**, MLT
  Instructor
- **Tara Leigh Donovan**, BHSc, MSc
  Instructor
- **Sue Lafferty**, RN, BScN, CIC
  Instructor/Facilitator
- **Lesley McLeod**, BSc, MSc, CIC
  Instructor
- **Anne Augustin**, MLT, CIC
  Facilitator
- **Tina Stacey-Works**, MLT, CIC
  Facilitator

For more information on upcoming course offerings, see IPAC Educational Opportunities on the website.

2017 ECOLAB poster contest

An annual poster contest is sponsored by Ecolab and supported by a chapter of IPAC Canada to give infection prevention and control professionals (ICPs) an opportunity to put their creative talents to work in developing a poster which visualizes the infection Control Week theme. 2017 National Infection Prevention and Control Week is October 16-20.

THEME: Infection Prevention and Control –
It's a Team Thing!

PRIZE: Waived registration to 2017 IPAC Canada National Education Conference or $500.

REMINDER: Posters should have meaning for the public as well as all levels of staff across the continuum of care. The poster should be simple and uncluttered, with strong visual attraction and minimal text.

Judging will be on overall content. Artistic talent is helpful but not necessary. The winning entry will be submitted to a graphic designer for final production. Your entry will be become the property of IPAC Canada.

HOST CHAPTER: IPAC Nova Scotia

SUBMISSION: Submissions will only be accepted by email. Send submission to *info@ipac-canada.org*.
Email title: 2017 Ecolab Poster Contest
Submission format:

- Electronic file in Word or PDF format only.
- Files less than 5 MB preferred.
- File Size – must print out to 8.5″x11″ paper.
- Name, address and telephone number must be included in the covering email.
- DO NOT include identifiers in the poster submission.

DEADLINE: January 31, 2017

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Moira Walker Memorial Award for **International Service**

This award honours an individual or group that has demonstrated extraordinary efforts to bring about change or improvement related to infection prevention and control in parts of the world that are under developed or under resourced. The annual award is in honour of Moira Walker, RN, CIC, a Past President of IPAC Canada (formerly CHICA Canada) and Past Honourary Secretary of the International Federation of Infection Control. Moira's life was dedicated to enhancing the physical and spiritual health of her many friends and colleagues.

NOMINATION GUIDELINES

Preferred: Current IPAC Canada members in good standing

The award may be presented to individuals, prior nominees, or a group of individuals, but not past award recipients, who have demonstrated international cooperation in the field of infection prevention and control or public health. Fundraising efforts alone will not be sufficient criteria for this award. Lifetime achievement in international service would be considered.

Who May Nominate

Any member of IPAC Canada or a chapter of IPAC Canada may submit a nomination. The IPAC Canada Board of Directors (the Board) may also nominate candidates. The nomination form is available at *www.ipac-canada.org* (Opportunities).

How to Nominate

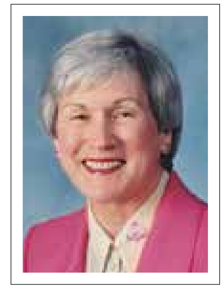
A completed nomination form and covering letter outlining the nominee's projects that have resulted in this nomination must be forwarded to the Membership Services Office no later than March 31st of each year.

Selection Process

The Board will select the recipient(s) through an evaluation process.

Award

Artwork with a First Nations and Inuit art theme. The accompanying engraved plate will announce the recipient's award. In addition, award winner(s) will be provided with travel (economy) to the 2016 conference, two nights' accommodation, and a complete waived registration for the national education conference at which the award is presented.



In the case of a group award, one representative of the group will be provided with the full award.

Deadline

The deadline for nominations is March 31, 2017.

Announcement and Presentation

The award winner(s) will be advised by April 15th of each year. The award will be presented at the Opening Ceremonies of the IPAC Canada National Education Conference.

Award Sponsor

The Moira Walker Memorial Award for International Service is made possible through the generous support of Sage Products LLC.

2017 Champions of Infection Prevention and Control

In collaboration with 3M Canada, IPAC Canada established the Champions of Infection Prevention and Control Award in 2009. The Award recognizes IPAC Canada members who have demonstrated innovative initiatives to prevent infection, raise awareness, and improve the health of Canadians.

The candidate may also be nominated for lifetime achievement. The nomination may be made by a member of IPAC Canada or by an IPAC Canada chapter. Formal presentation of the Award will be made at the Opening Ceremonies of the 2017 National Education Conference (Charlottetown, June 18, 2017).

Deadline for 2017 nominations is **March 1, 2017.**

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*Quaternary Disinfectant Cleaner	CAS –No.	**Concentration %
Octyl decyl dimethyl ammonium chloride	32426-11-2	0.1016
Dioctyl dimethyl ammonium chloride	5538-94-3	0.0406
Didecyl dimethyl ammonium chloride	7173-51-5	0.0609
Alkyl dimethyl benzyl ammonium chloride	68424-85-1	0. 1354
Alcohol ethoxylate	68439-46-3	0.1000
		Total 4,385 ppm

*Hydrogen Peroxide Cleaner Disinfectant	CAS –No.	**Concentration %
Hydrogen Peroxide	7722-84-1	0.5 to 2
Benzyl Alcohol	100-51-6	1-5
Not disclosed detergent surfactants	mixture	0.1 Min
		Total 16,000 min ppm

*** PCS 7000 at use dilution of 200 ppm	CAS –No.	**Concentration %
Sodium carbonates	mixture	136
Sodium chloride	7647-14-5	0.69
Sodium hypochlorite	7681-52-9	200
Sodium hydroxide	1310-73-2	61
		Total 398 ppm

***PCS 7000 sporicidal undiluted	CAS –No.	**Concentration %
Sodium carbonates	mixture	5100
Sodium chloride	7647-14-5	260
Sodium hypochlorite	7681-52-9	7500
Sodium hydroxide	1310-73-2	2295
		Total 15,155 ppm

*National brand information taken from Safety Data Sheet
** Concentration % expressed as parts per million (PPM)
*** Data supplied by independent technical support group.

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Clorox Healthcare	137-139	866-789-4973	www.cloroxprofessional.com
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Ecolab USA Inc.	143	800-352-5326	www.ecolab.com/healthcare
GOJO Canada, Inc.	183	800-321-9647	www.GOJOCanada.ca
Hygie	146	866-588-2221	www.hygie.com
Hygiene Performance Solutions	186	905-361-8749	www.hygieneperformancesolutions.com
Marlatek Inc. / Glo Germ	193	800-909-3507	www.germwise.com
Metrex Corp.	184	800-841-1428	www.metrex.com
Olympus Canada	188	800-387-0437	www.olympuscanada.com
Nanosonics	182	844-876-7466	www.trophon.com/ca
PDI - Professional Disposables International, Inc.	OBC	800-263-7067	www.pdihc.com
Process Cleaning Solutions	201	877-745-7277	www.processcleaningsolutions.com
Retractable Technologies, Inc.	140	888-703-1010	www.vanishpoint.com
Sage Products LLC	190	800-323-2220	www.sageproducts.com
SciCan Ltd.	144	800-667-7733	www.scican.com
Sealed Air Diversey Care	142	800-558-2332	www.sealedair.com
Surgically Clean Air	192,199	877-440-7770	www.surgicallycleanair.com
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