Hospital-acquired infections

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Abstract

Hospital-acquired infections (HAI) are defined as infections developing after 48 hours of hospitalization or stay at a healthcare facility that was not present or incubating at the time of admission. HAI have been associated with increasing medical costs, length of stay, complication rates, and worsening overall morbidity and mortality. Many countries and hospitals have adopted policies and regulations in recent years attempting to decrease the impact of these healthcare-associated infections. They encompass a diverse list including skin and surgical site infections, urinary tract infections, pneumonia, bacteraemia, and hospital-associated diarrhoea. For the purpose of this review we will address the predominant resistant healthcare associated pathogens including methicillin-resistant *Staphylococcus aureus*, *Clostridium difficile*, and vancomycin-resistant enterococci.

Keywords *Clostridium difficile*; healthcare-associated infection; hospital-acquired infection; methicillin-resistant *Staphylococcus aureus*(MRSA); vancomycin-resistant enterococci (VRE)

Hospital-acquired infections (HAI) are defined by the World Health Organization as infections developing after 48 hours of hospitalization or stay at a healthcare facility that were not present or incubating at the time of admission. This can include infections that occur following discharge (usually within 4 weeks) from one of these facilities.[1] In the United States there were at least 1.7 million hospital-acquired infections yearly with 16% of them reported as resistant to the antibiotics commonly used to treat them.[2] The annual cost of HAIs is estimated to be $9.8 billion.[3] HAI have become a progressively more important issue over the past decade as it has become clear that they often increase medical costs, length of stay, complication rates, and overall morbidity and mortality. Many countries and hospitals have adopted policies and regulations in recent years attempting to decrease healthcare-associated infections.

The types of HAI encompass a broad list including skin and surgical site infections, urinary tract infections, pneumonia, bacteraemia, and hospital-associated diarrhoea. While the types of infections are diverse it has become increasingly common for these infections to be caused by one of the resistant healthcare-associated pathogens. For the purpose of this review we will address methicillin-resistant *Staphylococcus aureus* (MRSA), *Clostridium difficile*, and vancomycin-resistant enterococci (VRE), which are the predominant pathogens that have taken a central role as the focus on healthcare-associated infections has increased in recent years.

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Methicillin-resistant *S. aureus* (MRSA)

MRSA was identified in the late 1960s shortly after the development of methicillin; however, rates peaking in 2004–2005 have drawn public attention to this pathogen in the past decade. With incidence and mortality due to MRSA infections rising in the early 2000s, both the US and UK have made concerted efforts to document MRSA infections and have had success at decreasing bacteraemia rates in recent years. The Department of Health documented 862 reports of MRSA bacteraemia in England in the year between April 2013 and March 2014 showing an almost 81% reduction since 2007.[4]

Definition and virulence factors

S. aureus is a Gram-positive facultative anaerobe that can be both part of the normal human bacterial flora as well as act as a virulent pathogen. It produces numerous surface proteins that allow it to adhere to host tissue and evade detection by the host's defences including: biofilms, an antiphagocytic capsule, and protein A. In addition, *S. aureus* will secrete chemotaxis inhibitory protein, leukocidins, and various other proteins helping it to cause infection.[5] *S. aureus* secretes a penicillinase that hydrolyses penicillin preventing its binding and inhibition of the penicillin-binding protein (PBP) in the bacterial cell wall. Methicillin, developed in the late 1950s, was initially effective against *S. aureus* because it contains a bulky side chain making it resistant to the bacteria's pencillinase; however, methicillin resistance soon developed in the early 1960s. MRSA contains a variant penicillin-binding protein (PBP2a) that binds methicillin with lower affinity and easily releases it preventing methicillin inhibition of cell wall synthesis. High-level methicillin resistance is coded for on the mecA gene, but it requires additional accessory genes (fem genes) to produce the peptidoglycan precursor molecules from which PBP2a forms the bacterial cell wall.[5] Not all MRSA has high-level resistance and there is considerable predominance of low-level resistance as well. Other mechanisms that may account for this low-level methicillin resistance include overexpression of penicillinase, other types of PBPs, and acquired mutations in the PBPs.

Transmission and colonization

MRSA can be transmitted by direct contact with infected or colonized individuals and their environment. It can colonize either the skin or nares of otherwise healthy individuals for weeks to years leaving them asymptomatic without progression to active infection. Many studies have examined the role of screening and isolation of these patients upon admission to the hospital; however, most of these studies implement multiple interventions, making it difficult to identify the key factors in disrupting the chain of transmission. Despite the limitations, evidence suggests that screening for MRSA and subsequent isolation of patients within special wards, nursing cohorts, single rooms, and barrier precautions should be implemented in areas with increased prevalence and incidence of MRSA until further evidence disputes these recommendations.[6] A study from northern Scotland in 2012 showed a 41% decrease in *S. aureus*

bacteraemia after implementation of universal MRSA screening with isolation and decolonization of individual carriers.[7]

Early evidence did not support attempts at MRSA decolonization using topical or systemic antibiotics and suggested that it may only be appropriate in small subsets of patients and may increase the risk of resistance.[8] This was disputed in a 2011 Cochrane review recommending topical decolonization in surgical, haemodialysis, and other patients at high risk of infection after their review of nine randomized controlled trials showed decreased risk of *S. aureus* infection (RR = 0.55, 95% CI 0.34 −0.89) in MRSA carriers given intranasal mupirocin for at least 5 days. Although there was an increase in infection from other microorganisms (RR = 1.38, 95% CI 1.118−1.72), five of the studies showed no evidence of antimicrobial resistance during their study periods.[9]

Infections

Healthcare-acquired MRSA causes a diverse range infections depending upon its virulence factors, type of toxin production, and the site of inoculation. This includes skin infections (cellulitis, abscesses, surgical site infections, necrotizing fascitis), gastroenteritis, pneumonia, urinary tract infections, endocarditis, osteomyelitis, and bacteraemia. Common risk factors for infection include hospitalization or stay in a healthcare facility, previous colonization, immunosuppression, diabetes, dialysis, and medical interventions such as surgery, mechanical ventilation, or intravascular catheters.[10]

Diagnosis

MRSA can be cultured from blood, sputum, urine, or other suspected sites of infection. Swab and culture of the nares can be used for screening to determine colonization of individuals.

Treatment

Initially, treatment of any hospital acquired MRSA infection involves supportive care, drainage of abscesses or wounds, removal of the source of infection (catheters or lines) and control of diabetes and other systemic illnesses. If endocarditis is suspected, the patient will require an echocardiogram. Antibiotic choice is also critically important and depends upon the site and severity of infection as well as the hospital's current antibiotic resistance data. Table 1, based on the Clinical Practice Guidelines by the Infectious Disease Society of America, details the common antibiotic options used for various types of MRSA infections.[11]

C. difficile

The past decade has shown a dramatic rise in both the incidence and severity of *C. difficile* infections in the USA, Europe, and Canada. The incidence of *C. difficile* infection rose dramatically in England from roughly 1170 cases per year in 1990 to over 46,500 cases in 2004 based on voluntary reporting.[12] Much of this increase is believed to be linked with numerous outbreaks due to a hypervirulent strain (ribotype 027, NAP-1) that produces increased levels of both clostridial exotoxins. Starting in 2004 it became mandatory in England to report cases of *C. difficile* diarrhoea for patients over 65 years of age and remained voluntary for the rest of the population. This changed in 2007 when case reporting became mandatory for all cases in patients over 2 years old. With active efforts to improve reporting and decrease infection rates England saw a 76% decrease in *C. difficile* infections from 2007 to 2013.[4]

Definition and virulence factors

C. difficile is a Gram-positive anaerobic bacillus considered to be the primary cause of healthcare-associated diarrhoea commonly following the administration of antibiotics. It exists in an active vegetative form releasing toxins responsible for diarrhoea, cell damage, and inflammation as well as in a dormant spore form that is highly resistant to harsh conditions such as heat, alcohol, and stomach acid. *C. difficile* produces two primary exotoxins responsible for its virulence within the environment: toxin A (Tcd A) and toxin B (Tcd B). These clostridial exotoxins are genetically coded within the pathogenicity locus and collectively bind to intestinal epithelial cells causing inflammation, mucous and fluid secretion, and damage to the mucosal layer. Tcd A plays an important role in the recruitment and activation of the inflammatory cells and mediators causing the release of various cytokines (interleukin-6 (IL-6), IL-8, IL-1, TNFα). Tcd B contributes to the cytotoxic effects and is essential for the organism's virulence. Additionally, some strains of *C. difficile* produce binary toxin which may increase the effects of Tcd A and Tcd B contributing to more severe disease; however, its complete role is not entirely understood at this time.[13]

Transmission and colonization

C. difficile is transmitted through the faecal−oral route either from a colonized or infected person to person or from a contaminated environment to person. Normally, human intestinal flora acts as a barrier against colonization by *C. difficile*. When the natural flora is disrupted or altered by antibiotics or other causes, exogenous or endogenous *C. difficile* spores are able to germinate into their active vegetative form. The bacteria then multiply, colonizing the intestinal environment. The prevalence of asymptomatic *C. difficile* colonization affects between 10% and 52% of defined populations.[14] A recent systematic review showed that patient factors that increase the risk for colonization are older age, recent hospitalization, longer hospitalization, use of multiple antibiotics, longer antibiotic duration, proton pump inhibitors, chemotherapy, chronic kidney disease, and feeding tubes.[14] Patients who are colonized with *C. difficile* will test positive for the infection and have a detectable immunoglobulin G (IgG) response, but will have no evidence of associated symptoms such as diarrhoea. Colonization occurs in one-quarter to one-third of in patients and most likely plays a critical role in perpetuating healthcare-associated diarrhoea as these asymptomatic patients can contaminate the skin of healthcare providers or their environment leading to transmission to other individuals.[15]

Infections

The most common risk factor for developing a *C. difficile* infection is exposure to antibiotics within the prior month. Clindamycin, broad-spectrum cephalosporins, and fluoroquinolones are most commonly implicated; however, any antibiotic exposure can lead to infection. This risk increases with the duration of therapy and number of antibiotics used. Other risk factors include age >65 years, increased severity of illness, and prior or