MINI-REVIEW

Diabetes-associated infections: development of antimicrobial resistance and possible treatment strategies

Muhammad Sajid Hamid Akash[1] · Kanwal Rehman[2] · Fareeha Fiayyaz[1,3] · Shakila Sabir[1,4] · Mohsin Khurshid[3]

Abstract

Diabetes mellitus is associated with various types of infections notably skin, mucous membrane, soft tissue, urinary tract, respiratory tract and surgical and/or hospital-associated infections. The reason behind this frequent association with infections is an immunocompromised state of diabetic patient because uncontrolled hyperglycemia impairs overall immunity of diabetic patient via involvement of various mechanistic pathways that lead to the diabetic patient as immunocompromised. There are specific microbes that are associated with each type of infection and their presence indicates specific type of infections. For instance, *E. coli* and *Klebsiella* are the most common causative pathogens responsible for the development of urinary tract infections. Diabetic-foot infections commonly occur in diabetic patients. In this article, we have mainly focused on the association of diabetes mellitus with various types of bacterial infections and the pattern of resistance against antimicrobial agents that are frequently used for the treatment of diabetes-associated infections. Moreover, we have also summarized the possible treatment strategies against diabetes-associated infections.

Keywords Diabetic-foot infections · Diabetes-associated surgical site infections · Antimicrobial resistance

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder and one of the major causes of morbidity globally (Matusda and De Fronzo 1999). It is estimated that risk of DM will be greatly increased in the future. Between 1990 and 2010, the incidence of DM nearly tripled with 1.9 million new cases diagnosed in 2010 in USA (Yu et al. 2014). According to the World Health Organization, America, Bangladesh, India, Italy, Brazil, Russia, Pakistan, China, Japan and Indonesia, are the top ten countries with highest number of diabetic patients (Noor et al. 2015). T2DM is a heterogeneous group of disorders characterized by impaired insulin secretion, variable degrees of insulin resistance, and increased glucose production which is more common and mainly known disease of the elderly age. In adults, there is increased chance of early-onset of DM especially in industrialized countries. In 2011, the incidence of DM in people older than 65 years was 26.9% in USA and 11.3% in people older than 20 years (Apelqvist et al. 2000).

DM is a known risk factor for certain infectious diseases because diabetic individuals are in an immunocompromised due to their uncontrolled diabetes mellitus notably hyperglycemia (Shah and Hux 2003; Muller et al. 2005). Due to which there is a higher risk of number of other medical complications including eye problems and blindness, cardiovascular disease, lower extremity amputations and renal disease in diabetic individuals as compared to that in non-diabetic individuals. Among the various causative factors, hyperglycemia is one of the main culprits to impair the overall immunity of diabetic patient via involvement of various mechanistic pathways. Immunocompromised state is invariable in all diabetic patients. Not all diabetic patients are

✉ Muhammad Sajid Hamid Akash
  sajidakash@gmail.com

✉ Kanwal Rehman
  kanwalakash@gmail.com

1 Department of Pharmaceutical Chemistry, Government College University, Faisalabad, Pakistan

2 Department of Pharmacy, University of Agriculture, Faisalabad, Pakistan

3 Department of Microbiology, Government College University, Faisalabad, Pakistan

4 Department of Pharmacology, Government College University, Faisalabad, Pakistan

immune-compromised except those patients having uncontrolled diabetes are considered immunocompromised due to negative effects of hyperglycemic environment that favors immune dysfunction such as damage to neutrophil function, impairment of antioxidant system and humoral immunity as shown in Fig. 1 (Casqueiro et al. 2012a; Calliari et al. 2019). High blood glucose impairs both innate and adaptive immunity through various mechanisms. Chronic hyperglycemia in diabetic patients can result in acidosis, which reduces the activity of immune system. Upon treatment of acidosis and hyperglycemia, the effects can be reversible (Casqueiro et al. 2012b). Immune-compression is a heterogeneous group of diseases affecting various components of the immune system. The immune-compromised states can lead to different disorders that results in impairment of human immune system including human immunodeficiency virus infection, primary immune deficiency, and immunosuppression-related medical treatment, such as high-dose corticosteroid uses or transplantation therapy. Among these, human immunodeficiency virus infections are the most notorious. Clinical complications in immune-compromised patients vary from severe infections to unusual malignancies affecting major organs (Zheng and Zhang 2014).

In this article, we have summarized the findings of studies related to the association of DM with infectious diseases and risk of infection that is more common in diabetic patients. We have also focused that how antimicrobial resistance is developed during infection against antibiotics given to the diabetic patient. Furthermore, we have also provided the possible treatment strategies against DM-associated infections.

Urinary tract infections in diabetic conditions

Diabetic patients are at increased risk of infectious diseases and most important and frequent site of infection is urinary tract (Patterson and Andriole 1997; Joshi et al. 1999; Shah and Hux 2003; Boyko et al. 2005). In general population, one of the most common bacterial infection is urinary tract infections with an overall estimated rate of incidence of 17.5/1000 person in a year (Laupland et al. 2007). In American study conducted on a health service data base with more than 70,000 patients with type 2 diabetes, it has been found that 8.2% were diagnosed with urinary tract infection during 1 year with incidence increasing with age (Yu et al. 2014). In another database study, it was also found that urinary tract infections were more common in diabetic patients as compared to that of non-diabetic patients among 89,790 matched pairs of patients with and without type 2 diabetes mellitus (Fu et al. 2014). Patients with DM are at increased risk of developing acute pyelonephritis, asymptomatic bacteriuria and other complications of urinary tract infections. For the development of symptomatic urinary tract infections and asymptomatic bacteriuria, the most common causative agents are *K. pneumoniae* and *E. coli* (Ribera et al. 2006). It has been warned that urinary tract infections would be positioned among the top ten concurrent or complicating illnesses during the lifetime course for the management of DM (Wheat 1980). It has been reported that up to 50% of women had at least one urinary tract infection during
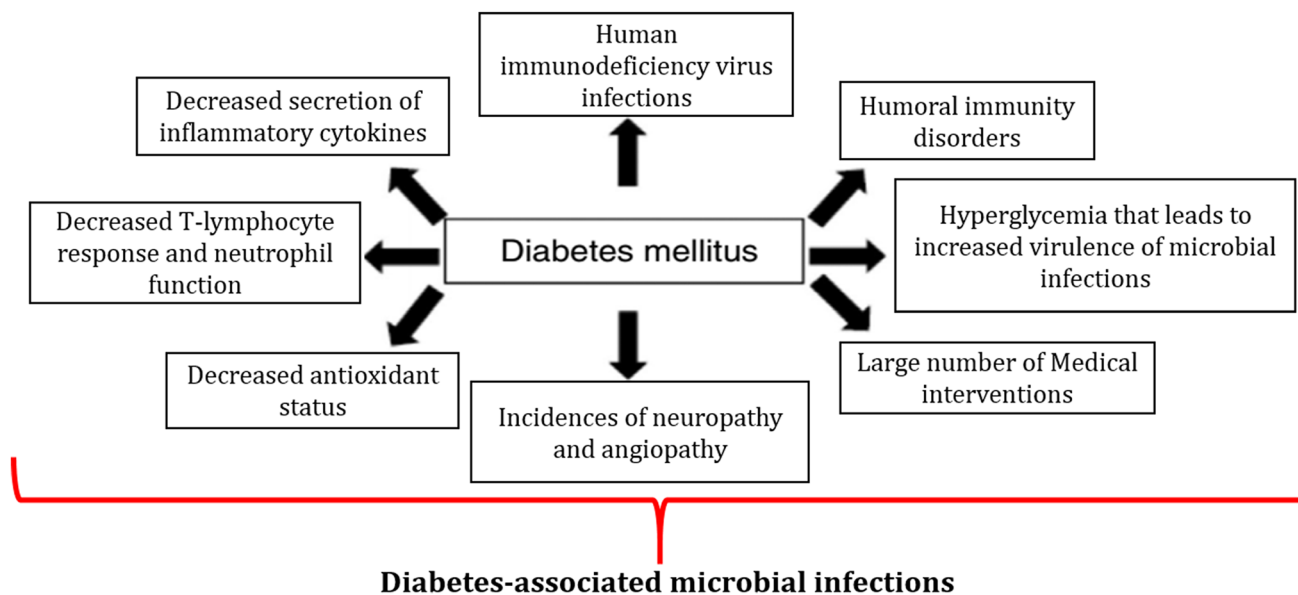

Fig. 1 Schematic representation of pathogenesis of diabetes-associated infections. Adapted from (Casqueiro et al. 2012a; Calliari et al. 2019)

their period of life (Barnett and Stephens 1997). More severe manifestations of urinary tract infections seemed to be associated with T2DM. A 12-month prospective cohort study proved that like T2DM, patients with T1DM are also at higher risk of urinary tract infections, lower respiratory tract infection as well as skin and soft tissues infections, indicating increased risks of common infections in both type 1 and type 2 diabetes (Muller et al. 2005). Similar to T2DM, T1DM is also mainly engaged with impairment in innate and adaptive immune system, ultimately leading towards increased risk of infections. Several evidences have suggested that hyperglycemia is the promoting factor for bacterial infections, also leading towards increased consumption of antibiotics. Additionally, these infections may lead to kidney injury either by direct invasion of pathogen or endotoxin, causing further complications (Simonsen et al. 2015). Asymptomatic bacteriuria to lower urinary tract infections, pyelonephritis, and severe urosepsis are the spectrum of urinary tract infections in patients suffering from DM. Emphysematous cystitis and pyelonephritis, renal abscesses and renal papillary necrosis are serious complications occurring in urinary tract infections. All these complications are frequently found in T2DM as compared to general population (Kofteridis et al. 2009; Mnif et al. 2013). In one study, the probability of hospital-acquired acute pyelonephritis was estimated to increase in case of DM by 20 to 30-fold in patients with less than 44 years of age, while, in patients over the age of 44 years, probability was 3–5-fold (Nicolle et al. 1996). Incidence of bilateral kidney infection also found to be increased in patients with DM (Hakeem et al. 2009). Additionally, there are more chances of bacteremia in diabetic patients owing urinary tract infections in comparison to non-diabetic individuals (Carton et al. 1992).

Several factors are associated with increased risk of urinary tract infections in diabetic patients includes, long term complications, metabolic control, age, primarily diabetic cystopathy and nephropathy (Brown et al. 2005). 22 observational studies (5 follow-up and 16 cross-sectional studies)

published between 1966 and 2007 have reported that there is risk of asymptomatic bacteriuria in diabetic patients. Meta-analysis revealed that the chances of asymptomatic bacteriuria was found in 12.2% diabetic patients which was less likely to occur in 4.5% of patients that were taken from the healthy control group. In both women and men, prevalence of asymptomatic bacteriuria was higher either with DM or compared with healthy controls (Raz 2003). Recently, a study conducted on health service database with more than 70,000 patients with T2DM, has found that 8.2% were diagnosed with urinary tract infections during 1 year (Yu et al. 2014). In this study, it was also found that urinary tract infections were more common in men and women with DM than in those individuals without DM.

Bacteriology of urinary tract infections in diabetic conditions

Bacteria that are more likely to involve in urinary tract infections are found to be similar in both the individuals with and without DM but also elicits complicated urinary tract infections (Nicolle 2001). In diabetic patients, identified bacteria, i.e., *Enterococcus* spp. (4%), *Staphylococcus* spp. (5%), *Klebsiella* spp. (6%), and *E. coli* (71%). *Enterococcus* spp. were more commonly found than *Klebsiella* spp. and *Staphylococcus* spp. in patients without DM. Rates of other species such as *Proteus* spp., *Pseudomonas* spp. and other bacteria such as *Streptococcus B* were found close in both groups of individuals (Table 1) (Malmartel and Ghasarossian 2016). As *E. coli* causes majority of infections in uncomplicated urinary tract infections. However, in these patients, other strains are also cultured frequently. For example, one study reported that 47% of urinary tract infections in diabetic patients and 68% chance of urinary tract infections in non-diabetic patients was due to more common uropathogen named as *E. coli* (Lye et al. 1992). Uropathogen other than *E. coli* also found in diabetic individuals, include *Enterococcus faecalis*, *Proteus* spp., *Klebsiella* spp., *Enterobacter* spp., and Group B *Streptococci* (Cook et al.

Table 1 Bacteria responsible for urinary tract infection in patients with and without diabetes mellitus after matching. Adopted from (Malmartel and Ghasarossian 2016)

Bacteria	Patients with diabetes $N=124$ (%)	Patients without diabetes $N=246$ (%)	*P* value	Patients with uncontrolled diabetes $N=100$ (%)	Patients with controlled diabetes $N=24$ (%)	*P* value
Escherichia coli	88 (71)	169 (69)	0.74	72 (72)	16 (67)	0.79
Enterococcus spp.	5 (4)	25 (10)	0.07	5 (5)	0	–
Klebsiella spp.	8 (6)	11 (4)	0.57	5 (5)	3 (13)	0.17
Proteus spp.	3 (2)	10 (4)	0.56	3 (3)	0	–
Staphylococcus spp.	6 (5)	6 (2)	0.23	4 (4)	2 (8)	0.3
Pseudomonas spp.	1 (1)	11 (4)	0.07	1 (1)	0	–
Other bacteria	13 (10)	14 (6)	0.14	10 (10)	3 (13)	0.7

1989; Zhanel et al. 1990b, 1995). Some studies have also noted that patients with DM are at greater chance of getting infection from a resistant uropathogen (Johnson and Stamm 1989; Lye et al. 1992).

Antimicrobial resistance in urinary tract infections in diabetic conditions

It has been observed that isolated strains of *E. coli* show similar rates of resistance against nitrofurantoin, ciprofloxacin, ampicillin and co-trimoxazole in both diabetic and nondiabetic patients. An association has been found between the presence of co-trimoxazole resistance and DM due to recent hospitalization and use of the same drug (Wright et al. 1999) but no correlation has been reported between *E. coli* resistance against co-trimoxazole or quinolones and DM in out-patients (Steinke et al. 1999; Meiland et al. 2004).

Treatment strategies for urinary tract infections in diabetic conditions

Antimicrobial treatment

Regarding the outcomes of treatment strategies for asymptomatic bacteriuria in patients with DM, few clinical trials have been conducted (Forland et al. 1977; Forland and Thomas 1985). The results of these clinical trials indicate that (1) 2 weeks and 6 weeks of treatment have same effectiveness; (2) the rate of recurrence of urinary tract infection was high, even after following antibiotic treatment for longer duration; (3) mostly re-infections were recurrent (4/8 weeks post-therapy) and these reversions were not with same microorganism. Among bacteriuric women with DM, physician should have awareness about high prevalence of underlying structural genitourinary abnormalities (Forland and Thomas 1985). If asymptomatic bacteriuria leads to serious complications as functional deterioration of kidney then there is need for screening of asymptomatic bacteriuria in diabetic female (Nicolle 2000). Since due to unavailability of such evidences (Schmaldienst et al. 2002) but not including all (Zhanel et al. 1990a; Patterson and Andriole 1997) believe that there is no justified treatment for asymptomatic bacteriuria. A randomized controlled trial has been conducted in which 108 diabetic women with asymptomatic bacteriuria diagnosed by two urine cultures showing ≥ 105 colony forming units of an organism per milliliter were randomized to receive a 3 or 14-day course of either co-trimoxazole or placebo (Harding et al. 2002). Patients in group of antibiotic treatment who were infected with resistant microorganism was provided with ciprofloxacin but this study was discontinued due to the occurrence of early relapses in first six patients that were prescribed to an antibiotic regimen of 3-day. Screening of all patients were

done after every three months for the detection of bacteriuria. Further suppressive antimicrobial therapy was provided to women confirmed as bacteriuric that were assigned to group of antibiotic therapy. When compared with 20% of women who received antibiotics, only 78% of placebo recipients showed bacteriuria following 4 weeks at the end of initial course of therapy. 23 out of 55 women (42%) in antimicrobial-therapy group and 20 out of 50 women (40%) in the placebo group had at least one episode of symptomatic urinary tract infections during mean follow-up of 27 months. In placebo and antimicrobial-therapy group, the time to first symptomatic episode was similar as were the rates of hospitalization for urinary tract infections and any symptomatic urinary tract infections which exhibited that treatment of asymptomatic bacteriuria in diabetic women fails to decrease the risk of complications. For the screening and/or treatment of asymptomatic bacteriuria, DM itself should not be considered as an indication (Harding et al. 2002). Infectious Diseases Society of America recommends a 3-day course with co-trimoxazole as standard therapy for uncomplicated acute phase of bacterial cystitis. Alternative treatment can be used in which diabetic patient can be prescribed fluoroquinolone or trimethoprim alone. Other fluoroquinolones also show similar rate of effectiveness but these should only be used as alternative treatment in communities with higher resistance to co-trimoxazole (Warren et al. 1999). For the treatment of complicated lower urinary tract infections, the efficacy of 5-day ofloxacin treatment was compared with 10-day regimen that was performed by double-blind study (Hoepelman et al. 2003). 416 women were included in this study with no confirmed information that how many of them have DM. The authors concluded that both treatments have similar effectiveness (Hoepelman et al. 2003). Another randomized double-blind study which recruited 85 (20%) women with DM, concluded that 7-day treatment with ciprofloxacin or with ofloxacin resulted in cure rate of 90% and 87%, respectively (Raz et al. 2000). Cefixime, a third-generation cephalosporin is well absorbed when taken orally and has plasma half-life of 3–4 h, elicits better efficiency against urinary tract infections (Chaudhary et al. 2015). But unfortunately, resistance against cefixime is increased in diabetic patients, suggesting amendments in treatment strategies for urinary tract infections in diabetic patients (Malmartel and Ghasarossian 2016).

Preventive measures

The need for additional non-antimicrobial strategies is due to increasing problem of resistant uropathogens (Gupta et al. 1999). General advice comprises sufficient intake of fluid, minimum spermicides use, during voiding make sure that the bladder is completely emptied and restrictive use of catheter. Ingestion of cranberry juice is an interesting

possible preventive measure. At first, it was thought that cranberry juice had beneficial role in the acidification of urine. Recently, it has been recognized that cranberry juice inhibit the adherence of bacteria to the uroepithelial cells and considered as one of most important preventive measure (Raz et al. 2004). Oral or vaginal administration of *Lactobacilli* is another possible preventive strategy to control urinary tract infections in diabetic conditions. They are thought to protect against urinary tract infections by competitive exclusion of uropathogens and are the part of commensal vaginal flora (Boris et al. 1998). The recurrence of urinary tract infections in women with *E. coli* infection is reduced by a regular drinking of cranberry juice but not of *Lactobacillus GG* drink (Kontiokari et al. 2001). The recurrence rate of urinary tract infections in postmenopausal women is reduced by the estrogen administration especially if administered vaginally (Hextall 2000). An essential step in the pathogenesis of urinary tract infections is adherence of *E. coli* to uroepithelial cell. Preventive measures would lead to decreased incidence of urinary tract infections. Recently, attention has been diverged towards the vaccine development. This vaccine is based on type 1 fimbriae of *E. coli*. It has been observed that this vaccine is helpful in decreasing the incidence of urinary tract infections through the inhibition of *E. coli* attachment to uroepithelial cells in monkeys to whom vaccine were provided (Langermann et al. 1997, 2000). It is also demonstrated that decrease in the adherence of type-1 fimbriated *E. coli* to diabetic uroepithelial cells by addition of vaccine-induced antiserum to uroepithelial cells was occurred that was isolated from diabetic women (Meiland et al. 2001). Although, this vaccine is safe but it proved to be only 30% effective in young sexually active women, so further clinical studies have been stopped. Bacterial vaginosis, mainly responsible for vaginal discharge in women of reproductive age, also engaged with high recurrence rate. Probiotics are helpful for preventing recurrences of bacterial vaginosis (Parma et al. 2014). Generally, normal vaginal microbiota is dominated by *lactobacilli*, and strong evidence has suggested negative association between bacterial vaginosis and presence of *lactobacilli*. Although, some conflicting studies are still present. Yet, most studies have suggested positive outcomes upon supplementation with probiotics (Falagas et al. 2007).

Skin and soft tissue infections in diabetic conditions

In diabetic individuals, skin and soft tissue infections are leading causes of morbidity and occasionally mortality (DiNubile and Lipsky 2004; Kao et al. 2005; Homer-Vannia-sinkam 2007; Sendi et al. 2008). At all anatomic sites, these infections can occur but the most common site is foot and

it is frequently affected in diabetic patients (Frykberg et al. 2006). Annually, about 111,000 diabetic persons suffering from foot infections are hospitalized in America. It contributes to nearly 60% of total lower extremity amputations (Lipsky 2004). Both in ambulatory and hospitalized patients, *S. aureus* is most common pathogen that is present in skin and soft tissues infections (Kirby et al. 2002; Liu et al. 2008; Odell 2010). It is estimated that lifetime risk of developing a foot ulcer is up to 25% in patients with DM (Singh et al. 2005). Approximately 3% incidences of diabetic-foot ulcers are reported annually while, in America and United Kingdom, the reported incidences of diabetic-foot ulcers are as high as 10% (Reiber et al. 1999). Once after the development of foot ulcer, risk of wound progression increases that may finally lead towards amputation. The risk of diabetic ulceration is up to 85% of the cases that leads to amputation (Reiber et al. 1999).

For the development of diabetic-foot infections, there are several factors that influence the diabetic patients. These factors include immunopathy, neuropathy and vasculopathy. Peripheral neuropathy is considered the most prominent risk factor that occur early in the pathogenesis of diabetic foot infections and also diabetic foot ulcers (Clayton and Elasy 2009). Neuropathy results in diabetic foot ulcers that is more than 60% (Dyck et al. 1999; Bowering 2001). In diabetic patients, neuropathy is established in sensory, motor and autonomic parts of the nervous system (Bowering 2001). An imbalance between flexion and extension of the affected foot occur as a result of impairment in the innervations of intrinsic muscles of the foot. Abnormal bony prominences and pressure points is due to the abnormalities of anatomic foot that will gradually lead towards ulceration and skin breakdown. A reduction in functionality of sweat and oil gland is due to autonomic neuropathy. So, natural ability of foot to moisturize the overlying skin is lost and skin becomes dry. It also becomes more susceptible to tears and it will subsequently lead towards the development of infection. The loss of sensation impairs the development of ulcerations. Patients are often unable to detect their lower extremities as trauma occurs at the affected site. Many wounds go unnoticed because of this and gradually become worst.

Microbiology of skin and soft tissue infections in diabetic conditions

The skin and mucous membranes of diabetic patients have certain common bacterial and fungal pathogens, such as *Candida albicans* and *S. aureus*. Pathogenic bacteria that may predispose susceptible patient to lower extremity infection is found to colonize in diabetic foot ulcerations. According to a study of 84 randomly selected hospitalized patients with severe diabetic foot infections, 83% of cultures demonstrated that existence of polymicrobial flora with an

average of 2.8 species per specimen and ratio of aerobic to anaerobic bacteria is 3:1 (Hobizal and Wukich 2012). *Staphylococcus epidermidis*, *S. aureus*, and *Streptococcus* species were the most frequently isolated organisms. *Peptostreptococcus magnus* and *Bacteroides fragilis* were observed among anaerobes (Calhoun et al. 2002). In various studies, it is found that the most common organisms were aerobic gram-positive cocci isolated from the wounds of diabetic patients, especially diabetic foot infections. *Staphylococcus aureus*, *Enterococcus*, facultative gram-negative bacilli, and group B streptococci are most commonly identified pathogens in the cultures of limb-threatening infections.

Treatment strategies for skin and soft tissue infections in diabetic conditions

Preventive measures

For the treatment of diabetic foot infections, there is a formulated guidelines and key recommendations provided by infectious diseases society of America. According to these guidelines, it is stated that an empirical treatment of antimicrobial agents should be applied on the basis of likely pathologic agents and infection severity (Lipsky et al. 2006). Antimicrobial agent is more active against gram-positive cocci with special attention for methicillin-resistant *Staphylococcus aureus* which are included in the antibiotic treatment. Extended coverage for gram-negative *bacilli* and enterococcus species included in the previously treated or severe diabetic foot infections. Anti-anaerobic therapy is required for foul smelling and gangrenous wounds. In the selection of treatment program as well as concerned side effects of potential drug, bioavailability, pharmacokinetics, route of administration and frequency are all important factors and have their role in the cost of therapy (McKinnon et al. 1997). It has been reported that patients treated with ertapenem have clinical and microbiological outcomes that were equivalent to those treated with piperacillin/tazobactam (Singh et al. 2005). This study recommends that dose of ertapenem that is given once a daily is beneficial in setting of diabetic foot infections, although the fact about the ertapenem is unable to provide protection from most of *P. aeruginosa* or *enterococci*. It also indicates that in polymicrobial diabetic foot infections, these organisms may only be contaminants. Based upon clinical studies, the duration of antibiotic therapy that is considered an optimal duration has yet to be properly defined. In general, treatment of mild and severe diabetic foot infections started from 2–4 weeks of antibiotic therapy and route of administration is intravenous and another is started from 4–6 weeks of antibiotic therapy. Another way for the control of moderate to severe diabetic foot infection, is the surgical management and it includes drainage, debridement of non-viable soft tissue and bone

and aggressive incision. Modern approach is to use adjunctive therapies which include application of negative pressure wound therapy, hyperbaric oxygen treatment and use of antibiotic impregnated beads (Armstrong and Lavery 2005; Krause et al. 2009; Chen et al. 2010). The role of antibiotics remains unclear for the treatment of foot ulcers in patients with DM (Lipsky et al. 2004). However, a high priority for the management of infected diabetic foot as part of multidisciplinary care (Reiber and Raugi 2005) is revascularization (van Baal 2004). The roles of adjunctive therapies are yet to be established (Cavanagh et al. 2005).

Treatment strategies

It is recommended that regular foot inspection and adequate footwear are important measures that should be taken by diabetic patients to control diabetic foot infections (Robson et al. 1998; Boulton et al. 1999; Foot 2007). However, the majority of diabetic patients do not care their feet and or regular inspections of their feet (Uccioli et al. 1995; Robson et al. 1998; Boulton et al. 1999). These studies indicate that strategies including regular inspection and examination of feet and footwear, identification of high risk patient, education of patient, family and health care staff, use of appropriate footwear, and treatment of nonulcerative pathology can increase the awareness of the problem and aptitude for self-management and ability to decrease the incidence of minor foot lesions. Several studies have reported that combination of chiropodist care and other strategies reduce the prevalence of non-ulcer pathology (Litzelman et al. 1993, 1997; Rönnemaa et al. 1997). Proper treatment of callosities, cracked skin, dry skin and nail deformities is essential and specific skills are required (Boulton et al. 1999). A study conducted in Sweden has found that only a few chiropodists had a close cooperation with the health care system, and only 14–22% had any kind of education with regard to diabetic foot (Apelqvist et al. 2000). In a cross-sectional population-based study, 80% of diabetic individuals older than 25 years claimed to have access to chiropodist (Gottrup 2004). A number of studies have shown that such footwear, when available and used, can prevent re-ulceration in patients with previous foot ulcers (Edmonds et al. 1986; Chantelau et al. 1990; Breuer 1994; Chantelau and Haage 1994; Mueller 1997).

Respiratory tract infections in diabetic conditions

Increased hospitalizations in diabetic individuals as compared to those without diabetes are the most important cause of respiratory tract infections. Bacterial, fungal and viral are the most common etiological factors in diabetic patients

(Kornum et al. 2007; Peleg et al. 2007; Casqueiro et al. 2012a). Lung inflammation that occurs in about 48 h after admission of patient in hospital is hospital-acquired pneumonia. Hospital-acquired pneumonia is a group of diseases that refers to pneumonia infections and linked with mechanical lung ventilation. It is an inflammation that occurs at about 48–72 h of ventilation in patients, as well as pneumonia that makes an association with exposure to pathogens associated with health care. The incidence is estimated to be 5–15 cases per 1000 hospitalizations in European countries with estimated rate of mortality of 30–50% (Fleming et al. 1991). However, the percentage of diabetic patients hospitalized with community-acquired pneumonia was < 5% which is similar to the frequency of diabetes in several communities (Woodhead et al. 1987). Similarly, in another study, a higher mortality was observed among diabetic patients in a meta-analysis of 33,000 patients with community-acquired pneumonia (Fine et al. 1996). In diabetic individuals, the main reason for pneumococcal pneumonia is bacteremia (Watanakunakorn and Bailey 1997; Kalin et al. 2000) but the death rate with pneumococcal pneumonia in diabetic condition was found to be similar to that of pneumococcal pneumonia in non-diabetic patients (Thomsen et al. 2004). However, during influenza epidemics, the adverse effect of DM on the rate of morbidity and mortality has long been identified (Barker and Mullooly 1982). During influenza epidemics, the risk of hospitalization is sixfold higher in diabetic patients than that non-diabetic individuals (Diepersloot et al. 1987) but the high prevalence of co-morbid conditions, such as cardiac failure and metabolic compromise are also important (Finelli et al. 2008). The mortality rate of diabetic patients with pulmonary tuberculosis approaches to 50% (Casqueiro et al. 2012a). The increased susceptibility to tuberculosis in diabetic patients may be due to the impairment of immune functions (Restrepo and Schlesinger 2013). Pulmonary tuberculosis still poses a potential threat to diabetic individuals. According to an investigation done by a Japanese study that over 6-year period, 13.2% patients hospitalized with tuberculosis were identified with DM (Yamagishi et al. 1996).

Bacteriology of respiratory tract infections in diabetic conditions

The type of organisms that are responsible for community-acquired pneumonia in diabetic patients vary from that of non-diabetic individuals, with an increased prevalence of Gram-negative bacteria such as *K. pneumoniae* and *S. aureus* [81]. Most important causative organism that are responsible for the occurrence of respiratory tract infections -associated with DM are *S. pneumoniae* and influenza virus (Arancibia et al. 2014). It has been expected that in diabetic patients, the cases of fungal infections that are caused by Mucorales are 50–75% while predisposing factor is acidosis. For onychomycosis in diabetic patients, the second responsible microorganism is Aspergillus (Jones 2010). It has been found that during the first four days of hospitalization, the most common bacteria causing hospital-acquired pneumonia are *S. pneumoniae*, *Enterobacter*, *K. pneumoniae*, *Serratia*, *E. coli*, *S. aureus* (methicillin-susceptible), *Proteus* and *Haemophilus influenzae* (Zhang et al. 2014; Klekotka et al. 2015). The predominance of bacteria from the 5th day of hospitalization include *Acinetobacter* spp., *Staphylococcus aureus* (methicillin-resistant MRSA), *E. coli*, *L. pneumophila*, *Pseudomonas aeruginosa*, and *K. pneumoniae* (Klekotka et al. 2015). In European countries and America, *S. aureus* is most commonly isolated bacteria associated with hospital-acquired pneumonia (Jones 2010b).

Antimicrobial resistance in respiratory tract infections in diabetic conditions

Klebsiella pneumoniae showed resistance to fosfomycin (26.7% vs 37.6%) and sulfamethoxazole (22.7% vs 32.5%) in pneumonia among diabetic patients. In intensive care unit, resistance rates of *K. pneumoniae* have been reported to be significantly lower in diabetic patients than that in non-diabetic individuals against fosfomycin (42.6% vs 62.6%) aztreonam (53.4% vs 69.5%), tobramycin (42.5% vs 61.0%), meropenem (37.7% vs 59.8%), amikacin (37.8% vs 52.8%) and cefotetan (45.2% vs 63.2%). Only sulfamethoxazole

Table 2 Pooled estimates of association of diabetes mellitus with surgical site infections. Adopted from (Martin et al. 2016)

Surgery type	No. of studies	Pooled estimate	95% prediction interval	I^2 or %
Gynecological	6	1.61	1.15–2.24	4.0
Colorectal	7	1.16	0.93–1.44	9.5
Arthroplasty	6	1.26	1.01–1.66	11.7
Breast	5	1.58	0.91–2.72	2.7
Cardiac	15	2.03	1.13–4.05	22.4
Spinal	14	1.66	1.10–2.32	8.1
Other/Multiple surgery types combined	37	1.46	1.07–2.00	41.5

Table 3 Treatment strategies of common microbial infections in diabetic conditions. Adapted from (Peleg et al. [2007])

Type of infections	Organisms	Empirical antimicrobial treatment[a]		Other treatment
		First line	Alternative	
Skin and soft tissue[b]				
Cellulitis	S. aureus, S. pyogenes, less common gram-negative aerobes and anaerobes	Nafcillin/flu/dicloxacillin/1–2 g/IV 4–6 h	Cephazolin 1 g IV 8 h or clindamycin 600 mg IV 8 h or 300–450 mg PO 8 h or vancomycin 1 g IV 12 h	N/A
Diabetic foot infection	S. aureus, S. pyogenes, gram-negative aerobes including Pseudomonas aeruginosa, anaerobes. often polymicrobial	**Mild–moderate** Usually an oral regimen to cover gram + ve and common gram-negative organisms, e.g., Amoxicillin-clavulanate 875/125 mg PO 12 h or ampicillin/sulbactam 3 g IV 6 h **Severe** Ticarcillin-clavulanate 3.0–0.1 g IV 6 h or Piperacillin-tazobactam 3.375 g IV 8 h or Mero/imipenem-cilastatin 500 mg–g 8/6 h	**Mild–moderate** Cephalexin 500 mg PO 6 h plus metronidazole 400 mg PO 8–12 h, broad-spectrum fluoroquinolone, or ciprofloxacin 500 mg PO 12 h plus Clindamycin 600 mg IV 8 h or 300–450 mg PO 8 h **Severe** Ciprofloxacin 750 mg orally 12 h plus clindamycin 600 mg IV 8 h or lincomycin 600 mg IV 8 h. Add vancomycin 1 g IV 12 h if MRSA isolated	Surgical review, assess requirement for revascularization, wound debridement, avoidance of pressure-induced ischaemia with orthotic devices N/A
Necrotizing fasciitis	S. pyogenes or Clostridium spp. or polymicrobial	Meropenem 1 g IV 8 h plus clindamycin 600 mg IV 8 h or lincomycin 600 mg IV 8 h	Ampicillin-sulbactam 1.5–3 g 6–8 h or piperacillin-tazobactam 3.375 g 6–8 h, plus ciprofloxacin400 mg IV 12 h plus clindamycin 600–900 mg IV 8 h	Surgical removal of devitalized tissue is the basis of treatment
Community acquired pneumoniae	S. pneumoniae, M. pneumoniae, C. pneumoniae, Legionella spp., H. influenzae, S. aureus, K. pneumoniae, M. tuberculosis	**Mild** An advanced macrolide[d] or amoxycillin 1 g PO 8 h plus doxycycline 200 mg PO for first dose and then 100 mg PO daily **Moderate** An advanced macrolide[d] Plus, a β-lactam (benzyl penicillin 1.2 g IV 6 h or ampicillin 1 g IV 6 h or cefotaxime/ceftriaxone 1 g IV daily or ampicillin–sulbactam) **Severe**[b] Ceftriaxone 1 g IV daily or cefotaxime 1 g IV 8 h plus either an advanced macrolidec or a respiratory fluoroquinolone[d]	A respiratory fluoroquinolone[d] A respiratory fluoroquinolone[d] An antipseudomonal β-lactam plus, either an advanced macrolide[c] or a respiratory fluoroquinolone[d]	N/A N/A Requirement for antipseudomonal cover will depend on risk factors Local prevalence rates of community-acquired MRSA should guide empiric treatment and may include vancomycin 1 g IV 12 h or linezolid 600 mg IV 12 h
Urinary tract infections				
Asymptomatic bacteriuria	Various, most frequently Enterobacteriaceae	No treatment	N/A	N/A

Table 3 (continued)

Type of infections	Organisms	Empirical antimicrobial treatment[a]		Other treatment
		First line	Alternative	
Cystitis	*Enterobacteriaceae, Staphylococcus saprophyticus, Enterococcus* spp., rarely *Candida* spp.	3 days oral antibiotic treatment guided by local antibiotic sensitivity pattern e.g. trimethoprim-sulfamethoxazole orally daily	Trimethoprim 300 mg or norfloxacin 400 mg orally 12 h or ciprofloxacin 500 mg orally 12 h	N/A
Pyelonephritis		14 days' oral/IV antibiotic treatment guided by local antibiotic sensitivity pattern. Ciprofloxacin 500/400 mg PO/IV 12 h or ampicillin 2 g IV 6 h plus gentamicin (see local dosing and monitoring guidelines) or ampicillin/sulbactam 1.5 g IV 6 h	Ceftriaxone 1 g IV daily or cefotaxime 1 g IV 8 h or ticarcillin-clavulanate 3.0–0.1 g IV 6 h or piperacillin-tazobactam 4.0–0.5 g IV 8 h	Emphysematous pyelonephritis is a rare but serious complication requiring early surgical intervention. Post-treatment urine microscopy and culture recommended in all
Other soft tissue infections				
Necrotizing otitis externa	*P. aeruginosa*	Ciprofloxacin 400 mg IV 12 h or ticarcillin-clavulanate 3.0–0.1 g IV 6 h or cefepime 2 g IV 12 h or ceftazidime 2 g IV 8 h plus gentamicin 4–6 mg/kg IV daily	Imipenem-cilistatin/meropenem 1 g IV 6/8 h	Otolaryngology review
Rhinocerebral mucormycosis	*Rhizopus* (>90%), *mucor* and *absidia* species	Amphotericin B 0.8–1.5 mg/kg IV daily	Lipid-based amphotericin B for those with renal impairment or posaconazole 800 mg PO daily in 2–4 divided doses	Control diabetic ketoacidosis if present. Surgical debridement required

[a] All treatment regimens are for average sized, non-pregnant patients with normal renal and liver function

[b] If community-acquired MRSA is documented in the geographic area then empirical treatment for life-threatening infections should include vancomycin 1 g IV 12 h. An alternative treatment may be linezolid 600 mg IV 12 h or linezolid 600 mg IV 12 h. Treatment of other infections should be based on sensitivity data and may include clindamycin 300–450 mg orally 8 h or trimethoprim/sulfamethoxazole160/800 mg orally 12 h.

[c] Azithromycin or clarithromycin.

[d] Moxifloxacin, levofloxacin, gemifloxacin

exhibited a low resistance (13.8% vs 25.6%) in non-intensive care unit. Those with a higher HbA1c level showed significantly lower resistance to sulperazone (11.7% vs 40.0%) and fosfomycin (14.3% vs 66.7%) when compared with diabetic individuals having HbA1c < 6.5%.

Treatment strategies for respiratory tract infections in diabetic conditions

There are no known effective treatment strategies for respiratory tract infections in diabetic conditions. It has been reported that diabetic subjects having respiratory tract infections, respond appropriately to anti-tuberculous treatment (Kameda et al. 1990).

Surgical site infections in diabetic conditions

In United States, prevalence of DM is increasing day-by-day (Cheng et al. 2013) and nowadays, it has become an important that there should be an appropriate control and management of patients with DM to make possible prevention from infections-associated with hospital. It has been found that DM influence the surgical site infections and influence of hyperglycemia on surgical site infections has also been confirmed (Zimlichman et al. 2013). A total of 90 studies provided the estimates for the association between DM and surgical site infections have been summarized in Table 2 (Martin et al. 2016). Among the patients undergoing cardiac surgery, the actual pooled estimate was found highest. Mostly, diabetic patients do not survive long due to increase development of antimicrobial resistance against infections. This has been found that increased risk of surgical site infections was consistent across surgery types among diabetic patients except the gynecological and obstetrical surgery (Mu et al. 2011). It has been reported that glucose levels remain consistently higher in diabetic patients with surgical site infections receiving colorectal resection when compared with uninfected diabetic patients (Sehgal et al. 2011). Increased rates of infection in colorectal and bariatric surgery,(Kwon et al. 2013) orthopaedic spine surgery (Caputo et al. 2013) and cardiac surgery (Zerr et al. 1997; Furnary et al. 1999; Wilson and Sexton 2003) has been found to be associated with raised blood glucose level (Hardy et al. 2010; Jeon et al. 2012).

Treatment strategies

There are no known possible and effective treatment strategies for surgical site infection associated with DM. In Table 3, we have summarized the infections associated with DM and their possible treatment strategies (Peleg et al.

2007). The rates of morbidity and mortality increase due to these infections.

Conclusion

The aforementioned convincingly evidences strongly suggest the utmost need of appropriate hygiene conditions for diabetic patients in hospitals. Subsequently, such a palliative strategy can prophylactically secure future complication of antimicrobial resistance in diabetic patients. As it is better to spend one once on prevention then two once on treatment because the normal treatment regimen is ineffective against diabetic patients suffering from microbial infections in contrast to non-diabetics. Thus, radical amendments in hospital diabetic wards such as by providing them isolated and hygienic conditions can ultimately, subsides the consequences of antimicrobial resistance in diabetic patients. Additionally, further well-designed and randomized studies are required for accessing the significance of hygienic conditions and possibly expected favorable outcomes. Surely, such types of studies will also helpful for better understanding of radiological, laboratory as well as clinical characteristics of infections affiliated with diabetic patients. Furthermore, this study also urges policy makers to formulate an antimicrobial policy for diabetics for rational use of antibiotics.

Compliance with ethical standards

Conflict of interest Authors declare that they do not have conflict of interest for this article.

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