The Perfect Storm: Emerging Trends and Pathogens in Healthcare

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LEARNING OBJECTIVES:

1. Explain how vulnerable populations, current healthcare delivery, and emerging pathogens have contributed to an increase in healthcare-associated infections.
2. Compare and contrast pathogens that occur in persons with HIV/AIDS, persons with cancer, and persons undergoing transplants.
3. Identify ways that community-based healthcare delivery may increase risk of HAIs.
4. Discuss the role of antibiotic overuse and international travel in the development of emerging pathogens.
5. Plan activities that are effective in preventing HAIs.

ABBREVIATIONS: AIDS – Acquired Immune Deficiency Syndrome, CA-MRSA – Community-Associated Methicillin Resistant *Staphylococcus aureus*, CDC – Centers for Disease Control and Prevention, CRE - carbapenem-resistant Enterobacteriaceae, CMV – Cytomegalovirus, FDA - Food and Drug Administration, HA-MRSA – Healthcare-Associated Methicillin Resistant *Staphylococcus aureus*, HAI – Healthcare-Associated Infections, HCW – Healthcare Worker, HIV – Human Immunodeficiency Virus, KPC-Kp – *Klebsiella pneumoniae* Carbapenemase Producing, MERS – Middle Eastern Respiratory Syndrome, MDRO – Multiple Drug Resistant Organisms, MRSA – Methicillin Resistant *Staphylococcus aureus*, NICU – Neonatal Intensive Care Unit, NHSN – National Health Safety Network, PPE – Personal Protective Equipment, RSV – Respiratory Syncitial Virus, VRE - Vancomycin-resistant *Enterococci*

INDEX TERMS: Antibiotic resistance, *C. difficile*, CDI, Healthcare-associated infections, HAI, Healthcare worker safety, Multiple drug resistant organisms, MDROs, MRSA, Patient safety

Clin Lab Sci 2016;29(1):32-38

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INTRODUCTION

In 1999, the article To Err is Human brought healthcare-associated infections (HAI) to the nation's attention. However, the risk posed by healthcare facilities to those who went there for healing had not developed overnight. Decades of changing demography, microbial evolution, and –ironically-- healthcare advancements had resulted in this perfect storm. Since the change in paradigm in healthcare that nosocomial or healthcare-associated infections are a natural consequence of treatment to a practice of surveillance

and prevention, hospital acquired infections are no longer considered consequences of inpatient treatment. Prevention of healthcare-associated infections includes protecting patients, healthcare workers, visitors, volunteers and health science students. This paper aims to describe the contributory roles of affected populations with their attendant, diverse healthcare sites and healthcare workers, and emerging pathogens.

Affected Populations

Prior to the identification of the Acquired Immune Deficiency (AIDS) virus, persons with chronic immune deficiencies were anomalies—"bubble children" who were occasionally brought to the public's attention through the media. With the advent of HIV/AIDS, healthcare facilities faced the daunting task of caring for many individuals with immune deficiency on a long-term basis. Just as many infectious diseases seemed to have been conquered through vaccine or antibiotics, healthcare was called upon to manage a new infectious disease with no treatment and also to protect those individuals from other potential infections including pathogens that did not cause disease in persons with healthy immune systems. HIV/AIDS required healthcare facilities not only to protect their patients but their workers from a high fatality disease that was particularly well-suited for transmission within the healthcare setting both from patient to healthcare worker and from healthcare worker to patient.

Currently 75 million people have become infected with HIV in every country world wide.[1] HIV continues to be a major problem in healthcare settings with an estimate of more than a quarter of a million people exposed in risky conditions or due to unsafe practices.[2] Many of these exposures occur in underdeveloped countries where the incidence of HIV infection rate is high in the general population and there is limited access to safety devices or personal protective equipment. Approximately 1000 incidents of exposure are likely to result in HIV infection annually worldwide.[2,3]

Cancer patients are another prime example of a population of patients where the treatment of the disease can also markedly impair the integrity and function of the immune system. Two major risk factors have been identified and monitored for the development of infectious disease in cancer patients; neutropenia and mucositis (mucosal inflammation). Patients with a granulocyte count of between 500 – 1000 cells/mm^3 are at high risk for infections. Mucositis provides a portal of entry for oral or intestinal pathogens and is often associated with severe and frequently polymicrobial infections.[4] The healthcare environment and management of cancer patients has changed thus no longer confining them to hospitals or hospice centers. Cancer patients are often treated and remain at home for long term care. Therefore, infections associated with cancer patients are no longer strictly confined to nosocomial infections. A study of 223 cancer patients with infectious episodes found only 42% were actually nosocomial.[4] Therefore, the classification of infections in immune compromised patients that are cared for outside of a healthcare facility are still considered healthcare-associated. The incidence of healthcare-associated infections in cancer patients is likely under-reported due to the high-risk nature of acquisition among the patient population.[5] Cancer treatment often requires surgical removal of the affected tissue. Surgery, independent of the underlying associated condition in itself, is a risk factor for the development of a healthcare-associated infection. In a 10 year study of healthcare-associated infections following major surgery for the removal of cancer 2,502,686 patients underwent procedures; 10.5% of the surgical patients developed one or more HAI.[5] In a multivariable analysis in the same study, it was determined that any occurrence of HAI resulted in an 8.7 fold increased odds of in-hospital mortality with up to a 17.3 fold likelihood of dying in a postoperative setting from an acquired blood stream infection.[5]

Cancer is a disease that modern medicine will continue to battle, but the incidence and effect on the patient's immune system are uncontrollable. However, new technologies and breakthroughs in medicine such as organ transplantation, which utilizes immunosuppressive therapy to minimize rejection of the organs, have also created a population of immunosuppressed patients at risk for healthcare-associated infections. The earliest clinical organ transplantation was performed in 1954 by using organ donors of identical twins for kidney failure.[4] More than 28,000 organ transplants are currently performed each year in the United States.[4] The primary clinical challenge with transplantation is rejection; however, the most prominent secondary problem is the occurrence of a variety of infections. These infections vary depending

on the type of transplant, the level of immunosuppressive therapy, and the type of pathogen. Transplant patients are at higher risk for infection during the first six months following the procedure. During this time when they are given large doses of immunosuppressive drugs, they are recovering from the surgical procedure and likely spending a significant amount of time in an intensive care unit of a major hospital. During this time the patient is at the highest risk for infection with what are referred to as the "classic" transplant opportunistic pathogens; cytomegalovirus (CMV), *Aspergillus*, *Toxoplasma*, *Nocardia* and *Pneumocystis*.[4,6]

In addition to traditional transplant patients, hematopoietic stem cell transplant patients also suffer complications of healthcare-associated infections. Similar to the traditional transplant patient, these individuals' risk factors are also dependent on the level and length of immunosuppressive therapy, cutaneous and mucosal inflammation, neutropenia, lymphopenia and hypogammaglobulinemia.[4] Due to the severe immunosuppressive condition in hematopoietic stem cell transplant patients, clinical signs of infection are also often masked by the clinical profile of the cancer resulting in the delay of appropriate therapy for the infecting agent. The severity of healthcare-associated infections in this population should not be taken lightly. In a recent study of 74,381 patients who underwent surgical resection in 2005-2012 for esophageal, gastric, hepato-biliary, colorectal or lung cancer 9,479 or 12.7% developed one or more healthcare-associated conditions.[7]

Although traditional pathogens associated with blood stream infections occur in transplant patients, multi-drug resistant organisms have become an increasing problem. In one study of patients with hematological malignancies, 68% of the device related bacteremias identified were caused by gram negative bacteria.[4] Among the gram negatives, *Klebsiella pneumoniae* has become one of the major agents of infections in solid organ and hematopoietic stem cell transplant patients, with a 30 day mortality rate reaching 48%.[8] Respiratory Syncytial Virus (RSV) has also been associated with transmission and development of lower respiratory infections in oncology and hematopoietic stem cell transplant patients. The virus has been implicated in outbreaks in inpatient hematology-oncology and transplant wards.[9]

RSV is also one of many pathogens of concern in neonatal intensive care units (NICU). The rate of preterm births has risen by more than one-third in the last three decades.[10] While medical interventions have improved the likelihood of survival for these infants, long hospital stays have increased their potential for HAI. In addition to RSV, other pathogens of special concern in NICU include methicillin resistant *Staphylococcus aureus* (MRSA), *Clostridium difficile*, and invasive fungi such as *Candida, Aspergillus, Pichia*, and *Malassezia*.[11]

At the other end of the life spectrum, those over 65, is also increasing in numbers dramatically with approximately 10% of the world population currently over 65 years old and an estimated 22% or two billion people over 65 by the year 2050.[4] Often these individuals have reduced mobility and other underlying chronic medical conditions including poor circulation and a compromised immune system. In the U.S., 13.6 million hospital discharges from short-term care facilities occurred in this age group in 2010.[12] Urinary tract infections, respiratory infections, pressure sores or skin infections, endocarditis, infectious diarrhea, bacteremia and central nervous system infections plague this population. Blood stream infections are an increasing problem in the elderly population. In a study involving eight hospitals, among elderly patients who experienced one or more positive blood cultures within 48 hours of admission, 830 cases were classified as healthcare-associated. Among the infections, 81% were classified as central line associated. The pathogens included methicillin resistant *Staphylococcus aureus* (23%), methicillin susceptible *S. aureus* (10.6%), *Enterococcus* spp. (6.1%) and coagulase negative staphylococci (5.4%). Gram negative pathogens accounted for 29.8% of the infections.[13]

Healthcare Delivery

In addition to the increase in the elderly population, family mobility has left more elderly people far from children and grandchildren, and traditional care givers are more often in the work force. Long-term care services (adult day care services, home healthcare, hospices, nursing homes, and assisted living) have become integral to society. In 2012, regulated long-term care services providers served about 8 million

people in the United States.[14] Long term care services pose unique infection control and prevention challenges. In contrast to hospitals where patients are at least in partial isolation, social integration is essential for participants in long term care services, yet the ability of the participants to maintain personal hygiene has declined. Long term care services staff typically do not have the same level of training in infection prevention protocols as those in hospitals. Frequent transitions between acute care and long term care facilities results in a revolving door of exposure to new pathogens and transmission to new contacts.

Since the 1980's, more patients are being treated in ambulatory care and community-based settings. Patient care is being administered in hospital-based outpatient clinics, non-hospital based clinics, physician offices, ambulatory surgical centers and other specialized care centers.[15] Vulnerable patients, such as those previously discussed in this document, rely heavily on frequent use of ambulatory care to maintain their health. These types of facilities typically lack the resources to monitor and prevent healthcare-associated infections. Outbreaks associated with methicillin resistant *Staphylococcus aureus, Klebsiella pneumoniae, Enterobacter aerogenes,* additional Gram-negative organisms, Hepatitis C and other viruses have recently been attributed to invasive treatments completed in outpatient settings.[15] Many of the adverse effects reported were a result of breakdowns associated with standard infection prevention procedures.[15]

Although HIV infections, cancer, transplants, high-risk neonates and the elderly are particularly susceptible to healthcare-associated incidences of infection, every individual under the right circumstances either as a patient, healthcare worker, visitor or student is at risk for infection. As healthcare incorporates new methods to monitor and protect individuals from infection and provide alternate community-based settings and outpatient clinics to maintain quality healthcare, emerging pathogens continue to pose new challenges.

Emerging Pathogens

Additional healthcare-associated pathogens are emerging from the manipulation of the natural environment at both the molecular level and the macro environment. The introduction of antibiotics in the 20th century represents one of the greatest medical interventions for the prevention of infection. It now has become one of the greatest threats to populations worldwide, with approximately 60% of all hospitalized patients receiving antimicrobial therapy,[4] and antibiotic resistance has grown apace.

Among the most prevalent of the antibiotic-resistant bacteria is methicillin-resistant *Staphylococcus aureus* (MRSA). This pathogen emerged in a British hospital in 1961, just two years after the introduction of methicillin.[4] Strains of MRSA that express intermediate to high level of resistance to vancomycin have been identified since 1996.[4] In the 2000s, MRSA emerged in community settings such as correctional facilities, college campuses, and athletic departments resulting in the distinction between healthcare-associated MRSA (HA-MRSA) and community-associated MRSA (CA-MRSA).[16-18] Although genetically distinguishable, the nomenclature has lost its meaning as CA-MRSA soon became entrenched in the healthcare setting as well. Of the *S. aureus* infections associated with central lines, catheters, ventilators and surgical site infections reported through the CDC's National Healthcare Safety Network (NHSN) approximately half are oxacillin (methicillin) resistant. Vancomycin resistance in enterococcus is also endemic with over 80% of *E. faecium* resistant in central line-, catheter-, ventilator-associated infections reported to NHSN.[19] MRSA and VRE are considered "serious threats" on the CDC's hazard levels.[20]

A multi-drug resistant gram negative organism, *Acinetobacter baumanni*, isolated from blood stream infections of immunocompromised, critically ill patients was thought to be unusual.[4] The organism appears to have an unusual ability to acquire and/or develop antibiotic resistance to virtually all antibiotics in use, including the carbapenems.[1] The pathogen is more often associated with colonization instead of infection, however it is often difficult to distinguish in a clinical setting. Ventilator-associated pneumonia and blood stream infections have been documented and associated with a high degree of mortality.[1] Recently recognizing it as a "serious threat" and in an effort to prevent these organisms from becoming endemic as had MRSA, the CDC urged states to make multi-drug resistant organisms (MDROs) reportable.[20] For example, the State of Texas made multi-drug resistant *Acinetobacter* reportable in 2014. Although the reporting was

voluntary for the first four months of the year, 1401 cases of MDROs were reported during that first year of reporting with transmission often occurring among networks of healthcare facilities such as acute, long term acute, and long term.[21]

On the CDC's list of "urgent threats" along with *Clostridium difficile* and drug resistant *Neisseria gonorrhoeae* are the carbapenemase-resistant Enterobacteriaceae (CRE).[20] First identified in the United States in 1990, *Klebsiella pneumoniae* carbapenemase producing (KPC-Kp) has caused mortality rates in patients ranging from 28 – 68% with a four times the increased risk of death compared with other healthcare-associated infections.[1,8] This is often due to delayed identification of the resistant strain as well as the limited available therapy for the treatment of such infections. *N. gonorrhoeae* was traditionally treated with sulfonamides, with resistance developing as early as the 1940's. Penicillin and tetracycline resistance spread in the 1980's, followed by fluoroquinolone in the 1990's.[1] Cephalosporins remain the only effective antimicrobial agent for gonococcal infections with emergent resistant strains now threatening the last known treatment.[1]

The problem of antimicrobial resistance extends far beyond the realm of bacteria and includes the need for medications to treat viral agents, fungi and parasites. Invasive fungal infections in particular are on the rise due to the increase in the numbers of immune compromised populations. The most serious fungal infections typically occur in patients affected by HIV/AIDS, cancer, organ transplantation and those on steroid therapy.[1] A 2004 retrospective study of data from the Healthcare Cost and Utilization Project-Nationwide Inpatient Sample indicated that there are approximately 13,412 patients diagnosed annually in the U.S. with invasive fungal infections.[6] The primary pathogens included *Candida* spp., *Aspergillus* spp. and other mycoses resulting in a 14.8% increase in mortality rates.[6]

While the population of immunocompromised patients continues to grow and antibiotic resistance is fostered domestically, the threat of infection with exotic organisms is literally just a plane ride away. In 2014, Middle Eastern Respiratory Syndrome (MERS) and Ebola were diagnosed in the United States for the first time. Both MERS and Ebola were diagnosed in persons who had recently traveled from endemic countries. In May 2014, two unrelated MERS cases were diagnosed in Indiana and Florida, and no transmission occurred within the community nor within the facilities where they received care.[22] The first case of Ebola diagnosed in the United States occurred in September 2014 in Texas. The only in-country transmission to date in the U.S. was to healthcare workers who cared for the patient during his most viremic state, not to household members who were with him in the early stages of the disease. Because of a highly functioning healthcare system in the U.S., persons with exotic or high consequence infectious pathogens acquired abroad through community contacts will most likely be quickly hospitalized, ironically making healthcare facilities the most likely site of transmission in this country.[23-25]

Responses

Although we are in the midst of a perfect storm, healthcare providers, public health officials, researchers and regulatory agencies are mobilizing responses. Standard precautions, HAI reporting, and judicious use of antibiotics all provide a means to safeguard the advances mankind has made in surviving infectious diseases.

With the enhanced awareness of blood borne pathogens resulting from the characterization of HIV and Hepatitis C the concept of "universal precautions," later "standard precautions" was born, and with it, the challenge to maintain vigilance in observing those precautions. Standard precautions were instituted to prevent the spread of infections within the healthcare environment and initially focused primarily on isolation and personal protective equipment. As multiple other pathogens, their modes of transmission, and the risk that all healthcare workers – independent of their role – face the likelihood of coming into contact with these pathogens became more widely recognized, infection prevention activities evolved encompassing a much broader outlook in scope of control and prevention activities. Competent infection prevention now includes education of healthcare workers, patients, and lay care-givers regarding risks and interventions, outbreak investigation, judicious use of antibiotics, hand hygiene, and environmental practices.[26]

In order to effectively monitor the results of such

efforts, a more detailed protocol was created that included a constant surveillance of base line rates of healthcare-associated infections to identify when an increase or decrease occurs. To compare these data across facilities throughout the nation, the CDC developed a data tracking system known as the National Healthcare Safety Network. This system allows online data entry at the unit level for any enrolled facility. The data are risk adjusted, compared to national baselines, and analyzed for statistical significance. Data are collected at the facility unit level for both surgery-site specific infections and treatment associated device-specific infections. Healthcare providers are using the data to improve their procedures and reduce risk to their clients.

Infection prevention activities and the data they generate have fostered another strategy in the control of HAI—HAI reporting. By reporting HAI, the public and insurance companies have data to use in making choices about healthcare providers. Public reporting of HAI provides additional motivation to facilities to review the data and use it to identify and correct problem areas and reduce risk. In the next article of this series, The Legal Landscape: HAI Public Reporting in the United States, we will discuss this topic in detail.

Underscoring the imperative to maintain a functional arsenal of antibiotics, on September 18, 2014, President Obama issued an Executive Order -- Combating Antibiotic-Resistant Bacteria.[27] The President called for multidisciplinary efforts by both providers and the public to use antibiotics more judiciously. In our estimation, it will require a multi-modal effort in this war against antibiotic resistance in both the healthcare environment as well as the general community.[28]

Federal efforts are also being focused toward preparing hospitals for adequate infection prevention in the face of newly emerging or imported pathogens. During the height of the Ebola epidemic in Africa and consequent to the Ebola cases treated in the U.S. the CDC dispatched Rapid Ebola Preparedness teams to assist hospitals to have adequate infection prevention tools in place to assess and/or treat persons with Ebola exposures or disease. Guidelines have been released by CDC for all healthcare personnel which refers to all people, working in healthcare settings who have the potential for exposure to patients and/or to infectious materials, including body substances, contaminated medical supplies and equipment, contaminated environmental surfaces, or aerosols generated during certain medical procedures.[29]

The "perfect storm" of HAI is *here and present, now* – it's not a future event. Healthcare-associated infections are an omnipresent factor in every healthcare system. They are varied, diverse, complex, and often misunderstood. Many are caused by MDROs that can be difficult to diagnose and treat. It is our responsibility and in our greater interest to reduce the acquisition and risk to HAI for patients, clinicians, healthcare professionals and the general public. Through collaboration and cooperation and by following common sense guidelines, we can all reduce the risk of HAI. A persistent multi-modal and multi-interdisciplinary approach without shortcuts is the primary vehicle for all of us to reduce the threat of a critical, ongoing global threat from HAI.[28]

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