**Name of Journal:** World Journal of Diabetes

**Manuscript NO:** 95176

**Manuscript Type:** EDITORIAL

**Urgent call for** attention to diabetes-associated hospital infections

Yu XL *et al.* Diabetes mellitus and healthcare-associated infections

Xue-Lu Yu, Li-Yun Zhou, Xiao Huang, Xin-Yue Li, Qing-Qing Pan, Ming-Ke Wang, Ji-Shun Yang
Abstract
In this editorial, we discuss the recent article by Zhao et al published in the *World Journal of Diabetes*, which highlights the importance of recognizing the risk indicators associated with diabetes mellitus (DM). Given the severe implications of healthcare-associated infections (HAIs) in hospitalized individuals—such as heightened mortality rates, prolonged hospitalizations, and increased costs—we focus on elucidating the connection between DM and nosocomial infections. Diabetic patients are susceptible to pathogenic bacterial invasion and subsequent infection, with some already harboring co-infections upon admission. Notably, DM is an important risk factor for nosocomial urinary tract infections (NUTIs) and surgical site infections (SSIs), which may indirectly affect the occurrence of nosocomial bloodstream infections (NBSIs), especially in patients with DM with poor glycemic control. Although evidence regarding the impact of DM on healthcare-associated pneumonias (HCAPs) remains inconclusive, attention to this potential association is warranted. Hospitalized patients with DM should prioritize meticulous blood glucose management, adherence to standard operating procedures, hand hygiene practices, environmental disinfection, and rational use of drugs during hospitalization. Further studies are imperative to explore the main risk factors of HAIs in patients with DM, enabling the development of preventative measures and mitigating the occurrence of HAIs in these patients.

**Key Words:** Diabetes mellitus; Healthcare-associated infections; Nosocomial urinary tract infections; Surgical site infections; Nosocomial bloodstream infections


**Core Tip:** Diabetes mellitus (DM) is an important risk factor for nosocomial urinary tract infections (NUTIs) and surgical site infections (SSIs), which may indirectly affect the occurrence of nosocomial bloodstream infections (NBSIs), especially in DM patients.
with poor glycemic control. Diabetic patients should therefore pay more attention to the prevention of healthcare-associated infections (HAIs), with a focus on the management of their blood glucose level.

INTRODUCTION

Originally denoting infections linked to hospitalization (formerly termed nosocomial infections)[1], healthcare-associated infections (HAIs) now encompass infections occurring in hospital environments among patients or medical personnel. This includes infections emerging during hospitalization, as well as those arising within hospitals and after discharge (e.g. 48 h post-hospitalization, within 30 days after receiving health care, or up to 90 days after undergoing certain surgical procedures), excluding infections existing pre-admission or present upon admission[2]. The prevalence of HAIs ranges from 3-10%[3], presenting a significant challenge to healthcare workers (HCWs). HAIs can affect the treatment of primary diseases, increasing mortality and disability rates, as well as escalating the economic burden on patients' families and society, thereby straining healthcare systems worldwide, especially in developing countries[4]. HAIs yield worse outcomes than community-acquired infections, attributed to the compromised health status of hospitalized patients and the higher prevalence of multidrug-resistant bacteria in hospital settings compared to community settings[5]. Severe HAIs often induce sepsis, estimated at 48.9 million cases globally in 2017 and remaining a leading cause of mortality worldwide[6]. In the recent issue of the World Journal of Diabetes, Zhao et al[7] presented an insightful article entitled “Prevalence and risk factors of diabetes mellitus among elderly patients in the Lugu community”. Through an analysis of diabetes mellitus (DM) prevalence and risk factors among the elderly, the authors proposed that heightened attention to the abnormalities of related risk signs can aid in improving their overall health. This prompts consideration of HAI management in hospitalized patients with DM, given their higher risk of infection compared to the general population.
IS DM A RISK FACTOR?

The microenvironment shaped by DM triggers molecular changes in key components of the defense system, including neutrophils, natural killer cells, and macrophages, thereby affecting innate immunity[8]. Concurrently, hyperglycemia disrupts cytokine equilibrium, inhibiting the adaptive immune response against invading pathogens, and further increasing the susceptibility of diabetic patients to microbial infections[8]. Compared to the general population, patients with DM face an elevated risk of infection [9]. The severity of systemic microangiopathy in diabetic patients can lead to tissue damage, creating a favorable milieu for pathogenic bacteria due to the high sugar content, thereby fostering the growth of fungi and bacteria. Consequently, these wounds may serve as sites for secondary infections or facilitate the spread of infection to adjacent soft tissues or deeper into bones [10]. A significant proportion of hospitalized patients with DM present with preexisting infections upon admission, predominantly complex skin and soft tissue lesions. These patients carry common pathogens such as methicillin-resistant *Staphylococcus aureus*, thereby increasing the likelihood of HAI occurrence, prolonged hospital stays, and increased susceptibility to adverse drug events [9, 11]. Genito et al. [12] revealed that co-infection with *Staphylococcus aureus* and *Pseudomonas aeruginosa* in diabetic mice enhanced virulence potential. Meta-analyses corroborate the established association between HAIs and DM prevalence [13, 14]. Notably, patients with severe DM, particularly those with elevated HbA1c levels, exhibit heightened susceptibility to intensive care unit (ICU) infections compared to non-diabetic patients and those with well-controlled blood glucose (Table 1). During the coronavirus disease 2019 (COVID-19) pandemic, patients with DM experienced a more severe disease course and heightened mortality rates[15]. Poor blood glucose management in patients with diabetes often precipitates recurrent infections, consequently escalating disability rates[10]. Therefore, heightened vigilance is imperative for preventing HAIs in hospitalized diabetic patients.

*Nosocomial urinary tract infections*
Nosocomial urinary tract infections (NUTIs) represent a prevalent form of nosocomial infection, with approximately 80% of cases attributed to catheter-associated urinary tract infections (CAUTIs) [2,16]. Between 15% and 25% of hospitalized patients undergo short-term indwelling urinary catheterization [17]. The insertion of urinary catheters, typically via the urethra or pubic bone, facilitates bacterial colonization of catheter surfaces or the formation of biofilms, thereby predisposing to infection [16]. Notably, the risk of CAUTIs increases with the duration of catheterization [2].

Patients with DM are at a heightened risk of developing NUTIs due to the high-sugar environment that favors the proliferation of bacteria [9, 17]. The American College of Radiology has explicitly identified DM as a risk factor for acute pyelonephritis [18]. Evidence from a cross-sectional study conducted in Pakistan involving 1,074 participants revealed a significantly elevated incidence of NUTIs among diabetic individuals compared to the non-diabetic group [19]. In the study reported by Kang CY et al [20], DM with chronic complications was an independent risk factor for postoperative NUTIs in patients with colorectal cancer. Furthermore, Girard R et al [21] retrospectively analyzed three prospective cohorts of 4669 older patients, including 4045 without catheterization, and reported a lack of significant association between DM and NUTIs, possibly attributed to the inclusion of all diabetic patients irrespective of catheterization status. However, a case-control study involving 7,295 hospitalized patients with indwelling urinary catheters ≥ 60 years reported DM as an independent risk factor for CAUTIs [22]. Notably, the heightened risk of NUTIs may predominantly pertain to cases of complex insulin-dependent diabetes [21] and those related to Trichosporon asahii [23].

Crucial strategies for CAUTI prevention include minimizing unnecessary catheterizations and shortening catheterization durations [24]. Emphasis should also be placed on aseptic insertion, proper maintenance of medical devices, and adherence to established practices such as hand hygiene. A notable example is the implementation of comprehensive unit-based safety plans across 603 hospitals in the U.S. between 2011 and 2013, which led to a reduction in non-ICU catheter-related urinary tract infection rates through coordinated education efforts and resource distribution [25]. Future
Advancements in catheter materials hold promise for mitigating bacterial growth and CAUTI incidence.

**Healthcare-associated pneumonias**

Healthcare-associated pneumonias (HCAPs) represent a significant subset of HAIs with notable lethality. HCAPs are commonly categorized into hospital-acquired pneumonias (HAPs), occurring 48-72 h post-admission, and ventilator-acquired pneumonias (VAPs), manifesting 48-72 h post-endotracheal intubation\(^2\). Patients treated in ICU are at an increased risk of death not only due to their underlying conditions but also attributable to HAIs \(^1\). Moreover, ICU patients often require endotracheal intubation and invasive mechanical ventilation, with VAPs affecting approximately 9% to 27% of these patients \(^1\). The primary route of acquisition for non-ventilator HCAPs is bacterial, viral, and fungal aspiration\(^2\). The etiology of HAPs/VAPs varies geographically, influenced by ICU patient profiles, durations of hospitalization and ICU stays pre-onset, and risk factors for multidrug-resistant pathogens \(^2\). In ICUs, gram-negative bacteria (GNB) predominantly cause bacterial pneumonia, often exhibiting high antibiotic resistance, while viral pneumonia is commonly attributed to influenza and respiratory syncytial virus \(^2\).  

Bacterial pneumococcal pneumonia is relatively common in patients with DM\(^3\). The adverse effects of DM on morbidity and mortality have been well-documented during influenza and COVID-19 epidemics \(^2\). A prospective longitudinal study in ICUs identified a strong correlation between DM and heightened mortality rates from HAPs \(^3\). A retrospective observational epidemiological study in Spain demonstrated a higher incidence of pneumonia in patients with type 2 diabetes mellitus (T2DM) compared to those without T2DM\(^3\). Another recent retrospective analysis of 1093 patients with acute cerebral infarction found that 80% of patients with DM had lung infections caused by GNB, which was significantly higher than those without DM (72.2%)?. However, the results are not conclusive. Another study, also from China, reported that DM was not a risk factor for pneumonia in elderly patients with acute ischemic cerebral...
infarction\textsuperscript{[33]}. Similarly, Vardakas KZ \textit{et al.}\textsuperscript{[34]} reviewed 87 articles between January 1950 to April 2005 and found that DM was not a risk factor for the development of HAP or the increased mortality associated with HAP in hospitals. Moreover, Hu \textit{et al.}\textsuperscript{[35]} conducted a meta-analysis of articles from Jan 1996 to Aug 2022, revealing that multidrug-resistant (MDR) bacteria-induced VAPs were not associated with DM. Similarly, another meta-analysis including 11 studies on VAPs after cardiac surgery concluded that the occurrence of VAPs was not associated with DM\textsuperscript{[36]}.

Evidence suggests that diabetic immune dysfunction alone may not suffice to precipitate clinically significant respiratory infections in the ICU. Multiple factors, including micro aspirations, illness severity, and mechanical ventilation duration, likely contribute to VAP occurrence\textsuperscript{[37]}. For diabetic patients, prevention of aspiration, disinfection of respiratory apparatus, active hand washing, and reduction of GNB through oral care can reduce the occurrence of VAPs\textsuperscript{[2]}. Factors such as infection control protocols, hospital environment, medication management, and invasive procedure utilization appear to play pivotal roles in HAP development in DM\textsuperscript{[34, 37]}. Vaccination emerges as an effective strategy for reducing pneumonia incidence in patients with DM.

**Surgical site infections**

Surgical site infections (SSIs) afflict 2-11\% of all surgical interventions\textsuperscript{[38]}, with patients’ endogenous pathogens, including skin bacteria or gut bacteria in gastrointestinal surgeries, typically implicated\textsuperscript{[38]}. In hospitalizations surpassing 5-7 days, exogenous and nosocomial flora are dominant, with \textit{Staphylococcus aureus} emerging as the most frequently isolated pathogen\textsuperscript{[38]}.

DM poses a notable risk factor for SSIs, attributed not only to its strong association with morbid obesity but also the effects of hyperglycemia and glycosylation on cell-mediated immunity\textsuperscript{[39]}. Numerous studies have been published on the effect of diabetes on the increased incidence of SSIs and the potential relationship between hyperglycemia and SSIs. Zhao \textit{et al.}\textsuperscript{[40]} conducted a meta-analysis of 23 studies, which focused on risk factors for SSIs after anterior cruciate ligament reconstruction, with
Moderate evidence from nine studies affirming the effect of DM on surgical site infection. In a retrospective analysis of 632 patients with head and neck cancer who underwent surgery, Gan et al.\cite{41} reported that the risk of SSIs in diabetic patients increased by more than three times compared with those without DM. Similarly, Martin et al.\cite{42} summarized the independent association between DM and SSIs across multiple surgical procedures, encompassing 90 published studies between December 1985 and July 2015, and found that DM was an independent risk factor for SSIs for multiple surgical procedure types, with cardiac surgery exhibiting the highest association.

King et al.\cite{43} retrospectively analyzed 55,408 individuals with DM who underwent various noncardiac surgeries and found that poor glycemic control in the first 24 h after surgery, during which mean serum glucose concentrations of over 150 mg/dL were associated with an increased incidence of postoperative infectious complications. It is strongly recommended to implement perioperative glycemic control measures, maintaining perioperative plasma glucose levels below 11.1 mmol/L in both diabetic and non-diabetic patients.\cite{39} Moreover, preoperative risk factors can be mitigated through smoking cessation, addressing malnutrition, and judicious antibiotic therapy. Rigorous preoperative skin antisepsic and appropriate surgical preparation are imperative for SSI prevention.\cite{2,38}

**Nosocomial bloodstream infections**

Nosocomial bloodstream infections (NBSIs) constitute a grave bacterial infection with significant morbidity and mortality, frequently associated with intravascular devices, of which central venous catheters account for 72%\cite{2}. The causative microorganisms of NSSIs are mainly coagulase-negative Staphylococcus, Staphylococcus aureus, gram-negative Bacilli, and Candidal.\cite{44,45}. The occurrence of NBSIs correlates with factors such as underlying diseases, catheter type and cleanliness, infused fluid type, and HCWs procedures (e.g., time of catheter placement, frequent catheter manipulation, and catheter location).\cite{45}. 
Patients with DM experience prolonged abnormal glucose metabolism, fostering a state of negative nitrogen balance characterized by decreased anabolism and increased catabolism, which puts the body in a state of negative nitrogen balance. Concurrently, reduced immunoglobulin synthesis diminishes immunity, augmenting infection susceptibility. Extensive antibiotics used during treatment can disrupt the microbial balance in the body, further increasing the risk of infection. While previous studies have suggested that DM is a risk factor for NBSIs,[45-47] two prospective observational studies from Greece have presented conflicting evidence regarding DM’s independent association with NBSIs, yet consistently emphasize a significant association between DM and BSIs.[37, 48]. Similarly, in China, a prospective survey of 2,605 ICU patients reported that the incidence of catheter-related BSIs (CRBSIs) in diabetic patients was 4.32 times higher than that in non-diabetic patients.[49] Furthermore, a recent descriptive cross-sectional study among patients with COVID-19 revealed that patients with DM were at a higher risk of developing NBSIs.[50] A prospective registry study in Germany collected data on the long-term survival of 1,975 patients with sepsis, identifying DM as a predictor of shorter survival.[51]

Prevention strategies for NBSIs include stringent infection control measures (hand hygiene, environmental disinfection), meticulous preparation before line insertion (skin preparation), adherence to correct operation protocols, and HCW education (e.g., aseptic operation, removal of unnecessary catheters, insertion site of catheters, immediate replacement of moistened or detached catheter dressings, and timely removal of catheters).[22, 52]

PREVENTION OF HAI S IN HOSPITALIZED DIABETIC PATIENTS

Vulnerable populations such as the elderly (>60 years of age) and infants (<1 year of age) face heightened susceptibility to HAI s, with underlying diseases, illness severity, and autoimmune status further increasing their susceptibility.[5] A retrospective study from China involving 472 patients with non-Hodgkin lymphoma reported that hospitalization duration, clinical stage, bone marrow infiltrate presence, and peripheral
blood neutrophil count were independent risk factors\textsuperscript{[53]}. Another case-control study from China found that different ABO blood types may be susceptible to certain types of HAI\textsuperscript{[54]}. Notably, in a vicious cycle, HAI\textsuperscript{s} increase the length of hospital stay and prolonged hospitalization increases the risk of exposure to microorganisms in the hospital environment \textsuperscript{[5]}. Microorganisms persist in the environment for a few hours or even months, making the hospital environment a significant contributor to the transmission of hospital pathogens to patients, especially from high-touch infected surfaces such as bedside tables, bed rails, faucets, or doorknobs\textsuperscript{[55]}. In the ICU, the patient’s oxygen masks, ventilators, and bed linen are the most contaminated\textsuperscript{[56]}. Additionally, HCWs are susceptible to microbial contamination of their hands and/or gloves, as well as mobile phones used in their daily work, due to their frequent contact with the environmental surfaces of patient’s rooms\textsuperscript{[57]}. Additionally, water reservoirs in aqueous medical devices also provide a favorable environment for the growth of microorganisms such as non-tuberculous mycobacterial\textsuperscript{[58]}. For instance, dental waterlines can be contaminated not only by microorganisms in the aquatic environment but also by bacteria from the patient’s oral cavity, posing a risk of infection to both HCWs and patients\textsuperscript{[59]}. Moreover, invasive procedures, nasogastric tubes, urinary and vascular catheters, central venous catheters, antibiotic abuse, and immunosuppressant use are other risk factors for HAI\textsuperscript{s}\textsuperscript{[2, 5, 60]}. Notably, the most common interventions in the ICU are endotracheal intubation and tracheostomy, as well as mechanical ventilation\textsuperscript{[61]}.

Approximately 20-50\% of HAI\textsuperscript{s} occur in the ICU, mainly attributed to the patients’ severe immunocompromised state. The emergence of multidrug-resistant organisms has reduced the efficacy of antibiotics in treating many common infectious diseases, contributing to increased HAI-related mortality rates\textsuperscript{[2]}. Additionally, the relatively enclosed hospital environment, dense population, and inadequate ventilation pose challenges for infection control\textsuperscript{[62]}.

Risk factors for diabetes-associated hospital infections are summarized in Figure 1. These infectious factors can be intervened with strict prevention and control measures. In 2015, the U.S. Centers for Disease Control and Prevention conducted a point-
prevalence survey of 12,299 patients from 199 hospitals, wherein 3.2% of hospitalized patients were reported to develop HAIs, which was a decrease from 4% in 2011. This decrease could be attributed to the effective control of surgical site and urinary tract infections. Pathogens can also be transmitted through the hands of HCWs or contaminated objects/aerosols. In a hospital setting, the operating room, ICU environment, and related equipment have strict hygiene requirements, and strict adherence to these requirements can reduce the rate of HAIs. HCWs should pay attention to hand hygiene and the standardized use of medical devices. Additionally, health education for patients can encourage self-management and behavioral changes in the hospital wards. Furthermore, especially in patients with DM, glycemic control and nutritional support during hospitalization can be beneficial for HAI prevention. Nutritional support, such as natural dietary supplements, vitamins, minerals, trace elements, and probiotics in appropriate doses, not only improves blood sugar control but also enhances immune regulation.

CONCLUSION
Hospitalized patients with DM exhibit weakened skin and mucosal barriers, decreasing the body’s ability to synthesize immunoglobulins and antibodies, rendering them more susceptible to pathogenic bacterial invasion and infection. Elevated blood glucose concentrations further exacerbate microbial reproduction and provoke inflammatory responses. While the current evidence falls short of conclusively establishing DM’s role in HCAPs, it has unequivocally identified DM as a high-risk factor for NUTIs and SSIs, which may indirectly impact the occurrence of NBSIs. Further studies are required to improve our understanding of the role of DM and glycemic control in HAIs, so as to refine the guidelines for blood glucose control synchronously. Undoubtedly, heightened attention to HAI prevention, especially blood glucose management, is imperative for patients with DM.
<table>
<thead>
<tr>
<th>#</th>
<th>Source URL</th>
<th>Match Words</th>
<th>Similarity Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>bmcinfectdis.biomedcentral.com</td>
<td>20</td>
<td>1%</td>
</tr>
<tr>
<td>2</td>
<td>link.springer.com</td>
<td>17</td>
<td>1%</td>
</tr>
</tbody>
</table>

**Exclude Quotes:** ON

**Exclude Sources:** < 1%

**Exclude Bibliography:** ON

**Exclude Matches:** < 10 WORDS