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SHORT COMMUNICATION

Clinical and Microbiological Characteristics of Type 2 Diabetes Mellitus Accompanied with Sepsis

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SUMMARY

Background: **This study was conducted to investigate the clinical and microbiological characteristics of type 2 diabetes mellitus (T2DM) complicated with sepsis and to provide a reasonable basis for early diagnosis and treatment.**
Methods: **The clinical material of patients with T2DM complicated with sepsis enrolled from January 2019 to February 2022 in the Endocrinology Department of Sichuan Provincial People's Hospital were retrospectively analyzed.**
Results: **A total of 36 patients were included. T2DM patients with sepsis had bad blood glucose control, long hospital stays, poor nutritional status, severe infection, occult primary infection sites, and high detection rates of ESBL producing Escherichia coli and MRSA.**
Conclusions: **Multiple complex clinical factors made it difficult for T2DM patients with sepsis to be cured or improved and raised great challenges for antibiotic therapy.**
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KEYWORDS

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INTRODUCTION

The International Diabetes Federation (IDF) reported the worldwide diabetes prevalence was approximately 10.5% (536.6 million people) in 2021 [1], and type 2 diabetes mellitus (T2DM) accounts for 90% of all diabetes globally [2]. In China, it is estimated that the number of adults with undiagnosed diabetes was 72.8 million in 2021 and the number of patients with T2DM would be 164.1 million in 2030 [2]. Compelling evidence indicates that diabetes mellitus (DM) patients have an increased risk of various infections and a higher chance (about 2 to 6 times) to develop sepsis compared to non-diabetic individuals [3]. Especially, T2DM patients are more likely to have antibiotic-resistant urinary tract and respiratory infections [4]. In order to understand the association between hyperglycemia and sepsis, this study

summarized the clinical and pathogenic characteristics of T2DM patients accompanied with sepsis, including blood glucose and glycated hemoglobin levels, expressions of inflammatory markers, infection sites, and drug resistance of cultured pathogens.

We conducted a retrospective study by analyzing the clinical information of endocrinology inpatients from January 2019 to February 2022. Patients who had T2DM accompanied with sepsis when admitted were included. A total of 36 patients (21 male and 15 female) with a median age of 61 years old (range, 35 - 89 years) were included (Table 1). We observed 80.6% patients had fingerstick glucose concentrations greater than 11.1 mmol/L at admission, and the median venous blood glucose was 16.6 mmol/L (range, 6.4 - 63.9 mmol/L). Meanwhile, 88.9% of patients had glycated hemoglobin more than 6.5%, indicating most of the T2DM patients had bad control of glucose before hospitalization. Moreover, the median values of inflammatory markers included white blood cell count 12.1 x 10^9/L (range, 5.6 - 35.5 x 10^9/L), neutrophils ratio 88.2% (range,75.6 - 94.6%), C-reactive protein 127.8 mg/L (range, 5.5 - 294.0 mg/L), and procalcitonin 6.13 ng/mL (range, 0.1 - 143.3 ng/mL). Furthermore, 61.1% of all patients had anemia (hemoglobin less than 120 g/L for male or 110 g/L for female), 69.4% of the patients had albumin less than 30 g/L and 69.4% patients developed fever with body temperatures > 38.3℃, suggesting most of the T2DM patients with sepsis had severe infections and poor nutritional status. As a result, those patients spent a median of 15 days (range, 1 to 42 days) in the hospital. We noticed that 25 cases (69.4%) had two known sites of infection and 4 cases had more than 3 infectious sites, including pulmonary infection, diabetic foot ulcers (Wagner 3 - 4), deep abscess (deep neck space, liver, perinephric space, or perianal area), urinary tract infection, or osteomyelitis. Those complex co-infections or occult primary infections made it difficult for patients to be cured or improved, resulting in 9 patients being discharged for financial reasons unable to complete treatment.

What made the treatment more difficult was the drug resistance situation of pathogens. A total of 42 non repetitive pathogens were isolated, among which Gram-negative bacteria accounted for 64.3% (27/42), Gram-positive bacteria accounted for 21.4% (9/42), and fungi accounted for 14.3% (6/42) (Figure 1A). The top four bacteria were *Escherichia coli* (10/42), *Klebsiella pneumoniae* (10/42), *Staphylococcus aureus* (2/42), and *Enterococcus faecium* (2/42). Among them, *Escherichia coli* and *Klebsiella pneumoniae* producing extended-spectrum β-lactamases (ESBLs) accounted for 60% (6/10) and 10% (1/10), respectively. No carbapenem resistance was detected from *Escherichia coli* and *Klebsiella pneumoniae* (Figure 1B). As for those *Escherichia coli* isolates, imipenem (100%), amikacin (100%), cefoperazone-sulbactam (90%), and piperacillin-tazobactam (80%) were the most effective antibiotics. However, those *Klebsiella pneumoniae* isolates were sensitive to most of the antibiotics for Gram-negative bacteria (Figure 1B). Additionally, two cases were methicillin-resistant *Staphylococcus aureus* (MRSA). Luckily, vancomycin-resistant *Staphylococcus* and *Enterococcus* were not detected. As we can see from Figure 1C, the common bacteria that caused diabetic foot ulcers were *Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella pneumoniae*. *Klebsiella pneumoniae* was the most frequent bacteria detected in pus (Figure 1D). Interestingly, we noticed the culture positivity rates for urine and blood samples were 46.2% and 27.8%, respectively (Figure 1E - 1F).

It seems that patients with T2DM are more susceptible to various infections, and infections often lead to unmanageable hyperglycemia, thus creating a vicious cycle. Though the exact influence of diabetes on the development of sepsis is undefined, evidence shows that diabetes could reduce bacterial clearance, impair cytokine production, change procoagulant status, and induce immune dysregulation [5]. Chinese guideline suggests three key treatment principals for T2DM patients accompanied with infection: stringent control of blood glucose, adjustment of antibiotic therapies according to drug sensitivity tests, and positive surgical treatments [6]. First, Chinese Diabetes Society (CDS) set up a comprehensive target for T2DM patients: reaching 4.4 mmol/L to 7.0 mmol/L for fasting blood glucose, less than 10.0 mmol/L for non-fasting blood glucose, and less than 7% for HbA1c [6]. American Diabetes Association Professional Practice Committee (ADA) recommends glucose concentrations between 10 mmol/L and 13.9 mmol/L may be acceptable in patients with severe comorbidities [7]. Second, in our study, pulmonary infection (80.6%), diabetic foot ulcers (38.9%), liver abscess (19.4%), and urinary tract infection (13.9%) may be the main known sources of infections, which is consistent with the types of common infections in T2DM patients reported by the latest Chinese guideline [6]. However, Esper et al. reported a respiratory source of infection was present in 27% of DM patients with sepsis [8]. Lin reported bloodstream and urinary tract accounted for 43.06% and 20.78%, respectively, of the infection sites of DM patients with sepsis in the intensive care unit [9]. The differences may be due to different populations of patients. Additionally, piperacillin-tazobactam, levofloxacin or moxifloxacin are the most used antibiotics because *Escherichia coli* and *Klebsiella pneumoniae* are the top isolated pathogens in our study. Here, for T2DM patients who are accompanied with infection or even develop sepsis, regular summary of infection sources and drug resistance features of local hospitals or departments are highly recommended. Third, for diabetic foot infections, the care by a specialized surgeon to treat foot ulcers and wounds is suggested by the ADA [10]. In our study, most of the patients who had liver abscess, perirenal abscess, deep neck space abscess, perianal abscess or foot ulcer accepted puncture drainage or surgery as early as possible, indicating the importance of positive management of T2DM

Table 1. Clinical characteristics of enrolled patients.

Characteristics		Median (range)/n (percentage)
Gender	Male	21 (58.3%)
	Female	15 (41.7%)
Age		61 (35 - 89)
Fingerstick glucose (mmol/L)		15.5 (6.4 - 33.3)
< 11.1mmol/L		7 (19.4%)
> 11.1mmol/L		29 (80.6%)
Venous blood glucose (mmol/L)		16.6 (6.4 - 63.9)
Glycated hemoglobin (%)		10.9 (5.8 - 15.8)
< 6.5%		4 (11.1%)
> 6.5%		32 (88.9%)
White blood cell count (x 10^9/L)		12.1 (5.6 - 35.5)
Neutrophils ratio (%)		88.2 (75.6 - 94.6)
Anemia		22 (61.1%)
Platelet (x 10^9/L)		238.5 (15 - 538)
< 100 x 10^9/L		7 (19.4%)
> 100 x 10^9/L		29 (80.6%)
C-reactive protein (mg/L)		127.8 (5.5 - 294.0)
Procalcitonin (ng/mL)		6.13 (0.1 - 143.3)
Albumin (g/L)		27.8 (18.4 - 33.9)
< 30 g/L		25 (69.4%)
> 30 g/L		11(30.6%)
Hospital stay (day)		15 (1 - 42)
Maximum body temperature during hospitalization	< 37.3℃	3 (8.3%)
	37.3℃ - 38.3℃	8 (22.2%)
	> 38.3℃	25 (69.4%)
Days of body temperature recovery		4 (1 - 17)
Outcomes	Cured or Improved	26 (72.2%)
	Automatic discharges	9 (25%)
	Death	1 (2.8%)
Pulmonary infection		29 (80.6%)
Diabetic foot ulcers		14 (38.9%)
Culture positivity of section		80%
Culture positivity of blood		30%
Liver abscess		7 (19.4%)
Puncture drainage or surgery		100%
Culture positivity of pus		71.4%
Culture positivity of blood		28.6%
Lower urinary tract infection		5 (13.9%)
Culture positivity of urine		80%
Culture positivity of blood		60%
Other infections	Perirenal infection	4 (11.1%)
	Perirenal abscess	3 (8.3%)
	Osteomyelitis	2 (5.6%)
	Deep neck space abscess	1 (2.8%)
	Perianal abscess	1 (2.8%)

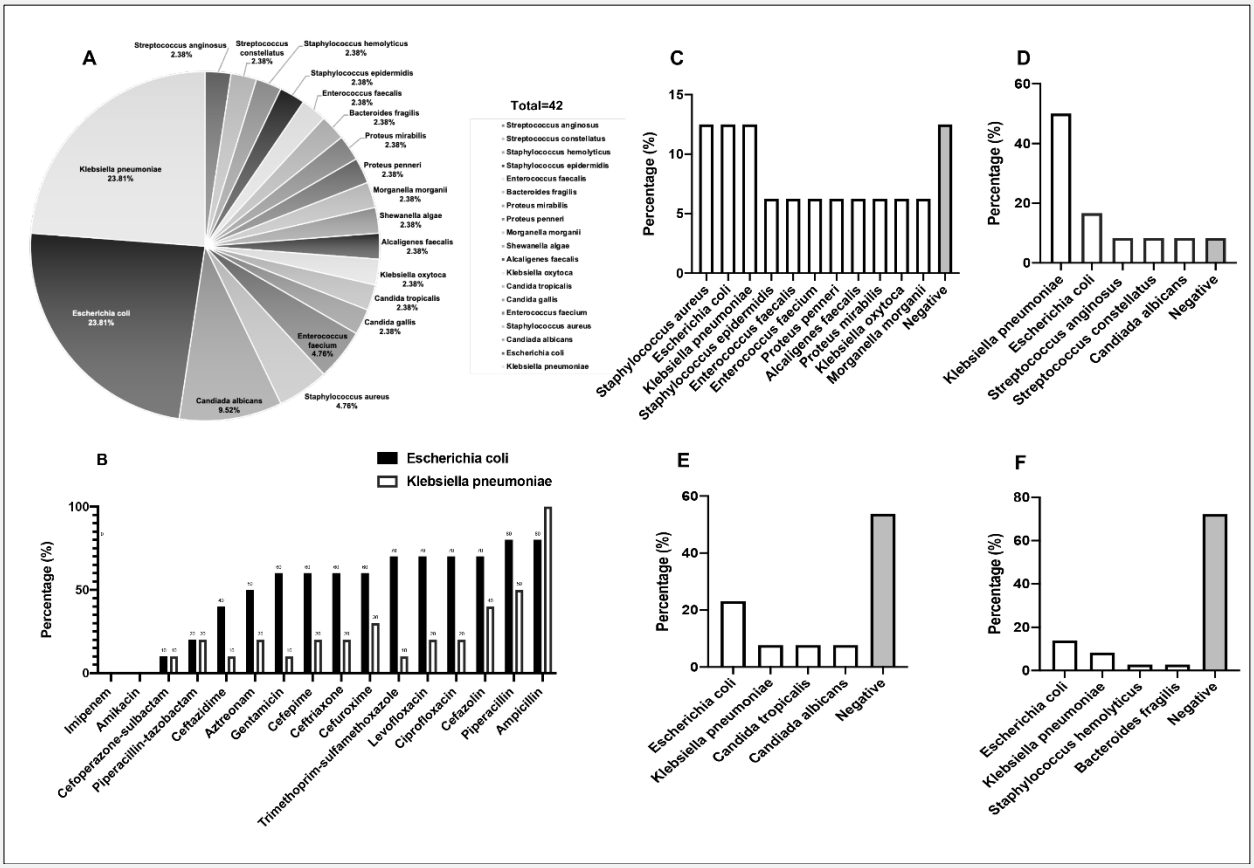

Figure 1. Characteristics of microbial species isolated from cultures.

(A) Composition ratios of all isolated pathogens (n = 42). (B) Antimicrobial resistance rates of the top 2 isolated bacterium. The culture positivity rates of pathogens isolated from (C) the secretion of diabetic foot, (D) pus, (E) urine, and (F) blood.

patients with abscesses or foot ulcers.

In conclusion, our study reveals T2DM patients with sepsis usually have poor glycemic management, aggravated concentrations of inflammatory markers, and multiple primary infection sites especially occult abscesses. Therefore, appropriate control of blood glucose, proper use of antibiotics, and positive surgical treatment may be beneficial for T2DM patients with sepsis during hospitalization, but the long-term prognostic benefit requires more investigations.

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Declaration of Interest:

The authors declare no competing interests.

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