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Review

Diabetes and acute bacterial skin and skin structure infections

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SUMMARY

Acute bacterial skin and skin structures infections (ABSSSIs) are associated with high morbidity, costs and mortality in patients with diabetes mellitus. Their appropriate management should include several figures and a well-organized approach. This review aims to highlight the interplay between diabetes and ABSSSIs and bring out the unmet clinical needs in this area. Pathogenetic mechanisms underlying the increased risk of ABSSSIs in diabetes mellitus are multifactorial: high glucose levels play a crucial pathogenetic role in the tissue damage and delayed clinical cure. Moreover, the presence of diabetes complications (neuropathy, vasculopathy) further complicates the management of ABSSSIs in patients with diabetes. Multidrug resistance organisms should be considered in this population based on patient risk factors and local epidemiology and etiological diagnosis should be obtained whenever possible. Moreover, drug-drug interactions and drug-related adverse events (such as nephrotoxicity) should be considered in the choice of antibiotic therapy. Reducing unnecessary hospitalizations and prolonged length of hospital stay is of primary importance now, more than ever. To achieve these objectives, a better knowledge of the interplay between acute and chronic hyperglycemia, multidrug resistant etiology, and short and long-term outcome is needed. Of importance, a multidisciplinary approach is crucial to achieve full recovery of these patients.

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Contents

1. Introduction

Acute bacterial skin and skin structures infections (ABSSSIs) are leading causes of morbidity and mortality in patients with diabetes mellitus [1] and are associated with significant health care costs and impaired quality of life [2]. The diagnoses of skin infections directly in the Emergency Department (ED) rose up by nearly 3-times during the last years [3]. Particular populations, including patients with diabetes mellitus, require more frequently hospitalization and advanced care for ABSSSIs and are more prone to have systemic complications and worse outcome [4].

In general, skin infections in patients with diabetes include a wide heterogeneous spectrum of conditions ranging from cellulitis to more complicated infections, such as deep tissue infections and diabetic foot infections (DFIs). The introduction of the new definition of ABSSSIs aimed to better standardize the diagnosis of skin infections and making populations included in clinical studies more homogeneous [5]. Since DFIs are usually characterized by microbiological heterogeneity and may represent a confounding factor in the assessment of outcome in clinical trials, ABSSSIs do not include DFIs [6]. According to new FDA definition, clinical studies should focus on ABSSSIs, including cellulitis/erysipelas, wound infections and major cutaneous abscesses (2013 FDA guidelines) while DFIs should be investigated as a distinctive disease entity [7,8]. Considering that ABSSSIs have peculiar features in patients with diabetes mellitus, a better knowledge of these infectionsa is needed.

This review is, therefore, intended to highlight the interplay occurring between diabetes and ABSSSIs and bring out the unmet clinical needs in this area.

2. Epidemiology

Several studies showed that patients with diabetes are more likely to develop skin infections compared to those without diabetes [9]. A retrospective study conducted in US from 2005 to 2010 showed that abscesses, cellulitis, and other skin infections were more frequent in patients with diabetes mellitus [10]. Moreover, patients with diabetes mellitus had a fourfold risk of skin complications compared to non diabetic patients [10]. A recent cohort study including more than 60,000 patients with diabetes and age-sex-region–matched non-diabetes controls showed that patients with diabetes mellitus had higher risk of skin infections (cellulitis and others) compared to controls [8]. Patients with diabetes also had a greater risk of intensive care unit (ICU) admission and death [8]. Moreover, diabetic patients are at high risk of surgical site infections (SSI), especially those who undergo lower extremity bypass surgery [11] as well as many other surgical procedures [12].

Epidemiological studies in patients with diabetes have seldom estimated the incidence of skin infections according to the more recent ABSSSI definition. As such, they often report a heterogenous group of skin infections, including several distinct entities. Therefore, proper data about the incidence and outcomes of ABSSSIs in patients with diabetes is still limited. Closing this knowledge gap is particularly important, considering that almost one third of skin infections in patients with diabetes occurred at locations other than foot [13].

3. Pathogenetic mechanisms of ABSSSI in diabetes mellitus

Pathogenetic mechanisms underlying the increased risk of ABSSSIs in patients with diabetes are complex and multifactorial. A major role in increasing such risk is played by poor glycemic control [14]. High glucose levels are associated with tissue damage via irreversible non-enzymatic glycation of proteins [15], impairment of the immune response [16] and generation of reactive oxygen species (ROS) that play a critical physiological role for regulating homeostatic cellular functions [17].

In spite of this, studies on the role of hyperglycemia in the specific context of ABSSSI remain scanty.

It is known that glucosuria either as a consequence of hyperglycemia or due to the use of SGLT-2 inhibitors may favor urinary tract and genital infections. Whether increased glucose concentration in the interstitial space of skin tissues exerts a similar predisposing risk of ABSSSIs is currently unknown. Delayed and inefficient wound healing in patients with diabetes is causally linked to hyperglycemia-induced damage. High glucose levels in the interstitial fluid alter hyaluronan in the skin microvessels and favor loss of the

glycocalyx on the endothelial cells leading to poor wound healing [18]. Animal models showed that skin barrier dysfunction and impaired proliferation/differentiation process of keratinocytes are directly attributable to hyperglycemia [19]. High glucose levels induce advanced glycation end (AGEs) products formation and deposition in the skin of patients with diabetes. AGEs may affect fibroblast activity, slow turnover rate of macromolecular collagen in extracellular matrix, increase oxidant stress and tissue inflammation [20]. Several studies showed that the levels of skin AGEs, measured both by biopsy and skin autofluorescence, predict the progression of microvascular complications and cardiovascular mortality in patients with diabetes [21,22], although the role of skin AGEs accumulation in favoring skin infections remains to be determined.

On the contrary, glycemic control is key for preventing infections, accelerating recovery and reducing the risk of poor outcome [23,24] in ABSSSIs as well.

Several aspects about the impact of hyperglycemia on risk of ABSSSIs remain under-investigated. For instance, little is known about the relative role of acute and chronic hyperglycemia. Since prior exposure to chronic hyperglycemia may generate a negative "metabolic memory" and activate a sequence of events leading to the development of complications of diabetes, achieving optimal glucose control from the time of diabetes diagnosis is critical for sustained prevention of complications [25]. Although, not directly investigated, it is likely this applies to the risk of skin infections as well. ABSSSIs may be the first manifestation of diabetes and occur at the time of poor glycemic control and studies are needed to evaluate the impact of optimal and durable glucose control on prevention and recovery of ABSSSIs in patients with diabetes.

Hyperglycemia is probably the most important pathogenetic factor responsible for the increased risk of infection. Other factors include neuropathy and vascular damage that contribute to the enhanced risk of skin infections and to greater severity of ABSSSIs. Neuropathy increases the infectious risk by the impairment of leucocyte migration in denervated tissues. Peripheral arterial disease reduces vascular flow, promoting bacterial replication and reducing the chances of antibiotic penetration at the site of infection. Immune system is also weakened in patients with diabetes mellitus: the decreased production of neuropeptides (such as substance P and nerve growth factor) affects the immune cell chemotaxis, opsonization and intracellular bacterial killing, delaying wound healing and enhancing the risk of bacterial infection [26].

4. Etiology and multidrug Resistance: An evolving issue

Etiology of ABSSSIs in patients with diabetes may be different from those observed in the population without diabetes. Two aspects about the peculiarity of ABSSSIs in patients with diabetes should be highlighted: the likelihood of atypical infections and atypical clinical presentation, and the risk of multidrug resistance (MDR).

Streptococcal and Fournier's gangrene, rhino-cerebral mucormycosis, synergistic necrotizing cellulitis with severe muscular involvement are serious infections that typically occur in patients with diabetes mellitus [26,27]. A prompt recognition of these clinical entities is required to avoid patient fatal outcome.

During the last decades, a significant increase in the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) has been detected among hospitalized patients with diabetes with skin infections [13]. Of note, the proportion of MRSA isolates increased for both non-foot and foot sites, highlighting the need of awareness of MDR etiology in patients with diabetes mellitus with ABSSSIs. Compared to DFIs, non-foot infections are more likely to be caused by MRSA but less likely to have polymicrobial isolates without MRSA [13].

MRSA is not a challenge only for hospitalized patients. Community-acquired MRSA (CA-MRSA) is a predominant cause of purulent ABSSSIs and is particularly challenging because it may carry genes encoding the Panton-Valentine leucocidin associated with tissue necrosis and more severe disease presentation [28,29]. The prompt identification of patients presenting at ED with ABSSSIs at highest risk of CA-MRSA is crucial to prompt initiation of appropriate therapy. The nasal carriage status may be useful to predict MRSA etiology in patients with ABSSSIs. Diabetes is already included in a bedside risk score for MRSA for patients hospitalized with acute bacterial skin and skin structure infections [30]. In patients affected by diabetes, the MRSA colonization rate is about 9%, ranging from 2% in those living in the community to 19% in those attending hemodialytic centers [31]. Although no risk score for MRSA has been specifically validated in patients affected by diabetes admitted to ED with ABSSSIs, the identification of these patients may have important clinical implications. First, in a considerable proportion of patients with non-foot skin infections, the etiological diagnosis remains unavailable. Thus, predicting MRSA etiology on the basis of risk factors for MRSA may help guiding antibiotic therapy. Second, the management of patients with diabetes and ABSSSI due to MRSA may be challenging particularly at the time of the Covid-19 pandemic. Identification of patients at high risk of MRSA etiology, may favor optimal allocation of new antibiotics, such as long-acting drugs, as dalbavancin, that may reduce hospitalization and allow outpatient management with ABSSSIs [32].

In hospitalized patients with diabetes and severe infections such and necrotizing fasciitis, major abscesses or surgical site infections, there is an increasing and worrying detection of Gram-negative bacilli (GNB). In a recent study, the vast majority of patients affected by diabetes with bloodstream infections from a skin source had a non-foot infection and about one third of the infections was caused by GNB (*Escherichia coli* and *Pseudomonas aeruginosa*) [33]. Of importance, infection due to GNB was the only factor independently associated with mortality [33]. The spread of MDR-GNB in the hospital setting represents an urgent public health threat and increases morbidity and mortality, especially in patients with multiple comorbidities [34–36]. There are no studies investigating the incidence of and risk factors for MDR-GNB etiology of ABSSSIs in patients with diabetes. Although DFIs are not included in the definition of ABSSSI, it should be mentioned that the risk of MDR organisms is particularly relevant in

patients with DFI [37,38]. Compared to non-diabetic patients with foot infections, those with DFI have high rate of resistant *Acinetobacter*, *Bacillus*, and *Citrobacter*. Carbapenem-resistance is also higher in patients with DFI compared to non-DFI [37].

5. Risk factors for ABSSSI in patients with diabetes mellitus

Several factors affect risk and outcome of ABSSSIs in patients with diabetes mellitus (Fig. 1). Beyond hyperglycemia, malnutrition, vascular damage, nephropathy and decreased compliance all contribute increasing the risk of ABSSSI, of failure to treatment and poor outcome. Poor nutritional status, low serum albumin concentrations and depletion of micronutrient, including vitamin D, might influence negatively the healing process and increase the risk of poor outcome in these patients [39]. Interestingly, some data indicate that supplementation of micronutrients might increase immune function and reduce the incidence of common infections in outpatients with Type 2 diabetes [40].

6. The challenging management of ABSSSI in patients with diabetes mellitus

The high clinical complexity of patients with diabetes and non-foot skin infections represents a challenge for clinicians. Fig. 2 shows a proposed algorithm for the management of these patients. Compared to DFIs, non-foot skin infections seem to occur more frequently in patients with multiple comorbidities. In a large study of patients with diabetes and skin infections, those with non-foot skin infections had more frequently history of congestive heart failure, chronic lung disease and chronic renal disease [13]. Non-foot location was a factor independently associated with mortality [13]. Thus, when treating patients affected by diabetes with ABSSSIs, clinicians should take into account all conditions that may influence the clinical course. The presence of nephropathy had multiple consequences on the management of these patients. Renal clearance affects serum levels of several antibiotics. On one hand, altered renal clearance may reduce the possibility to achieve optimal pharmacokinetic targets [41,42]; on the other hand, over-exposures related to reduced clearance of the drug may result in increased risk of adverse events [43]. Therapeutic drug monitoring of antibiotics may be useful and should be implemented, especially for treating patients with severe infections.

Comorbidities and polypharmacy further complicate the management of ABSSSIs in patients with diabetes. Drug-drug interactions may result in altered efficacy of antibiotics or increased risk of adverse events. Table 1 summarizes the main potential adverse events and drug-drug interactions between anti-Gram-positive antibiotics commonly used to treat ABSSSI and antidiabetic agents. Some antibiotics, such as vancomycin and trimethoprim-sulfamethoxazole, are associated with high risk of nephrotoxicity and may have a too little therapeutic window in patients with diabetes. Linezolid may induce thrombocytopenia and caution should be paid in patients taking selective serotonin reuptake inhibitors because of the risk of serotonin syndrome. Finally, some antibiotics, such as linezolid and fluoroquinolones, can interact with glucose-lowering drugs; their administration may result in hyper- or hypoglycemia and careful monitoring of blood glucose is recommended.

The occurrence of an ABSSSI in a patient with diabetes mellitus may also cause deterioration of glycemic control, that, in turn, affects negatively the clinical outcome of infection. The relationship between hyperglycemia and infection appears to be bidirectional and interdependent. Several studies examined the association between high blood glucose levels and risk of infection [44,45], but infection itself may act as a prominent stress condition, increasing the risk of low glucose control. Infectious episodes increase level of counter-regulatory hormones (e.g. cortisol, epinephrine, glucagon), activation of the inflammatory cascade, and oxidative stress [46,47]. Some infections, especially pneumonia and urinary tract infections, account for 20% to 55% of all precipitating causes of hyperglycemic crises. This relationship is of great importance for its clinical implications: 1) achieving an optimal glucose control in patients with infections may be challenging; 2) an optimal glucose control should not be underestimated and should be pursued in order to improve clinical outcome of patients with infections; good glycemic control should be ensured during the hospitalization for ABSSSI as it may favor the clinical cure; 3) the effect of ABSSSI on glucose control should be further investigated.

Considering that patients with diabetes, and in particular the elderly ones, are at risk of complications during the hospital stay (infection by MDR organism, delirium, loss of glycemic control, iatrogenic complication), a crucial goal in the management of patients with ABSSSI is to shorten hospitalization. Some patients with ABSSSIs could be safely treated as outpatients, decreasing the costs of hospitalization and increasing patients' satisfaction. One strategy favoring early discharge from hospital is represented by the sequential iv-to-oral therapy. In patients with diabetes mellitus, the rate and extent of absorption of oral drugs may be impaired due to delayed gastric emptying, altered gastrointestinal motility and vascularization. Thus, the use of intravenous long-acting antibiotics can provide a safe and effective therapeutic option in patients with diabetes [48,49]. Dalbavancin is a long-acting antibiotic with activity against Gram-positive organisms, including MRSA, and may offer the opportunity for earlier hospital discharge in patients with diabetes affected by ABSSSIs [50].

7. The role of narrative medicine in treating ABSSSI in patients with diabetes mellitus

The last, but not the least, educational aspects and implementation of narrative medicine in patients with diabetes and ABSSSIs may facilitate the achievement of clinical recovery [51]. Narrative medicine is a broad-spectrum approach for addressing the emotional and sociological aspects of persons affected by disease, and other stakeholders involved (health care professionals, caregivers, and family members). In the setting of ABSSSI and diabetes, narrative medicine is crucial for achieving clinical success through a coordinated multidisciplinary approach [52]. To this extent, a close collaboration is

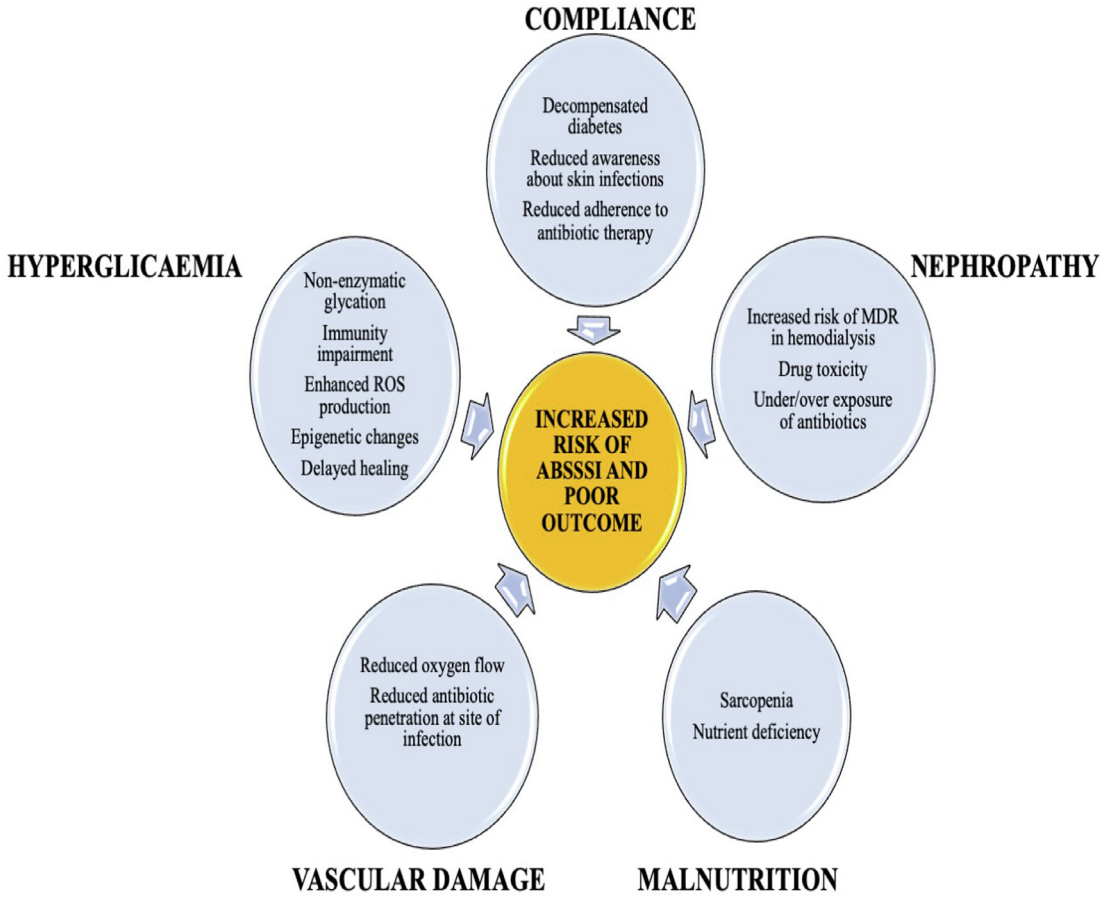

Fig. 1 – Risk factors for ABSSSI and poor outcome in patients with diabetes mellitus. ABSSSI: acute bacterial skin and skin structure infections, MDRO: multidrug resistant organisms, ROS reactive oxygen species.

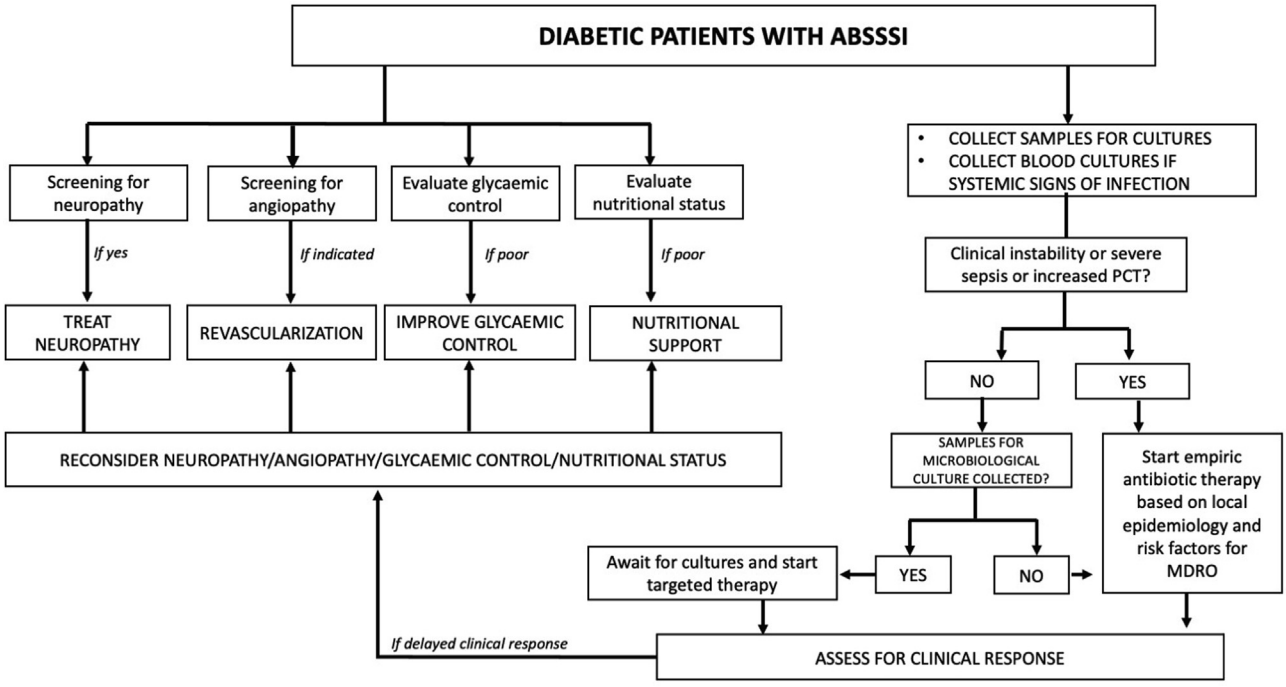

Fig. 2 – Clinical algorithm for the management of patients affected by diabetes mellitus with ABSSSI. ABSSSI: acute skin and skin structure infections; MDRO: multidrug resistant organisms; PCT: procalcitonin.

Table 1 – Potential adverse events of anti-Gram-positive antibiotics used for treating ABSSSIs and drug-drug interactions with antidiabetic agents.

Antibiotics	Dose adjustment for renal function	Potential adverse events	Potential drug-interactions with antidiabetic agents	
Vancomycin	Yes	Nephrotoxicity	None reported	
Linezolid	No	ThrombocytopeniaSerotoninergic syndrome	Metformin	Linezolid may increase the level or effect of metformin by unspecified interaction mechanism.
			Sulfonylureas	Linezolid may increase the hypoglycemic activities of glimepiride/ gliclazide.
Daptomycin Dalbavancin	Yes(Dalbavancin: requested for severe renal failure not requiring dialysis)	Increased CPK levels (daptomycin)	None reported	
Teicoplanin	Yes	Erythematous rashDrug-related fever	None reported	
Tetracycline	No	Permanent discoloration of teethGastrointestinal disordersHepatotoxicity	None reported	
TMP/SMX	Yes	Gastrointestinal disordersHematologic disorders (pancytopenia, anemia) Nephrotoxicity	Metformin	TMP/SMX may increase level of metformin by basic (cationic) drug competition for renal tubular clearance (Minor interaction).
			Sulfonylureas	TMP/SMX increases levels of glimepiride by plasma protein binding competition
			Repaglinide	TMP/SMX increases levels of repaglinide by decreasing metabolism and by plasma protein binding competition.
Fluoroquinolones	Yes	Warning in patients at risk of AAATendon ruptureC. *difficile* infectionDisorientation, agitation	Metformin	FQs increase effects of metformin by pharmacodynamic synergism
			Sulfonylureas	FQs increase effects of glimepiride by pharmacodynamic synergism
			Repaglinide	FQs increases effect of repaglinide by pharmacodynamic synergism.
			Acarbose	FQs increase effects of acarbose by pharmacodynamic synergism
			Pioglitazone	FQs increase effects of pioglitazone by pharmacodynamic synergism
			DPP-IV inhibitors	FQs increase effects of sitagliptin by pharmacodynamic synergism

AAA: abdominal aortic aneurism; FQ fluoroquinolones. TMP/SMX: Trimethoprim/sulfamethoxazole

The following antidiabetic drugs were tested for each antibiotic: metformin, sulfonylureas, repaglinide, acarbose, pioglitazone, DPP-IV inhibitors, GLP-1 analogues, SGLT-2 inhibitors

Table 2 – Clinical unmet needs in the field of ABSSSIs in patients with diabetes and proposed clinical studies.

Clinical questions	Proposed clinical studies
Which is the role of acute and chronic hyperglycemia in patients with diabetes and ABSSSIs?	Clinical study evaluating the role of acute and chronic hyperglycemia as risk factor for ABSSSI in hospitalized and non-hospitalized patients
Which extend hyperglycemia impacts on the outcome of patients with diabetes and ABSSSIs?	Clinical study evaluating whether hyperglycemia is an independent predictor of poor outcome in patients with diabetes and ABSSSIs
Which is the prevalence of severe ABSSSIs caused by MDR organisms?	Clinical/epidemiological study describing the prevalence of MDR etiology in hospitalized patients with diabetes and ABSSSI
Is MDR etiology a risk factor for poor outcome in patients with diabetes and ABSSSI?	Clinical study evaluating whether MDR etiology is an independent predictor of poor outcome in patients with diabetes and ABSSSIs
Which are risk factors for MDR etiology in patients with diabetes and ABSSSI?	Clinical study identifying risk factors for MDR etiology in patients with diabetes and ABSSSIs
Does hospitalization for ABSSSI impact on long term outcomes of patients with diabetes?	Clinical study evaluating long-term outcome (re-hospitalization rates, quality of life, sustained glycemic control) after a hospitalization for ABSSSI
Which is the best intervention to achieve clinical cure in patients with diabetes and ABSSSI?	Intervention study (e.g. before/after study) evaluating the efficacy of a multifaceted intervention in patients with diabetes and ABSSSI

ABSSSI: acute bacterial skin and skin structure infections.

expected between the diabetologist and infectious disease expert. Both specialists are expected to be familiar with problems regarding medical management of patients with ABSSSI and work in a coordinated manner in order to provide a multidisciplinary strategy ensuring optimal therapy and the highest probability of clinical success. Better education of physicians concerning new approaches for dealing with these patients is recommended, including increasing the ability to listen to patients in their narrative about their illness. Patient's quality of life is positively associated with a holistic caring approach, and this is feasible with a multidisciplinary approach [53].

8. Unmet clinical needs in ABSSSI in patients with diabetes mellitus

Table 2 summarizes the unmet clinical identified through this expert opinion paper. Further studies should elucidate the role of acute and chronic hyperglycemia in the specific setting of ABSSSI allowing to understand to which extent poor glycemic control can affect the risk and outcomes of ABSSSI. More information is needed with respect of the role of MDR organisms in ABSSSI in people with diabetes and to which extent this etiology affects patient outcomes, including morbidity, mortality, risk of re-hospitalization, and recurrence. More emphasis should be put on short and long-term outcome after hospitalization for an infectious episode [54] including rate of re-hospitalization, impact on glycemic control and quality of life. Finally, the role and efficacy of a multidisciplinary approach including infectious disease experts, diabetologists, surgeons, nutritionists, and diabetes educators remains to investigated in proper clinical studies.

9. Conclusions

ABSSSIs in patients with diabetes mellitus represent a peculiar clinical entity. Their management may be challenging, due to the complexity of the patient with diabetes and the diffusion of MDR organisms in hospital and community setting. A better knowledge of risk factors for ABSSSIs and predictors of poor outcome in patients with diabetes and ABSSSIs is required. Since ABSSSIs and diabetes mellitus may influence each other, a multidisciplinary approach is needed to achieve full recovery of these patients. Reducing unnecessary hospitalizations and prolonged length of hospital stay is of primary importance. This can be pursued through implementation of modern therapeutic strategies involving proper risk stratification, use of novel long-acting antibiotics, as dalbavancin, ensuring adequate glycaemic control, enhancing interaction between the health care providers and the patients, fostering a concerted team effort. In this view, the implementation of multidisciplinary teams of experts may favor safe and effective outpatient management.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: 'MF received speaker honoraria for

Angelini, MSD, Pfizer, and Nordic Pharma. JJM received personal fees from Astra Zeneca, Boehringer-Ingelheim, Eli Lilly, MSD, Novo Nordisk, Sanofi, Servier. JMA has received honoraria for speaking at symposia organized on behalf of Pfizer, Astellas, Merck Sharp & Dohme (MSD), Angelini, and Gilead Science and has sat on advisory boards on behalf of Pfizer, Astellas, MSD, Angelini, and Gilead Science. SDP reports grants and/or personal fees from Boehringer Ingelheim, Astra Zeneca, Novo Nordisk, Eli Lilly, GlaxoSmitheKline, MSD, Novartis Pharmaceuticals, Sanofi, Takeda. FM has participated in advisory boards and/or received speaker honoraria from Angelini, Correvio, MSD, Pfizer, Astellas, Gilead, BMS, Jansenn, ViiV, BioMerieux, Biotest, Becton-Dickinson, Nordic Pharma, Pfizer, Shionogi. All COI are outside the submitted study. All authors disclose personal fees from Ethos, during the conduct of the study.'

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