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Commentary

The damage response framework and infection prevention: From concept to bedside

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Abstract

Hospital-acquired infections remain a common cause of morbidity and mortality despite advances in infection prevention through use of bundles, environmental cleaning, antimicrobial stewardship, and other best practices. Current prevention strategies and further hospital-acquired infection reduction are limited by lack of recognition of the role that host–microbe interactions play in susceptibility and by the inability to analyze multiple risk factors in real time to accurately predict the likelihood of a hospital-acquired infection before it occurs and to inform medical decision making. Herein, we examine the value of incorporating the damage-response framework and host attributes that determine susceptibility to infectious diseases known by the acronym MISTEACHING (ie, microbiome, immunity, sex, temperature, environment, age, chance, history, inoculum, nutrition, genetics) into infection prevention strategies using machine learning to drive decision support and patient-specific interventions.

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The damage–response framework (DRF) is a theory of microbial pathogenesis that incorporates the role of the host as well as the microbe into the outcome of host–microbe interaction.[1] Based on the premise that the relevant outcome of host–microbe interaction is host damage, which can stem from microbial or host factors, or both,[2] the DRF depicts host–microbe interaction using a parabola in which damage on the y-axis is a function of the host response, and on the x-axis, ranges from weak (or insufficient) on the left to strong (or excessive) on the right. The y-axis descends below the 'zero' damage point to depict beneficial host–microbe interactions (eg, those stemming from the microbiome).[3] Importantly, the DRF disconnects microbial pathogenesis from microbe-centric or host-centric views, incorporating both host and microbial factors.

The DRF dispenses with terms such as 'pathogen,' 'nonpathogen,' and 'opportunist' by describing the state of a microbe in a host.[4] These states—commensalism, colonization, disease, and latency—only differ by the amount of damage that occurs in the host over time.[5] The DRF has advanced understanding of virulence[4,6]; the role of the microbiota in microbial pathogenesis,[7] fungal pathogenesis,[8] infection, and immunity; and host susceptibility to infectious diseases.[3] In the latter, the DRF was used to put forth 11 attributes of host susceptibility summarized by the acronym MISTEACHING: microbiome, immunity, sex, temperature, environment, age, chance, history, inoculum, nutrition, genetics.[3] This acronym was chosen to remind physicians and scientists interested in microbial pathogenesis to consider multiple variables and to avoid errors that come from focusing on singular causes. Together, the DRF and MISTEACHING attributes provide a construct to incorporate complex, multidimensional host and microbial variables into a schema to assess an individual's risk of developing an infection.

Currently, host variables are not part of most risk assessments for healthcare-associated infections (HAIs). However, the complex interactions of host, microbe, their environments, pressures upon them (eg, antimicrobial agents) and procedures that breach mucosal and/or cutaneous surfaces have significant potential to promote host damage. They contribute to the risk of infection and are highly relevant to the field of infection prevention and control (IPC). Current views of IPC are largely microbe-centric, focusing on the presence of microbes in healthcare settings. Although this approach is effective, incorporating host susceptibility into the assessment of HAI risk may make it more effective, with the potential to reduce HAIs by identifying those who are most vulnerable.

The current state of infection prevention and machine learning

Each year, an estimated 722,000 HAIs occur in acute-care hospitals including central-line associated bloodstream infections (CLABSIs), catheter-associated urinary tract infections (CAUTIs), *Clostridioides difficile* infections (CDIs), ventilator-associated pneumonias (VAPs), and surgical site infections (SSIs). More than

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half of these occur outside an intensive care unit (ICU).[9] IPC science continues to advance, yet the burden of HAIs remains high, resulting in significant cost, morbidity, and mortality. Experts estimate that 3.2% of all hospitalized patients have an HAI,[10] and many are deemed preventable. With successes in IPC science and improvements in patient safety, the proportion of preventable HAIs diminishes.[11] Nonetheless, hospitals experience external pressure from regulatory agencies to reduce HAIs through further optimization of current strategies applied broadly to patient populations. However, these strategies do not incorporate consideration of individual patient risk factors. This limits what can be achieved with further emphasis on existing bundles and best practices.

Consideration of the complexity and dynamic nature of host, microbial, and environmental factors that predispose patients to HAIs through advances in machine learning, a subset of artificial intelligence, could revolutionize IPC science and move it from reactive to proactive, perhaps with the ability to predict who is most at risk of an HAI. Machine learning focuses on the use of computer-driven algorithms and statistical models to utilize complex data sets.[12] Thousands of structured (ie, demographics, vitals) and unstructured variables (ie, information in clinical notes) can be instantly and repeatedly analyzed to make predictions on routine healthcare data. Machine learning harnesses the potential to use novel algorithms to bring big data into focus to support the human decision-making process by creating population and patient-specific infection prevention risk profiles that are continuously updated. Clinicians are already using machine-learning systems for rapid and accurate interpretations of diagnostic imaging and predicting sepsis in ICUs. Recently, the first applications of digital healthcare epidemiology have been reported.[12] Oh et al[13] built hospital-specific models that successfully estimated daily patient risk for CDI. Machine-learning systems have diagnosed SSIs following open abdominal surgery[14] or following any intervention on neonates.[15] Although promising, there are significant limitations in creating and executing clinically useful machine-learning algorithms in the healthcare setting. Despite high-quality electronic medical records (EMRs) and an advanced machine-learning system, the risk of recurrent CDI was not successfully predicted across Kaiser Permanente hospitals.[16] Even with state-of-the-art algorithms, machine learning may not readily identify predictors, or they may not be available. Data extraction may be difficult if data are low quantity or low quality or due to patients' poor access to healthcare systems and fragmented care. Despite these limitations and the unknown potentials of ML in clinical medicine, the field of digital healthcare epidemiology is growing,[12,13,16,17] and the time to continue to enhance IPC strategies is now.

Using the DRF to devise next-generation infection prevention strategies

Incorporating MISTEACHING attributes into risk assessments can make IPC practices more effective by promoting proactive prevention strategies and reducing preventable HAIs. Embedding machine learning into the EMR will make it possible to survey host attributes and environmental variables to generate population or individual risk profiles for HAIs. For example, a machine-learning algorithm embedded in the EMR indicates the baseline risk of a CLABSI in a patient with a central venous catheter (CVC). As host attributes change, the algorithm adjusts risk accordingly, increasing with each day of CVC use and alerting the provider to discontinue the CVC to minimize the risk of infection. Real-time feedback would allow providers to visualize how interventions affect patient risk of HAI. Moreover, rapidly updated risk assessment data could serve as a powerful tool to identify regional and environmental risks based on location (ie, ICU). Although the current science may be too nascent to assess all the host–microbe interactions that drive HAI, we discuss MISTEACHING attributes in the following sections in the context of IPC and variables that can be incorporated into HAI-specific machine-learning algorithms based on our current knowledge.

Microbiome

The state of a patient's microbiome and utilization of antibiotics should be part of daily risk assessments for the development of HAIs. The current state of microbiome science is constantly evolving, and significant work is needed to continue to define the microbiome and determine its clinical importance in the development of HAIs. When identified, microbiome "risk factors" for HAIs could be incorporated into the EMR. Until that time, a machine-learning algorithm can focus on what is known about the microbiome in the context of IPC science.

Nearly 70%–90% of all SSIs arise from patients' own microbiomes.[18] Multiple IPC strategies target alterations of patients' flora/microbiome to reduce HAI risk.[19] Chlorhexidine gluconate (CHG) is frequently used to reduce bioburden on patients' skin and can reduce risk of HAI in hospitalized patients.[20,21] A patient with an invasive medical device who is not undergoing daily CHG bathing may generate a higher risk profile than a patient with no medical device and no CHG bathing. Such a risk profile could facilitate bathing among patients, leading to further reduction of CLABSIs. Intranasal mupirocin reduces the bioburden of *S. aureus* in surgical and dialysis patients,[22] whereas preoperative screening and selective decolonization in individuals undergoing elective surgical procedures reduces SSIs.[19] Utilization of this preventative strategy will aid in generation of risk profiles for surgical patients and could alert a surgeon to delay an elective procedure if the IPC strategy needs to be completed.

Multiple classes of antibiotics or host inflammation can lead to expansion of microorganisms, such as *C. difficile*[23,24] or antibiotic-resistant bacteria.[25] Vaccine development for resistant bacteria or augmentation of the microbiota through delivery of healthy microorganisms or key nutrients[26] may be future strategies to strengthen or restore beneficial functions of the microbiota. Strict avoidance of antibiotics may be warranted in some patients or if antibiotics are deemed necessary, administration of novel adjuvants, such as oral ribaxamase to protect the gut microbiome,[27] should be considered. For patients on antibiotics, as the likelihood of *C. difficile* increases, more aggressive EMR prompts to de-escalate or discontinue antibiotic therapy could be deployed.

Immunity

Intact immunity can negate microbial virulence, whereas impaired immunity is a central component of susceptibility to infectious diseases. Measures of immune response have the potential to heighten the application of enhanced IPC practices (eg, avoidance of CVC placement or antibiotics or removal of an intravascular device). Historically, neutrophil counts were used to assess the risk of infection in individuals with cancer receiving chemotherapy. This measure revolutionized the care of patients with chemotherapy-induced neutropenia and saved countless lives, making further progress in treatment of malignancy possible. Similarly, use of CD4 counts to assess the need for preventative therapy for human

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immunodeficiency virus (HIV)–associated infectious diseases prolonged the lives of HIV-infected persons even before the advent of therapy.

Current advances in immunology make it possible to measure numerous host variables that can provide additional data on immune function and infection risk in vulnerable populations.[28] This approach led to identification of different phenotypes in patients with sepsis.[29] Even though incorporating patient specific phenotypes in the EMR does not seem feasible at this point in time, basic measurements of immune function (ie, absolute neutrophil or lymphocyte count) are laboratory values that could easily be incorporated into machine-learning algorithms to assess risk of HAI. The use of medications that compromise a patient's immune system (ie, steroids or chemotherapy) could also be easily extracted from the EMR and utilized to predict the risk of HAI. Other advanced measurements of immune function, which are not routine in hospitalized patients, could provide additional data to incorporate in patients' risk profiles in the future. Several promising and accessible potential markers for CDI have been identified, but the clinical utility of these specific innate and adaptive immune markers has not yet been validated.[30] Although promising, more research is needed to identify objective measures of the immunologic state that be translated to IPC science in the context of HAI.

Temperature

Temperature is a frequently recorded, structured variable that could be extracted from the EMR. Analysis of abnormal temperature patterns is predictive of hospital-acquired sepsis,[31] which in some clinical scenarios may be predictive of HAI. Abnormal analysis of temperature patterns may prompt a work-up for a HAI or even removal of an invasive device in a patient with a high-risk profile. Maintaining normothermia during the perioperative period is a risk reduction strategy for preventing SSIs in surgical patients who undergo anesthesia for at least 60 minutes.[32] Hypothermia may impair neutrophil function, and even mild hypothermia is associated with increased SSI rates.[33] Preoperative and intraoperative warming can reduce SSI rates and intraoperative blood loss.[34] Extracting temperatures during a critical surgical period can modulate a patient's SSI risk profile. Identification of type of surgery or providers most commonly implicated in hypothermia can stimulate additional investigations for risks associated with occurrences of SSI.

Environment

Reducing unnecessary use or limiting duration of invasive devices targets the internal host environment. Cleanliness of the external environment is a core prevention strategy to reduce risk of acquisition of healthcare-associated organisms. The use of UV light robots in conjunction with terminal disinfection may decrease individual colonization and infection.[11] Monitoring daily room cleaning and terminal disinfection and linkage of these data to a patient's EMR could be part of a patient's HAI risk profile. Patients who reside in rooms not cleaned with the appropriate products or applications may have a higher HAI risk than patients who reside in rooms cleaned properly. However, the importance of understanding environmental contributions to HAI risk is underscored by recent data that 'one size does not fit all' when examining transmission of resistant organisms in healthcare settings.[35]

Other environmental variables that could affect HAI risk include room temperature, air humidity, particulate and fungal spore counts, and light cycles with their potential to disrupt circadian rhythm. Although these are not currently used in IPC prevention practices, future research that associates these variables with HAI probability could lead to additional measures to reduce risk in vulnerable patients.

Sex and age

Sex and age are structured variables that should be easily extracted from the EMR as potential predictors in the development of HAI. When clinically feasible, providers may opt to avoid central-line placement in a neonate with an elevated risk of CLABSI. Notification at the time a urinary catheter or CVC is ordered for a patient with HAI risk due to age, such as elderly women at high risk of UTI, could prevent a risky intervention with HAI potential.

Chance

The element of chance includes variables that affect HAI susceptibility. For example, differences in the anatomical location of catheter placement, the health status of visitors and hospital providers, the location of the individual in a ward, environmental changes, etc, are variables that can all affect host susceptibility. Given the imperfect science of IPC, the often chaotic nature of healthcare systems, and pure chance, some HAIs will occur despite best efforts. Admission to the hospital for a routine procedure can result in the acquisition of a resistant organism. Also, a random event, such as a fall in the hospital, could place a patient at risk of exposure to devices that enhance HAI risk. Although getting to zero HAIs may be an unrealistic expectation, optimization of IPC should remain a high priority. Understanding and control of variables contributing to HAIs can provide a paradigm to improve outcomes with other microbial threats.

History

Patient histories are pertinent in estimating the risk of developing an HAI, and multiple patient history variables can be easily extracted from the EMR to predict HAI risks. Variables such as diagnoses (including previous HAI diagnoses), medications, allergies, procedure codes, surgeries, encounter history, treatments, laboratory values and microbiologic data are all important predictors for HAIs. Unfortunately, if patients have received fragmented care at healthcare systems in which the EMRs do not communicate, incomplete health data make it extremely difficult for a machine-learning system to accurately predict risk. One of the current challenges of incorporating machine learning into clinical medicine is ensuring interoperability between different technology platforms. The collection and mobilization of all health data, regardless of the healthcare system, is essential and may require standardization of healthcare data to a common format.

Inoculum

Potential exposure to pathogens is difficult to predict in healthcare settings, although some ward and hospital locations may put patients at a higher risk of acquisition of a multidrug-resistant (MDR) organism (ie, ICU setting); therefore, location may predict risk of HAI. A patient's previous microbiologic data may shed light on the different pathogens that exist in an individual's microbiome and may augment a HAI risk prediction profile.

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Nutrition

Malnutrition is a leading cause of immunodeficiency worldwide.[36] Alternatively, obesity can play a role in disease, including HAI. Obese patients are more likely to develop SSIs[37] and are also at higher risk of infectious complications after total joint arthroplasty.[38] Weight and body mass index are structured variables that can be easily extracted from the EMR and may predict risk of HAI. A high patient risk profile for an obese patient may prompt a surgeon to postpone an elective total joint arthroplasty until the patient has achieved significant weight reduction. A patient with a low body mass index may put a patient at risk of infection and CVC placement may be avoided.

Genetics

Although the exact drivers are unknown, host and microbial genetics likely play a role in the development of HAIs. Further research is needed to identify genetic factors that may protect against or predispose to microbial colonization and disease. When host and microbe genetics that increase the risk of host damage due to HAI are elucidated, this information can be integrated into predictive models.

In conclusion, there is already sufficient knowledge to incorporate certain MISTEACHING attributes into patient risk profiles that could reduce HAI risk in those who are most vulnerable. Initiating such an effort would encourage research to better understand the contribution of other variables, such as the roles that the microbiota, immunological, and genetic factors play in resistance and susceptibility to HAIs. The technologic infrastructure to support machine-learning systems based on host susceptibility does not currently exist, but the time is ripe to begin such efforts, which may play an important role in the future in ICP.

Whether machine learning will improve healthcare delivery or how to adequately translate it into clinical practice is not yet known. More research is needed to identify how to apply machine learning to healthcare epidemiology as well as understand the unintended consequences, but the ability to write code to incorporate variables such as age, disease state, and laboratory data is already here. The impressive work by Oh et al[13] has demonstrated the utility of a generalizable machine-learning system using data from the EMR in building a CDI risk stratification model tailored to an individual facility. This approach was retrospective and not equivalent to integration into an EMR system. Thus, we call for the creation of machine-learning algorithms by domain experts and machine-learning specialists to survey risk factors in real-time and to develop population and patient-specific HAI profiles.

We do not foresee that machine learning will cause us to step away from the art of medicine or will become a pathway to deskilling physicians; rather, it is a way to bolster the human decision-making process and potentially a step to further reduction of HAIs through efficient and effective deployment of enhanced IPC strategies. Magical, wild, and with huge potential, machine learning offers the possibility of improving patient safety and maximizing the return on preventable HAIs in a highly variable healthcare environment with constantly evolving risks.

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