Endotext

# DIABETES MELLITUS AND INFECTIONS

**Keren Zhou, MD,** Clinical Assistant Professor, Endocrinology and Metabolism Institute, Cleveland Clinic, Cleveland, OH. zhouk2@ccf.org
**M. Cecilia Lansang, MD, MPH**, Professor of Medicine, Endocrinology and Metabolism Institute, Cleveland Clinic, Cleveland, OH. lansanm@ccf.org

**Updated June 29, 2024**

## ABSTRACT

Diabetes presents a significant risk factor for all kinds of infections. It has been well described to increase rates of outpatient infection as well as the incidence of infections requiring hospitalization. This appears to be related to deficits in the immune system, particularly changes seen in innate immunity. Respiratory infections, skin and soft tissue infections, gastrointestinal and genitourinary infections all appear to occur more frequently in patients with DM. Not only are they more frequent, but these infections appear to have a poorer response to therapy and more rapid progression to severe forms of infection. There is good evidence that reduction of hyperglycemia can improve outcomes. Among the antihyperglycemic agents available, translational and clinical data exists that insulin can help to improve immune function and potentially metformin as well.

## INTRODUCTION

The 2020 release of the US Centers for Disease Control and Prevention National Diabetes Statistics Report revealed that in 2018, 34.2 million individuals had diabetes mellitus (DM), representing approximately 10.5% of the US population and a total cost of care in excess of US $300 billion (1). Part of these numbers reflects the impact of DM on infection rates and morbidity/mortality. Both type 1 and type 2 DM are associated with a significantly higher risk of infection, both in the outpatient and inpatient context, and the outcomes are generally worse than in those without diabetes. We will discuss here the impact of diabetes on the immune system, specific infections which are commonly seen in diabetes, and the influence of various therapies targeted both at glycemic control and also on immunomodulation on infection outcomes.

## EPIDEMIOLOGY

DM, both type 1 and type 2, is associated with a high risk of infection. A large retrospective study of primary care patients revealed that diabetes is likely to account for 6% of infection-related hospitalizations and 12% of infection-related deaths, with the strongest associations being for bone and joint infections, development of sepsis, and cellulitis (2).

### Outpatient

A number of studies have been performed on the rate of infection among patients with diabetes in the primary care and other outpatient settings. In a Canadian cohort of 1,779 patients with DM matched to 11,066 without DM the patients with DM had an increased risk of infection (adjusted odds ratio 1.21, adjusted for confounding variables). with skin and soft

tissue infections having the strongest association with having DM. Interestingly, DM was not found in this study to be associated with head and neck, musculoskeletal, or viral infections (3). Another large Canadian study including more than a million individuals matched those with DM to those without, and assessed all physician and hospital claims for infectious disease. It found that almost half of all individuals with DM had a claim for an infectious disease within a cohort year compared with 38% of those without DM. The risk ratio was skewed most towards those with DM for upper respiratory tract infections, cystitis, and pneumonia (4).

### Inpatient

In one study, having diabetes led to a 2-fold increased risk for hospitalization when presenting with an infection to the emergency room, and up to 12% of inpatient admissions in patients with diabetes were the consequence of an infection (5). A South Korean showed that those with diabetes had a significantly greater risk of infection-related ICU admission and death when hospitalized with infections of skin or soft tissue, central nervous system infection, or bone and joints (6). The previously-mentioned Canadian retrospective cohort study showed that, while the overall risk ratio for infection in those with diabetes versus without was 1.21, this number rose to 2.17 and 1.92 when considering infection which led to hospitalization and death, respectively (4). These and other studies (7,8) have revealed that not only is diabetes associated with (and causative of) an increased risk of infection, but also with higher rates of hospitalization, ICU stays, and death related to these infections. Of note, many of these patients with DM have other comorbidities which may not be able to be fully controlled for in these epidemiologic studies demonstrating higher estimates of the risk of infection with DM.

One important entity to consider in the inpatient arena is sepsis. The studies on sepsis are not consistent — though some show worse outcomes from DM, others have suggested either no effect or even a protective effect from DM (9). Data for the latter come from studies assessing acute respiratory failure and respiratory distress syndrome in the ICU, and it may be that the blunted immune response that we see in some patients with DM are responsible for the findings (i.e., reduced inflammation and injury related to impaired neutrophil function as described in section on Innate Immunity) (10). More studies are needed to better understand in what specific clinical contexts DM results in higher risk.

## PATHOPHYSIOLOGY OF DIABETES AND IMMUNE SYSTEM

There is well-known disruption of the immune system in diabetes which occurs at multiple levels. Innate and adaptive immunity are affected along with cytokine signaling within both. This dysregulation occurs both in those with type 1 and 2 DM. Microvascular complications such as neuropathy also increase susceptibility to an accidental lesion in the barrier of the skin which forms one of the first lines of defense. Furthermore, poor vascular flow to sites of infection can further compromise an appropriate immune response and healing leading to worsening or secondary infections (11,11b). In our discussion on alterations of the immune system, it is important to note that we have focused on alterations in function as opposed to baseline differences in the number of immune cells or cytokine levels between those with and without DM. Table 1 provides a summary of the alterations in immune dysfunction that are known.

### Innate Immunity

#### COMPLEMENT SYSTEM

The complement system plays a critical role in both innate and adaptive immunity and leads to the

opsonization, lysis and phagocytosis of pathogens along with recruitment of immune cells to the site of infection. There is known to be a reduction in the complement factor 4 (C4) level in those with type 1 DM, although it is unclear if that alone can precipitate an increased risk of infection (12). A variety of studies demonstrate that hyperglycemia can inhibit phagocytosis through the system, potentially by reducing complement binding to immunoglobulins. Glycosylation of C3 can also impair its ability to attach to the pathogen surfaces (13).

| **Table 1. Impact of Diabetes and Hyperglycemia on the Immune System** | |
|---|---|
| **Innate Immunity** | |
| *Complement System* | Reduction in C4 levels (Unclear relevance for infection risk)<br>Reduction complement binding to immunoglobulins<br>Glycosylation of C3 can impair binding to pathogen surface |
| *Recruitment and Pathogen Recognition* | Reduced CAM expression leading to reduced leukocyte recruitment<br>- In setting of hyperglycemia reduced production of chemokine in response to bacterial LPS<br>- Advanced glycation end products inhibit neutrophil transendothelial migration<br>Reduced expression TLR (which allows for recognition LPS) |
| *Cellular Dysfunction* | - Reduced $H_2O_2$ production leading to reduced bactericidal ability in both macrophage and neutrophils<br>- Impairment of macrophage phagocytic ability through complement pathway<br>Impaired metabolism of glucose in macrophages reducing activity<br>- NK cell activity reduced through reduced expression activating receptors NKG2D and NKp46 |
| **Adaptive Immunity** | Depletion and dysfunction memory CD4+ cells<br>Not as well described as alterations in innate immunity |
| **Cytokine Signaling** | - Deficiency of IL-1, IL-2, IL-6, IL-10, IL-22, IFN-γ, TNF α |
| **Skin and Mucosal Barriers** | Vascular compromise leading to impaired healing<br>Neuropathy making breakage of the skin more likely |

## RECRUITMENT AND PATHOGEN RECOGNITION

A number of older studies reported reduced chemotaxis of polymorphonuclear leukocytes (PMNs) in patients who have DM (14,15). One of the mechanisms appears to be related to disruption of cellular adhesion molecules (CAMs) which are critical for the recruitment of leukocytes to the site of infection. This was seen when db/db (a diabetic mouse model) and wild type mice were infected with West Nile Virus and subsequent analysis of the brains of the db/db showed less leukocyte recruitment consistent with reduced CAM expression compared with the brains of the wild type mice (16). When hyperglycemia was induced in mice exposed to Klebsiella pneumoniae, there was a reduced recruitment of granulocytes to the site of infection as compared with control mice. This was felt to be related to a reduction in the chemokine production able to be induced by the bacterial

lipopolysaccharide (LPS) (17). There are also in vitro data which reveal that advanced glycation end products are able to inhibit neutrophil transendothelial migration (18). A reduction in the expression of Toll-like receptors (TLR, which bind to LPS and allow for pathogen recognition) in patients with poorly controlled diabetes has been described as well (19).

## SPECIFIC CELLULAR DYSFUNCTION

Multiple immune cells are impacted in DM. Neutrophil recruitment is not only reduced, but there are also good data demonstrating their reduced phagocytic activity and hydrogen peroxide production, leading to reduced bactericidal ability (20-23). The mechanism for the alteration appears may be partially linked to impaired metabolism of glucose and glutamine, as was demonstrated in streptozotocin-induced diabetic rats (24). Macrophages are also similarly affected. Examination of cells from patients with type 2 DM have revealed that there is impairment of both the complement and Fc-gamma receptor-mediated pathways by which macrophages are able to phagocytize pathogens (25). When macrophages from diabetic mice were cultured in normal versus high glucose, there was a reduction in the phagocytic and bactericidal activity, apparently through a defect similar to that seen in neutrophils, specifically impaired metabolism of glucose (26). NK cell activity is also known to be reduced in a manner which is related to level of glycemic control, demonstrated in multiple studies comparing NK cells from patients with DM, prediabetes, and also without DM (27). The mechanism of the reduced activity may be in part related to decreased expression of activating receptors NKG2D and NKp46 on the NK cells in patients with DM (28).

### Adaptive Immunity

The adaptive immune system is activated in response to specific pathogens and involves the immunologic memory for those pathogens. There are two components of adaptive immunity, the humoral and cellular, which carry out the major purposes of generating an antibody and cellular (involving B and T cells) response to a specific antigen. The adaptive humoral immunity is involved in antibody production. This appears to be preserved in those with DM on the basis of overall appropriate response to various vaccines (29,30). However, there may be some dysregulation of the adaptive cellular immunity. There is a depletion of memory CD4+ cells that has been noted prior to the development of type 1 DM (31). Furthermore, a dysfunction of and an impaired response of these cells to Streptococcus pneumoniae has been described (32). However, the dysfunction seen in DM with innate immunity is better understood than that the dysfunction in adaptive immunity (33).

### Cytokine Signaling Defects

Cytokines play a vital role in the signaling cascades which underpin the immune system, allowing for full activation of both innate and adaptive immune responses. Multiple points of dysregulation have been identified in DM. With stimulation, multiple of these cytokines have been shown to be secreted at lower levels than would be typical with stimulation. In vitro studies done on monocytes isolated from patients without DM showed suppression of IL-1, IL-2, IL-6, and IL-10 secretion in the presence of hyperglycemia (34-36). In diabetic mice, there was noted to be immune dysregulation and also inflammation which was related to IL-22 deficiency reversed with provision of IL-22 (37). There is also evidence for impaired interferon gamma (IFN-γ) and TNF alpha production from T cells in the setting of methylglyoxal, a compound which is increased in those with DM (38). The end result of these deficits is that there is attenuation of the phagocytic and cellular immune response.

## COMMON INFECTIONS, OUTCOMES, AND GENERAL DRUG OF CHOICE

In addition to many infections having a worse course in those with diabetes, specific types of infections are also significantly more common in those with diabetes. We will review these diabetes-predominant infections (39-42). Table 2 also provides an overview of common infections and considerations in those with DM.

| **Table 2. Common infections seen in patients with diabetes with attention to diagnosis, common responsible organisms, management, and outcomes** | |
|---|---|
| **Respiratory Infections** | |
| *Pneumonia* | Higher rates of hospitalization and also mortality in those with DM compared with those without<br>Less commonly presents with purulent cough and pleuritic chest pain, more commonly with altered consciousness<br>Aspiration and skin colonization common etiologies<br>*S pneumonia*, *S aureus*, and *K pneumoniae* among most common organism<br>Rx with amoxicillin/clavulanate or cephalosporin + macrolide/doxycycline vs fluoroquinolone |
| *Tuberculosis* | Higher risk contracting with risk corresponding with level of glycemic control<br>Higher risk of treatment failure<br>Isoniazid needs to be taken with pyridoxine to prevent neuropathy<br>Rifampin can cause hyperglycemia and also induces cyp450 leading to increased clearance of various DM agents |
| **Skin and Soft Tissue** | |
| *Cellulitis/Abscess* | Most common SSTI seen in those with DM<br>Most common organism *Staph* species<br>For abscess culture is needed to determine organism and resistance<br>Oral abx: Doxycycline, clindamycin, TMP-SMX, cephalexin<br>Presence SIRS or other complication: IV vancomycin, linezolid, ceftaroline |
| *Necrotizing Fasciitis* | Comorbid DM much more common<br>Limb loss seen more often<br>Polymicrobial typically but can be only *K pneumoniae*<br>Surgical rx most common and need broad spectrum coverage |
| *Fournier Gangrene* | More commonly seen in those with DM<br>Anaerobic and aerobic bacteria such as *S aureus* and *Pseudomonas* species<br>Debridement a must<br>Seen with SGLT2 inhibitors |
| *Sternal Wound Infection* | DM one of strongest predictors for infection<br>Improved glycemic control with insulin shown to reduce rate of infection |

| | |
|---|---|
| **Gastrointestinal** | |
| *Hepatitis* | - HCV outcomes worse with more frequent cirrhosis and failure of Antivirals |
| *Emphysematous Cholecystitis* | Diagnosis through sonography or CT typically as first step<br>Most common organism C perfringens and E coli<br>Rx is typically cholecystectomy but can try abx in mild case |
| **Genitourinary** | |
| *Urinary Tract Infection* | Higher rate of infection and failure/relapse with rx<br>Most common organism E choli and Enterobacteriaceae<br>Urine culture is strongly recommended<br>Do not treat asx bacteriuria<br>Decision for abx is based on local organism and resistance trend<br>- Higher risk of progression to pyelonephritis which is more severe and often bilateral |
| **Head and Neck** | |
| *Necrotizing Otitis Externa* | DM higher risk of abscess formation requiring draining<br>- Vascular compromise and pseudomonal vasculitis much more commonly seen in DM<br>P aeruginosa most common organism<br>Confirm with CT<br>- Systemic abx with antipseudomonal action and local therapy to the canal including cleaning/debridement |
| **Fungal Infections** | |
| *Onychomycosis* | Potentially up to 1/3 of all patients with DM impacted<br>Diagnosis based on fungal culture/microscopy<br>Oral agents most effective |
| *Genitourinary* | Most common Candida specie<br>Increased ability to bind with receptor in DM<br>UTI<br>Communicate with lab on culture that Candida specie is suspected<br>If symptomatic, then fluconazole first line |
| *Mucormycosis* | Causative agents are the mucormycetes<br>Most commonly sinus +/- cerebrum/orbits<br>Respiratory tract second most common<br>Skin third most common and has ulcerative necrotic lesion<br>- Tissue biopsy needed and imaging helpful to identify extent of infection<br>Debulking of infection with adjuvant |

Abbreviations: Rx (Treatment), Abx (Antibiotics), Asx (Asymptomatic), SSTI (Skin and soft tissue infections), UTI (Urinary tract infection)

**Respiratory Infections**

Pneumonia is a frequently-seen infection in those with DM. In a large Danish population-based case-control study of 34,239 patients, the relative risk for hospitalization from community-acquired pneumonia was 1.26 compared with patients without DM. Furthermore, the risk appeared to be correlated with level of glycemic control with relative risk (RR) for those with HbA1c <7% being 1.22, versus a RR of 1.6 when HbA1c was ≥9% (43). A Portuguese study similarly showed DM prevalence was higher in those with pneumonia and that outcomes were worse with a longer hospital stay and significantly higher mortality in patients with DM versus those without (15.2% vs 13.5%) (44). These trends were also seen in another Danish study which showed mortality was greater in those with type 2 DM compared with other patients at both 30 and 90 days after the initial pneumonia episode (45). The presentation of pneumonia is potentially different in those with DM as typically bacterial pneumonia presents with a purulent cough and pleuritic chest pain, symptoms which are less commonly seen in those with DM. The hypothesis is that the lowered immune defense results in a decreased inflammatory response and symptoms. Notably, altered consciousness is more common on presentation with pneumonia in those with DM. The causative agent of pneumonia is similar in those with and without DM with the most common being Streptococcus pneumoniae (46). However, there is an over-representation of organisms such as Staphylococcus aureus and Klebsiella pneumoniae related to skin colonization and more frequent aspiration in those with DM. Management is using combination therapy with amoxicillin/clavulanate or cephalosporin and a macrolide or doxycycline versus monotherapy with respiratory fluoroquinolone (47). Use of certain DM medications like metformin have been shown to reduce the risk of development of bacterial pneumonia (odds ratio 0.89) and also morbidity and mortality when pneumonia develops, hypothesized to be related to improvement in function of the innate immune system and reduction in levels of inflammation which is explored later in this chapter (47b).

Diabetes also represents an important risk factor for contracting tuberculosis (TB). The odds of developing tuberculosis appear to be higher in those with DM compared to those without with the odds ratio ranging from 2.44-8.33 in various studies. Furthermore, severity of DM appears to be correlated with greater risk of contracting TB based on studies comparing the incidence of TB in those with insulin-dependent versus non-insulin dependent DM. Risk of treatment failure despite good adherence to medication regimen and also death from tuberculosis all appear to be increased (48). There are side effects of medications targeted at tuberculosis with particular relevance in DM. Isoniazid can cause peripheral neuropathy that could be mistaken for diabetic neuropathy, and pyridoxine should be administered to ameliorate this risk. Rifampicin has the ability to cause hyperglycemia. Rifampicin also is a powerful inducer of the cytochrome P450 system leading to increased clearance of multiple DM agents (i.e., sulfonylurea, pioglitazone, meglitinides). Hence while the regimen to treat TB seen in patients with DM is the same as the regimen in those without, special attention must be paid to these DM specific issues.

**Skin and Soft Tissue Infections (SSTI)**

There is a significantly increased risk of skin and soft tissue infections (SSTI) in DM. Up to 80% of patients with DM will experience a skin complication related to DM during their lifetime, many of which are SSTIs (48b). Using a large administrative claims database (HealthCore Integrated Research Database), Suaya et al were able to demonstrate complications from SSTI were five times higher, and hospitalization four times higher, in patients with DM than those without DM in their cohort (49). The most common agent of infection is Staphylococcus aureus (S aureus). The

foot represents the most common site of infection as well which has been expertly covered in another chapter (50). In the last few years, a number of therapies directed at improving immune function, blood flow, and better restoring integrity of the barrier of the skin have been developed that likely have implications for other non-foot related infections (50b).

For cellulitis, the diagnosis is typically clinical, as opposed to an abscess which often is cultured for organism identification and resistance profiling. The decision for antibiotics in cellulitis and with abscess is often empiric, and in those with DM it is imperative that the choice cover Staphylococcus species. Potential first line therapy for outpatient oral antibiotics includes doxycycline, clindamycin, trimethoprim-sulfamethoxazole, and cephalexin. If there is admission due to SIRS criteria being present or a suspected complication, then the recommendations change to IV predominant choices including vancomycin, linezolid, and ceftaroline (51).

Necrotizing fasciitis is a life-threatening condition involving the subcutaneous fat and deep fascial layers. A retrospective report of 59 necrotizing fasciitis cases at a single center revealed that 11 of the cases had DM, and another study showed that 51% of 84 patients in the cohort with necrotizing fasciitis had DM (52,53). Though most commonly a polymicrobial infection, Klebsiella pneumoniae is also commonly seen as a single isolate (53). Prognosis appears to be poorer in those with DM, with a higher rate of limb loss than that seen in those without DM. Broad spectrum antibiotics are utilized, related to the frequent polymicrobial nature of the infection. However, ischemia compromises appropriate antibiotic concentration at the site, therefore the management is primarily surgical involving a combination of debridement, necrosectomy, and fasciotomy frequently (54).

Fournier gangrene represents a particularly serious SSTI, defined as a necrotizing skin infection of the scrotum and penis or vulva. Typically, patients are between the age of 50-60 years and DM represents a serious risk factor for development. Usually, the infection will begin in the perianal or retroperitoneal region and then spreads to the genitalia or as a urinary tract infection which then also moves towards the genitalia. There will be necrosis and crepitus which is an indication of involvement of the underlying skin and soft tissue. The etiology is usually a mix of aerobic and anaerobic bacteria which can commonly include S aureus and Pseudomonas (51). Surgical debridement is typically necessary. This condition has become of particular relevance with the release of a warning from the US Food and Drug Administration in August 2018 that Fournier's represented a rare but serious complication of sodium-glucose cotransporter 2 inhibitors (SGLT2i), a newer but increasingly utilized class of DM medications (55). There were 55 cases of Fournier's reported to the FDA between March 2013 and January 2019 (56). However, it is important to note that while this number appears to be higher than for other anti-hyperglycemic agents, that there has not been a clear establishment of causality here. In fact, other studies including a meta-analysis of randomized controlled trials involving SGLT2i and a "real-world" study using IBM MarketScan were unable to confirm an increased risk of Fournier's Gangrene for those using SGLT2i versus those who did not (57,58). Intriguingly, a single center retrospective review of cases of Founier Gangrene admitted actually suggested use of SGLT2i and metformin were both protective in reducing length of ICU and hospital stay (58b).

Sternal wound infections after surgery are also known to occur more frequently in those with DM. After coronary artery bypass, presence of DM is one the strongest predictors for a deep sternal wound infection (odds ratio 2.6) (59). Improved glycemic control in the post-operative period has been shown to be able to significantly reduce the rate of sternal wound infection (60-62). Furnary et al in their seminal study were able to demonstrate in a prospective manner that use of an IV insulin infusion to keep glucose <200 mg/dL

resulted in a 66% reduction in risk of sternal infection compared with nonrandomized historical controls (60).

**Gastrointestinal Infections**

The presence of DM has been known to worsen viral hepatitis. The outcome in chronic hepatitis C infection is worse in those with DM as compared to those without, corresponding to a significantly increased risk for cirrhosis and a reduced response to antiviral therapy in those with DM and hepatitis C (63). Emphysematous cholecystitis is a rare progression of acute cholecystitis, defined as presence of gas in the gallbladder wall for which DM serves as a major risk factor. The prevalence of DM among those with emphysematous cholecystitis has been described as high as 50% in the literature (64). Sonography is able to detect the presence of gas within the gallbladder wall and an abdominal radiograph will show a curvilinear lucency around the gallbladder. CT can also detect the condition with nearly 100% sensitivity. The two most common causative agents are Clostridium perfringens and Escherichia coli. The treatment is often surgical with prompt cholecystectomy although for a mild case antibiotic therapy can be initiated but without improvement within 3-4 days then the recommendation is still for cholecystectomy (65).

**Genitourinary Infections**

Urinary tract infections (UTI) are significantly more common in patients with DM with a large UK study showing an incidence of UTI of 46.9 per 1000 person-years among those who had type 2 DM versus 29.9 for those without DM (66). The most common pathogens in those with DM are Escherichia coli and the Enterobacteriaceae (Klebsiella, Proteus, Enterobacter, etc.). There is an increased risk of drug-resistant organisms being present. In making the diagnosis, beyond the typical clinical symptoms of dysuria and increased frequency, it is important to note that a urine culture really should be obtained in all individuals with DM prior to therapy (67). Outcomes are worse in those with DM, being associated with increased relapse and reinfection (at 7.1% and 15.9% respectively in those with DM versus 2% and 4.1% in those without) (68). Asymptomatic bacteriuria should not be treated even in those with DM. In those with symptoms, trimethoprim-sulfamethoxazole and ciprofloxacin are good choices but the general consensus is to follow local infection and resistance trends and tailor antibiotic therapy towards those organisms (67). From a lower UTI, there is also more risk of progression to pyelonephritis (both emphysematous and nonemphysematous) which tends to be more severe requiring hospitalization and are often bilateral in those with DM (69,70).

It would be important to note that the class of medications called SGLT2i, previously mentioned under the section of Fournier gangrene, was initially thought to be associated with increased risk of UTIs. The purported mechanism is the increased glucose level in the urine, favoring the growth of microorganisms. However, database-driven studies and meta-analyses have not borne out this association (70b,70c). The initial observation of increased rates of UTI may have been related to surveillance bias or mycotic infections being mistaken for UTI in patients on SGLT2i.

**Head and Neck Infections**

Consistent with the findings in many types of infections, head and neck infections are more common and appear to be more severe in those with DM. An assessment of 185 patients at the National Taiwan University Hospital with deep neck infections found that those with DM had a significantly higher rate of abscess formation than those without (89.3% vs 71.3%) and that surgical drainage was required more frequently as well (86% vs 65.2%) (71). One concerning entity commonly associated with DM is necrotizing external otitis. This term references an infection which has spread to the temporal and

adjacent bones at the base of the skull. The causative agent is often Pseudomonas aeruginosa. The increased frequency of this in those with DM appears to be related in part to the vascular compromise seen in DM combined with a pseudomonal vasculitis (72,72b). A certain level of suspicion for this condition needs to be present when there is external otitis in a patient at risk of necrotizing progression. Imaging is often needed to confirm with CT used. Systemic antibiotics are a requirement along with local treatment of the canal (i.e., cleaning, antimicrobial topicals, etc.). The antibiotic chosen needs to have antipseudomonal action such as the fluoroquinolones with the understanding that poor vascularization of the area often means higher doses are required (72).

**Fungal Infections**

Infection with Candida species is common in those with DM (73). Skin and soft tissue along with mucosa can be commonly impacted. Assessment of mouth swabs from patients with and without DM revealed that there was a higher frequency of Candida infection in the patients with DM (74). This appears to be related to decreased salivary pH and salivary flow which promoted colonization with the yeast. But there is also the possibility that in DM there is increased ability of Candida to bind to its receptor (75). Onychomycosis, a fungal infection of the nails, is also very common with DM with some studies suggesting up to 1/3 of individuals with DM are impacted. Diagnosis is made based on a positive fungal culture for a dermatophyte or microscopy showing fungus prior to initiation of therapy. Oral agents tend to be the most efficacious but topical lacquers are used as well (76).

Beyond the skin and mucosa, there is a high rate of genitourinary infections with Candida species. Among fungal infections of the urinary tract system, the vast majority involve Candida species. For both outpatient and inpatient urinary tract infections where Candida species was the causative agent, DM is present as a comorbid condition in 29% and 39% of cases respectively. Initial work-up would be similar to that of any other for urinary tract infection including urinalysis and culture. If there is a concern for Candida then that should be communicated with the reporting lab as there can be slow growth on certain cultures. It is important to remember that symptomatic urinary tract infections with Candida are rare. However, if truly a symptomatic infection is felt to be present, then fluconazole is typically the first line therapy of choice because of its ability to accumulate in high concentrations within the urine. If there is progression to pyelonephritis then speciation and sensitivities will be required given the presence of resistant strains and often dual agent therapy is required (77).

Mycotic genital infections are driven by Candida species. in both men and women (78). A very large percentage of women will experience symptomatic vulvovaginal candidiasis within their lifetime, and DM represents a risk factor for development of infection, with worsening glycemic control predisposing to an even higher risk (73). This appears to be related to known defects in immune cell function (PMNs and macrophages) and the impact of glucose in the urine, leading to worsening virulence in addition to improved adherence of yeast. Clinically, women present with pruritis and discomfort. Diagnosis is best made with microscopy and can be suspected in those with a negative amine (“whiff”) test and normal pH. Treatment is typically with a short course of intravaginal imidazole or triazole as opposed to oral fluconazole (78). For male patients, a similar finding of increased risk of balanitis (i.e., inflammation of the glans penis and prepuce) with DM and with increasing HbA1c is noted (73,79). This condition also occurs almost exclusively in males who have not been circumcised. Diagnosis is best made based on clinical presentation (burning and itching of penis worse after intercourse) in combination with a subpreputial culture. Imidazole or triazole creams represent the mainstay of therapy (78).

It is worth mentioning that SGLT2i as a class are known to be associated with genital infections, particularly mycotic genital infections caused by Candida species. Using information from two US based health insurance databases, Dave et al were able to demonstrate in a retrospective cohort study that use of an SGLT2i compared with dipeptidyl peptidase 4 inhibitors and glucagon-like peptide 1 receptor agonists led to an approximately three-fold increase in risk of genital infection (80). This might be mitigated in part by improved hygiene (i.e., rinsing the genital area with water after every episode of urination and before going to bed) (81). Interestingly, the association between use of SGLT2i and genital infections does not appear to extend to UTIs (82). This may be related to increased volume and flow through the urinary tract preventing excess bacterial load from developing (83). As SGLT2i are increasingly a mainstay of therapy for patients with type 2 DM, this association with mycotic genital infections needs to be carefully considered.

Mucormycosis is a rare but life-threatening fungal infection caused by a mucormycetes, a group of molds (commonly the mucor and rhizppus species). A metanalysis of cases of mucormycosis showed that DM was the commonest underlying condition present in 40% of cases (84). Frequently the DM associated is type 2 and uncontrolled. It carries with it a high fatality rate which ranges from 32-57%. The most common site of infection (66% of cases in a large 929 case series) is the sinus-cavity leading to rhinocerebral infection which can also impact the orbits. In these cases, there are often symptoms of sinus congestion/inflammation, fever, facial swelling along with ophthalmoplegia, cellulitis, and cranial nerve palsies. Necrotic eschars in the nasal cavity and on the hard palate are classic findings and also indicate a rapidly progressive infection. The respiratory tract is the second most commonly affected location (16%) with endobronchial lesions commonly found in those with DM. The subsequent invasion of the vasculature can lead to more distant infection. Finally, the third most common site is the skin (10%). Cutaneous mucormycosis presents with erythematous or ulcerative necrotic lesions which can also lead to osteomyelitis (85,86). Tissue biopsy is a requirement for diagnosis while various imaging modalities can help provide further evidence of an infection. Debulking of the infection through surgery is necessary. Amphotericin B and isavuconazole have been utilized as adjunctive therapies (85,87).

**COVID-19 and DM**

There is clearly a significant interaction between DM and SARS-CoV-2 (causative agent of coronavirus disease 2019 (COVID-19)). Multiple risk factors for contracting and having a more severe course of COVID-19 have been identified, including advanced age and male gender, but both type 1 and type 2 DM are now known to be important risk factors for morbidity and mortality with the disease (88). An assessment of patients who contracted COVID-19 and were tested within the Vanderbilt University Medical system demonstrated that there was a significantly increased risk for hospitalization in those with DM compared to without DM (odds ratio 3.36 for type 2 and 3.9 for type 1) and also for more severe disease course (odds ratio 3.42 for type 2 and 3.35 for type 1) (89). From a cohort of patients in England, there is evidence that poorly-controlled DM as compared with well-controlled DM (HbA1c 6.5-7% versus greater than 10%) results in significantly increased mortality in both type 1 and type 2 DM (hazard ratio 2.23 and 1.61 respectively) (90). Increased mortality has also been seen in another English cohort (83). A more comprehensive review on this topic is offered by Lim et al, where the multiple points at which COVID-19 and DM interact – including the impact of glucotoxicity on the lungs, increased thromboembolic risk, worsened oxidative stress. and inappropriately high levels of cytokine production leading to organ damage – are outlined (91).

## IMPACT OF GLYCEMIC CONTROL AND OTHER THERAPIES

### Glycemic Control and Diabetes Therapies

There is good evidence that glycemic control is correlated with infection. A study of 69,318 patients with type 2 DM in Denmark revealed an association between increased risk for community- and hospital-treated infection in those with higher HbA1c ≥10.5% compared with HbA1c 5.5-<6.4% (92). Similarly, in a large English cohort there was an increasing risk of infection in parallel with HbA1c for patients with both type 1 and type 2 (2). In a Taiwanese study looking at outcomes from a community-based health screening program, the authors found that fasting plasma glucose >200 mg/dL and DM was associated with the highest risk of infection and also a 3-fold higher risk of death than those without DM (93). Looking at an older population, the risk of certain infections was significantly higher in those with poor glycemic control HbA1c >8.5% compared with good glycemic control (relative risk infections ranging from 1.28-2.38) (94). Intervening to lower glucose appears to mitigate the risks. Zerr et al assessed incidence of sternal wound infection in patients with and without DM before and after implementation of a postoperative continuous IV insulin protocol to keep blood glucose <200 mg/dL. They found that lower glucose in the first 2 days postoperatively was associated with a decrease in deep wound infection from 2.4% to 1.5% (62).

Insulin, in both translational and clinical studies, has been suggested to have a protective effect against infection risk in those with DM (Table 3). A large surgical ICU trial assessing tight (80-110 mg/dL) versus conventional (treatment with insulin only if glucose >215 mg/dL) glycemic control using IV insulin found a lower mortality with tight glycemic control, and the greatest reduction in mortality was seen in those with sepsis leading to multi-organ dysfunction. In those treated with IV insulin, there was a significant reduction in the risk of developing sepsis (46%) (95).

While these data were later brought into question by the findings of the NICE-SUGAR trial (96) which demonstrated increased mortality with intensive glycemic control using IV insulin, other studies have suggested that there is improvement in rates of infection with use of insulin (60,97) particularly in the post-cardiac surgery setting for sternal wound infections. Furthermore, the increased risk of mortality in the intensive glycemic control arm in NICE-SUGAR is felt to be related to an excess of hypoglycemia seen in the cohort compared with normal care. If improved glycemic control can be achieved without causing a significant increase in hypoglycemia, a different outcome may be able to be achieved (98). Translational studies have been able to show in vivo that T cells which lack insulin receptor expression are unable to proliferate and produce cytokines properly and that insulin enables the cells to take up nutrient which supports their function (99). As mentioned earlier chemotaxis of PMNs is impaired in patients with DM and it has been noted that provision of glucose and insulin can restore these to baseline (15).

While data for immune function improvement and infection using other antihyperglycemic medications are relatively sparse, there are some suggestions that therapies beyond insulin can have an immune-restorative effect (Table 3). Metformin has demonstrated an ability to increase the number and action of CD8+ tumor-infiltrating lymphocytes, resulting in improved production of cytokines IL-2, TNFα, and IFNγ (100). In a mice model with an absence of the TNF receptor-associated factor 6 (TRAF6), there is a relative inability to generate memory T cells that is related to defects in fatty acid metabolism. When TRAF6-deficient antigen specific effector T cells and TRAF6-deficient mice were exposed to metformin, there was a restoration of the production of memory T cells (101). While a number of other diabetes therapies have well-established anti-inflammatory effects (i.e., peroxisome proliferator-

activated receptor-γ agonists, glucagon-like peptide-1 receptor agonists, sodium-glucose cotransporter 2 inhibitors) data are lacking as to their specific impact on immune function with regards to infection risk apart from their reduction of hyperglycemia (102-104).

**Immunomodulating Therapies**

There are data showing that the use of granulocyte-colony stimulating factor (G-CSF), which induces differentiation and release of PMN from marrow, is able to assist with healing in foot infections (105). While a subsequent meta-analysis did not show that the use of G-CSF was able to significantly impact the resolution or healing of wounds, there was a reduction in risk of needing amputation or surgical intervention (106).

While not a "medication", physical activity has long been known to be associated with improvement in the immune system which are known to extend as well to those with DM (107). In diabetic rats, exercise was able to improve the neutrophil and lymphocyte count significantly (108).

**Table 3. Anti-Hyperglycemic Agents Associated with a Reduced Risk of Infection**

| | |
|---|---|
| **Insulin** | - T cells *in vivo* which lack insulin receptor are unable to proliferate and produce cytokines due to the inability to take up nutrients<br>Chemotaxis in PMNs impaired in DM which is restored with glucose and Insulin |
| **Metformin** | - Increase number of tumor-infiltrating lymphocytes and improved cytokine production<br>Restoration of production of memory T cells from effector T cells |

**CONCLUSION**

Diabetes represents an incredibly important risk factor for infection raising the likelihood of infection for both outpatient treated conditions and those which lead to hospitalization. Beyond raising the risk for contracting an infection, prognosis is frequently worse for many of these conditions which increases the frequency of rare and life-threatening infectious processes seen in those with DM. This is the consequence of disturbances in the immune system which have been well described involving both innate and adaptive immunity. However, glucose lowering therapies appear to be able to counteract some of the increased risk of infection and worsened prognosis by improving function of immune cells. More work is needed to fully elucidate if and how newer diabetes agents may be able to reduce risk of infection.

## REFERENCES


1. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2020. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Dept of Health and Human Services; 2020.

2. Carey IM, Critchley JA, DeWilde S, Harris T, Hosking FJ, Cook DG. Risk of Infection in Type 1 and Type 2 Diabetes Compared With the General Population: A Matched Cohort Study. Diabetes Care. 2018;41(3):513-521.

3. Abu-Ashour W, Twells LK, Valcour JE, Gamble JM. Diabetes and the occurrence of infection in primary care: a matched cohort study. BMC Infect Dis. 2018;18(1):67.

4. Shah BR, Hux JE. Quantifying the risk of infectious diseases for people with diabetes. Diabetes Care. 2003;26(2):510-3.

5. Korbel L, Spencer JD. Diabetes mellitus and infection: an evaluation of hospital utilization and management costs in the United States. J Diabetes Complications. 2015;29(2):192-5.

6. Kim EJ, Ha KH, Kim DJ, Choi YH. Diabetes and the Risk of Infection: A National Cohort Study. Diabetes Metab J. 2019;43(6):804-814.

7. Muller LM, Gorter KJ, Hak E, Goudzwaard WL, Schellevis FG, Hoepelman AI, Rutten GE. Increased risk of common infections in patients with type 1 and type 2 diabetes mellitus. Clin Infect Dis. 2005;41(3):281-8.

8. Fine MJ, Smith MA, Carson CA, Mutha SS, Sankey SS, Weissfeld LA, Kapoor WN. Prognosis and outcomes of patients with community-acquired pneumonia. A meta- analysis. JAMA. 1996;275(2):134-41.

9. Schuetz P, Castro P, Shapiro NI. Diabetes and sepsis: preclinical findings and clinical relevance. Diabetes Care. 2011 Mar;34(3):771-8.

10. Esper AM, Moss M, Martin GS. The effect of diabetes mellitus on organ dysfunction with sepsis: an epidemiological study. Crit Care 2009;13:R18

11. Forbes J.M., Cooper M.E. Mechanisms of diabetic complications. Physiological Reviews. 2013;93(1):137-188.

11b. Holt RIG, Cockram CS, Ma RCW, Luk AOY. Diabetes and infection: review of the epidemiology, mechanisms and principles of treatment. Diabetologia. 2024 Jul;67(7):1168-1180.

12. Vergani D, Johnston C, B-Abdullah N, Barnett AH. Low serum C4 concentrations: an inherited predisposition to insulin dependent diabetes?. Br Med J (Clin Res Ed). 1983;286(6369):926-928.

13. Jafar N, Edriss H, Nugent K. The Effect of Short-Term Hyperglycemia on the Innate Immune System. Am J Med Sci. 2016;351(2):201-11.

14. Delamaire M, Maugendre D, Moreno M, Le Goff MC, Allannic H, Genetet B. Impaired leucocyte functions in diabetic patients. Diabet Med. 1997;14(1):29-34.

15. Mowat A, Baum J. Chemotaxis of polymorphonuclear leukocytes from patients with diabetes mellitus. N Engl J Med. 1971;284(12):621-7.

16. Kumar M, Roe K, Nerurkar PV, Orillo B, Thompson KS, Verma S, Nerurkar VR.. Reduced immune cell infiltration and increased pro-inflammatory mediators in the brain of Type 2 diabetic mouse model infected with West Nile virus. J Neuroinflammation. 2014;11:80.

17. Martinez N, Ketheesan N, Martens GW, West K, Lien E, Kornfeld H. Defects in early cell recruitment contribute to the increased susceptibility to respiratory Klebsiella pneumoniae infection in diabetic mice. Microbes Infect. 2016;18(10):649-655.

18. Collison KS, Parhar RS, Saleh SS, Meyer BF, Kwaasi AA, Hammami MM, Schmidt AM, Stern DM, Al-Mohanna FA. RAGE-mediated neutrophil dysfunction is evoked by advanced glycation end products (AGEs). J Leukoc Biol. 2002;71(3):433-44.

19. Gupta S, Maratha A, Siednienko J, Natarajan A, Gajanayake T, Hoashi S, Miggin S. Analysis of inflammatory cytokine and TLR expression levels in Type 2 Diabetes with complications. Sci Rep. 2017 Aug 9;7(1):7633. doi:10.1038/s41598-017-07230-8. Erratum in: Sci Rep.201.;

20. Bagdade JD, Nielson KL, Bulger RJ. Reversible abnormalities in phagocytic function in poorly controlled diabetic patients. Am J Med Sci. 1972;263(6):451-6.

21. Bybee JD, Rogers DE. The phagocytic activity of polymorphonuclear leukocytes obtained from patients with diabetes mellitus. J Lab Clin Med. 1964;64:1-13.

22. Inoue S, Lan Y, Muran J, Tsuji M. Reduced hydrogen peroxide production in neutrophils from patients with diabetes. Diabetes Res Clin Pract. 1996;33(2):119-27.

23. Repine JE, Clawson CC, Goetz FC. Bactericidal function of neutrophils from patients with acute bacterial infections and from diabetics. J Infect Dis. 1980;142(6):869-75.

24. Alba-Loureiro TC, Hirabara SM, Mendonça JR, Curi R, Pithon-Curi TC. Diabetes causes marked changes in function and metabolism of rat neutrophils. J Endocrinol. 2006;188(2):295-303.

25. Restrepo BI, Twahirwa M, Rahbar MH, Schlesinger LS. Phagocytosis via complement or Fc-gamma receptors is compromised in monocytes from type 2 diabetes patients with chronic hyperglycemia. PLoS One. 2014 Mar 26;9(3):e92977.

26. Pavlou S, Lindsay J, Ingram R, Xu H, Chen M. Sustained high glucose exposure sensitizes macrophage responses to cytokine stimuli but reduces their phagocytic activity. BMC Immunol. 2018;19(1):24.

27. Kim JH, Park K, Lee SB, Kang S, Park JS, Ahn CW, Nam JS. Relationship between natural killer cell activity and glucose control in patients with type 2 diabetes and prediabetes. J Diabetes Investig. 2019;10(5):1223-1228.

28. Berrou J, Fougeray S, Venot M, Chardiny V, Gautier JF, Dulphy N, Toubert A, Peraldi MN. Natural killer cell function, an important target for infection and tumor protection, is impaired in type 2 diabetes. PLoS One. 2013;8(4):e62418.

29. Beam, T.R.J., Crigler, E.D., Goldman, J.R. and Schifmann, G. Antibody response to polyvalent pneumococcal polysaccharide vaccine in diabetics. J Am Med Assoc. 1980;244:2641-2644.

30. Diepersloot RJ, Bouter KP, Beyer WE, Hoekstra JB, Masurel N. Humoral immune response and delayed type hypersensitivity to influenza vaccine in patients with diabetes mellitus. Diabetologia. 1987;30(6):397-401.

31. Moutschen MP, Scheen AJ, Lefebvre PJ. Impaired immune responses in diabetes mellitus: analysis of the factors and mechanisms involved. Relevance to the increased susceptibility of diabetic patients to specific infections. Diabete Metab. 1992 May-Jun;18(3):187-201.

32. Martinez PJ, Mathews C, Actor JK, Hwang SA, Brown EL, De Santiago HK, Fisher Hoch SP, McCormick JB, Mirza S. Impaired CD4+ and T-helper 17 cell memory response to Streptococcus pneumoniae is associated with elevated glucose and percent glycated hemoglobin A1c in Mexican Americans with type 2 diabetes mellitus. Transl Res. 2014 Jan;163(1):53-63.

33. Geerlings SE, Hoepelman AI. Immune dysfunction in patients with diabetes mellitus (DM). FEMS Immunol Med Microbiol. 1999 Dec;26(3-4):259-65.

34. Mooradian AD, Reed RL, Meredith KE, Scuderi P. Serum levels of tumor necrosis factor and IL-1 alpha and IL-1 beta in diabetic patients. Diabetes Care. 1991;14(1):63-5. doi: 10.2337/diacare.14.1.63. PMID: 1991438.

35. Ohno Y, Aoki N, Nishimura A. In vitro production of interleukin-1, interleukin-6, and tumor necrosis factor-alpha in insulin-dependent diabetes mellitus. J Clin Endocrinol Metab. 1993;77(4):1072-7.

36. Reinhold D, Ansorge S, Schleicher ED. Elevated glucose levels stimulate transforming growth factor-beta 1 (TGF- beta 1), suppress interleukin IL-2, IL-6 and IL-10 production and DNA synthesis in peripheral blood mononuclear cells. Horm Metab Res. 1996;28(6):267-70.

37. Wang X, Ota N, Manzanillo P, Kates L, Zavala-Solorio J, Eidenschenk C, Zhang J, Lesch J, Lee WP, Ross J, Diehl L, van Bruggen N, Kolumam G, Ouyang W. Interleukin-22 alleviates metabolic disorders and restores mucosal immunity in diabetes. Nature. 2014;514(7521):237-41.

38. Price CL, Hassi HO, English NR, Blakemore AI, Stagg AJ, Knight SC. Methylglyoxal modulates immune responses: relevance to diabetes. J Cell Mol Med. 2010;14(6B):1806- 15.

39. Akash MSH, Rehman K, Fiayyaz F, Sabir S, Khurshid M. Diabetes-associated infections: development of antimicrobial resistance and possible treatment strategies. Arch Microbiol. 2020l;202(5):953-965.

40. Casqueiro J, Casqueiro J, Alves C. Infections in patients with diabetes mellitus: A review of pathogenesis. Indian J Endocrinol Metab. 2012;16 Suppl 1(Suppl1):S27-36.

41. Joshi N, Caputo GM, Weitekamp MR, Karchmer AW. Infections in patients with diabetes mellitus. N Engl J Med. 1999;341(25):1906-12.

42. Peleg AY, Weerarathna T, McCarthy JS, Davis TM. Common infections in diabetes: pathogenesis, management and relationship to glycaemic control. Diabetes Metab Res Rev. 2007;23(1):3-13.

43. Kornum JB, Thomsen RW, Riis A, Lervang HH, Schønheyder HC, Sørensen HT. Diabetes, glycemic control, and risk of hospitalization with pneumonia: a population-based case-control study. Diabetes Care. 2008;31(8):1541-5.

44. Martins M, Boavida JM, Raposo JF, Froes F, Nunes B, Ribeiro RT, Macedo MP, Penha-Gonçalves C. Diabetes hinders community-acquired pneumonia outcomes in hospitalized patients. BMJ Open Diabetes Res Care. 2016;4(1):e000181.

45. Kornum JB, Thomsen RW, Riis A, Lervang HH, Schønheyder HC, Sørensen HT. Type 2 diabetes and pneumonia outcomes: a population-based cohort study. Diabetes Care. 2007;30(9):2251-7.

46. Di Yacovo S, Garcia-Vidal C, Viasus D, Adamuz J, Oriol I, Gili F, Vilarrasa N, García-Somoza MD, Dorca J, Carratalà J. Clinical features, etiology, and outcomes of community- acquired pneumonia in patients with diabetes mellitus. Medicine (Baltimore). 2013;92(1):42-50.

47. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, Cooley LA, Dean NC, Fine MJ, Flanders SA, Griffin MR, Metersky ML, Musher DM, Restrepo MI, Whitney CG. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019;200(7):e45-e67.

47b. Yen FS, Wei JC, Shih YH, Hsu CC, Hwu CM. Metformin use and the risk of bacterial pneumonia in patients with type 2 diabetes. Sci Rep. 2022 Feb 28;12(1):3270

48. Dooley KE, Chaisson RE. Tuberculosis and diabetes mellitus: convergence of two epidemics. Lancet Infect Dis. 2009;9(12):737-46.

48b. David P, Singh S, Ankar R. A Comprehensive Overview of Skin Complications in Diabetes and Their Prevention. Cureus. 2023 May 13;15(5):e38961.

49. Suaya JA, Eisenberg DF, Fang C, Miller LG. Skin and soft tissue infections and associated complications among commercially insured patients aged 0-64 years with and without diabetes in the U.S. PLoS One. 2013;8(4):e60057.

50. Boulton AJM, Whitehouse RW. The Diabetic Foot. In: Feingold KR, Anawalt B, Boyce A, et al., eds. Endotext (Internet). South Dartmouth, MA; 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK409609/

50b. Oyebode OA, Jere SW, Houreld NN. Current Therapeutic Modalities for the Management of Chronic Diabetic Wounds of the Foot. J Diabetes Res. 2023 Feb 10;2023:1359537.

51. Stevens DL, Bisno AL, Chambers HF, Dellinger EP, Goldstein EJ, Gorbach SL, Hirschmann JV, Kaplan SL, Montoya JG, Wade JC; Infectious Diseases Society of America. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014;59(2):e10-52.

52. Cheng NC, Tai HC, Chang SC, Chang CH, Lai HS. Necrotizing fasciitis in patients with diabetes mellitus: clinical characteristics and risk factors for mortality. BMC Infect Dis. 2015;15:417.

53. Gürlek A, Firat C, Oztürk AE, Alaybeyoğlu N, Fariz A, Aslan S. Management of necrotizing fasciitis in diabetic patients. J Diabetes Complications. 2007;21(4):265-71.

54. Misiakos EP, Bagias G, Patapis P, Sotiropoulos D, Kanavidis P, Machairas A. Current concepts in the management of necrotizing fasciitis. Front Surg. 2014;1:36.

55. Fadini GP, Sarangdhar M, De Ponti F, et al Pharmacovigilance assessment of the association between Fournier's gangrene and other severe genital adverse events with SGLT-2 inhibitors BMJ Open Diabetes Research and Care 2019;7:e000725.

56. Bersoff-Matcha SJ, Chamberlain C, Cao C, Kortepeter C, Chong WH. Fournier Gangrene Associated With Sodium- Glucose Cotransporter-2 Inhibitors: A Review of Spontaneous Postmarketing Cases. Ann Intern Med. 2019;170(11):764-769.

57. Silverii GA, Dicembrini I, Monami M, Mannucci E. Fournier's gangrene and sodium-glucose co-transporter-2 inhibitors: A meta-analysis of randomized controlled trials. Diabetes Obes Metab. 2020;22(2):272-275.

58. Yang JY, Wang T, Pate V, Buse JB, Stürmer T. Real-world evidence on sodium-glucose cotransporter-2 inhibitor use and risk of Fournier's gangrene. BMJ Open Diabetes Res Care. 2020 Jan;8(1):e000985.'

58b. Venugopal S, Patel S, Wu Z. Improved Fournier's Gangrene Outcomes With Prior SGLT2i Or Metformin Usage. J Endocr Soc. 2023;7(Suppl 1):A388.

59. Borger MA, Rao V, Weisel RD, Ivanov J, Cohen G, Scully HE, David TE. Deep sternal wound infection: Risk factors and outcomes. Ann Thorac Surg 1998;65:1050-1056.

60. Furnary AP, Zerr KJ, Grunkemeier GL, Starr A. Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. Ann Thorac Surg 1999;67:352-360.

61. Kramer R, Groom R, Weldner D, Gallant P, Heyl B, Knapp R, Arnold A.. Glycemic control and reduction of deep sternal wound infection rates: A multidisciplinary approach. Arch Surg 2008;143:451-456.

62. Zerr KJ, Furnary AP, Grunkemeier GL, Bookin S, Kanhere V, Starr A. Glucose control lowers the risk of wound infection in diabetics after open heart operations. Ann Thorac Surg. 1997;63(2):356-61.

63. Hammerstad SS, Grock SF, Lee HJ, Hasham A, Sundaram N, Tomer Y. Diabetes and Hepatitis C: A Two-Way Association. Front Endocrinol (Lausanne). 2015;6:134.

64. Ito T, Shiraki K, Sekoguchi K. Metastatic gas gangrene of the leg due to acute emphysematous cholecystitis. Dig Dis Sci. 2001;46(11):2480-2483.

65. Safwan M, Penny SM. Emphysematous Cholecystitis: A Deadly Twist to a Common Disease. Journal of Diagnostic Medical Sonography. 2016;32(3):131-137.

66. Hirji I, Guo Z, Andersson SW, Hammar N, Gomez-Caminero A. Incidence of urinary tract infection among patients with type 2 diabetes in the UK General Practice Research Database (GPRD). J Diabetes Complications. 2012;26(6):513–516.

67. Nitzan O, Elias M, Chazan B, Saliba W. Urinary tract infections in patients with type 2 diabetes mellitus: review of prevalence, diagnosis, and management. Diabetes Metab Syndr Obes. 2015;8:129-36.

68. Gorter KJ, Hak E, Zuithoff NP, Hoepelman AI, Rutten GE. Risk of recurrent acute lower urinary tract infections and prescription pattern of antibiotics in women with and without diabetes in primary care. Fam Pract. 2010;27(4):379-85.

69. Kumar S, Ramachandran R, Mete U, Mittal T, Dutta P, Kumar V, Rathi M, Jha V, Gupta KL, Sakhuja V, Kohli HS. Acute pyelonephritis in diabetes mellitus: Single center experience. Indian J Nephrol. 2014;24(6):367-71.

70. Ronald A, Ludwig E. Urinary tract infections in adults with diabetes. Int J Antimicrob Agents. 2001;17(4):287-92.

70b. Dave CV, Schneeweiss S, Kim D, Fralick M, Tong A, Patorno E. Sodium-Glucose Cotransporter-2 Inhibitors and the Risk for Severe Urinary Tract Infections: A Population-Based Cohort Study. Ann Intern Med. 2019 Aug 20;171(4):248-256.

70c. Wilding J. SGLT2 inhibitors and urinary tract infections. Nat Rev Endocrinol. 2019 Dec;15(12):687-688.

71. Huang TT, Tseng FY, Liu TC, Hsu CJ, Chen YS. Deep neck infection in diabetic patients: comparison of clinical picture and outcomes with nondiabetic patients. Otolaryngol Head Neck Surg. 2005;132(6):943-7.

72. Handzel O, Halperin D. Necrotizing (malignant) external otitis. Am Fam Physician. 2003;68(2):309-12.

72b. Arsovic N, Radivojevic N, Jesic S, Babac S, Cvorovic L, Dudvarski Z. Malignant Otitis Externa: Causes for Various Treatment Responses. J Int Adv Otol. 2020 Apr;16(1):98-103.

73. Rodrigues CF, Rodrigues ME, Henriques M. Candida sp. Infections in Patients with Diabetes Mellitus. J Clin Med. 2019;8(1):76.

74. Mohammadi F, Javaheri MR, Nekoeian S, Dehghan P. Identification of Candida species in the oral cavity of diabetic patients. Curr Med Mycol. 2016;2(2):1-7.

75. Darwazeh AM, MacFarlane TW, McCuish A, Lamey PJ. Mixed salivary glucose levels and candidal carriage in patients with diabetes mellitus. J Oral Pathol Med. 1991; 20(6):280-3.

76. Cathcart S, Cantrell W, Elewski B. Onychomycosis and diabetes. J Eur Acad Dermatol Venereol. 2009;23(10):1119-22.

77. Thomas L, Tracy CR. Treatment of Fungal Urinary Tract Infection. Urol Clin North Am. 2015 Nov;42(4):473-83.

78. Nyirjesy P, Sobel JD. Genital mycotic infections in patients with diabetes. Postgrad Med. 2013 May;125(3):33-46.

79. Grandy S, Fox KM; SHIELD Study Group. Self-reported prevalence of vaginitis and balanitis among individuals with type 2 diabetes mellitus. Presented at: 70th Annual Scientific Sessions of the American Diabetes Association; June 25–29, 2010; Orlando, FL. Abstract 2369-PO.

80. Dave CV, Schneeweiss S, Patorno E. Comparative risk of genital infections associated with sodium-glucose co-transporter-2 inhibitors. Diabetes Obes Metab. 2019;21(2):434-438.

81. Williams SM, Ahmed SH. Improving compliance with SGLT2 inhibitors by reducing the risk of genital mycotic infections: the outcomes of personal hygiene advice. Diabetes. 2019;68(suppl 1):1224-P.

82. Liu J, Li L, Li S, Jia P, Deng K, Chen W, Sun X. Effects of SGLT2 inhibitors on UTIs and genital infections in type 2 diabetes mellitus: a systematic review and meta-analysis. Sci Rep. 2017;7(1):2824.

83. Fralick M, MacFadden DR. A hypothesis for why sodium glucose co-transporter 2 inhibitors have been found to cause genital infection, but not urinary tract infection. Diabetes Obes Metab. 2020 May;22(5):755-758.

84. Jeong W, Keighley C, Wolfe R, Lee WL, Slavin MA, Kong DCM, Chen SC. The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis of case reports. Clin Microbiol Infect. 2019;25(1):26-34.

85. Rammaert B, Lanternier F, Poirée S, Kania R, Lortholary O. Diabetes and mucormycosis: a complex interplay. Diabetes Metab. 2012;38(3):193-204.

86. Roden MM, Zaoutis TE, Buchanan WL, Knudsen TA, Sarkisova TA, Schaufele RL, Sein M, Sein T, Chiou CC, Chu JH, Kontoyiannis DP, Walsh TJ. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. Clin Infect Dis. 2005;41(5):634-53.

87. Jenks JD, Salzer HJ, Prattes J, Krause R, Buchheidt D, Hoenigl M. Spotlight on isavuconazole in the treatment of invasive aspergillosis and mucormycosis: design, development, and place in therapy. Drug Des Devel Ther. 2018;12:1033-1044.

88. Lim S, Bae JH, Kwon HS, Nauck MA. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. Nat Rev Endocrinol. 2021;17(1):11-30.

89. Gregory JM, Slaughter JC, Duffus SH, Smith TJ, LeStourgeon LM, Jaser SS, McCoy AB, Luther JM, Giovannetti ER, Boeder S, Pettus JH, Moore DJ. COVID-19 Severity Is Tripled in the Diabetes Community: A Prospective Analysis of the Pandemic's Impact in Type 1 and Type 2 Diabetes. Diabetes Care. 2021;44(2):526-532.

90. Holman N, Knighton P, Kar P, O'Keefe J, Curley M, Weaver A, Barron E, Bakhai C, Khunti K, Wareham NJ, Sattar N, Young B, Valabhji J. Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. Lancet Diabetes Endocrinol. 2020;8(10):823-833.

91. Dennis JM, Mateen BA, Sonabend R, et al. Type 2 Diabetes and COVID-19-Related Mortality in the Critical Care Setting: A National Cohort Study in England, March-July 2020. Diabetes Care. 2021;44(1):50-57.

92. Mor A, Dekkers OM, Nielsen JS, Beck-Nielsen H, Sørensen HT, Thomsen RW. Impact of Glycemic Control on Risk of Infections in Patients With Type 2 Diabetes: A Population-Based Cohort Study. Am J Epidemiol. 2017;186(2):227- 236.

93. Chang CH, Wang JL, Wu LC, Chuang LM, Lin HH. Diabetes, Glycemic Control, and Risk of Infection Morbidity and Mortality: A Cohort Study. Open Forum Infect Dis. 2019;6(10):ofz358.

94. McGovern AP, Hine J, de Lusignan S. Infection risk in elderly people with reduced glycaemic control. Lancet Diabetes Endocrinol. 2016;4(4):303-4.

95. van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in critically ill patients. N Engl J Med. 2001;345(19):1359-67.

96. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, Bellomo R, Cook D, Dodek P, Henderson WR, Hébert PC, Heritier S, Heyland DK, McArthur C, McDonald E, Mitchell I, Myburgh JA, Norton R, Potter J, Robinson BG, Ronco JJ. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360(13):1283-97.

97. Hruska LA, Smith JM, Hendy MP, Fritz VL, McAdams S. Continuous insulin infusion reduces infectious complications in diabetics following coronary surgery. J Card Surg. 2005;20(5):403-7.

98. The NICE-SUGAR Study Investigators. Hypoglycemia and risk of death in critically ill patients. N Engl J Med. 2012;367:1108.

99. Tsai S, Clemente-Casares X, Zhou AC, Lei H, Ahn JJ, Chan YT, Choi O, Luck H, Woo M, Dunn SE, Engleman EG, Watts TH, Winer S, Winer DA. Insulin Receptor-Mediated Stimulation Boosts T Cell Immunity during Inflammation and Infection. Cell Metab. 2018;28(6):922-934.

100. Eikawa S, Nishida M, Mizukami S, Yamazaki C, Nakayama E, Udono H. Immune-mediated antitumor effect by type 2 diabetes drug, metformin. Proc Natl Acad Sci USA. 2015;112(6):1809-14.

101. Pearce EL, Walsh MC, Cejas PJ, Harms GM, Shen H, Wang LS, Jones RG, Choi Y. Enhancing CD8 T-cell memory by modulating fatty acid metabolism. Nature. 2009;460(7251):103-7.

102. Bonnet F, Scheen AJ. Effects of SGLT2 inhibitors on systemic and tissue low-grade inflammation: The potential contribution to diabetes complications and cardiovascular disease. Diabetes Metab. 2018 Dec;44(6):457-464.

103. Croasdell A, Duffney PF, Kim N, Lacy SH, Sime PJ, Phipps RP. PPARγ and the Innate Immune System Mediate the Resolution of Inflammation. PPAR Res. 2015;2015:549691.

104. Lee YS, Jun HS. Anti-Inflammatory Effects of GLP-1-Based Therapies beyond Glucose Control. Mediators Inflamm. 2016;2016:3094642.

105. Yonem A, Cakir B, Guler S, Azal OO, Corakci A. Effects of granulocyte-colony stimulating factor in the treatment of diabetic foot infection. Diabetes Obes Metab 2001;3:332– 337.

106. Cruciani M, Lipsky BA, Mengoli C, de Lalla F. Are granulocyte colony-stimulating factors beneficial in treating diabetic foot infections?: A meta-analysis. Diabetes Care. 2005;28(2):454-60.

107. Nieman DC, Wentz LM. The compelling link between physical activity and the body's defense system. J Sport Health Sci. 2019;8(3):201-217.

108. Crespilho DM, de Almeida Leme JA, de Mello MA, Luciano E. Effects of physical training on the immune system in diabetic rats. Int J Diabetes Dev Ctries. 2010;30(1):33-7.