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EDITORIAL

Tofacitinib for the treatment of ulcerative colitis: A review of the literature

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Abstract

Ulcerative colitis (UC) is a chronic immune-mediated inflammatory condition affecting the colon. Recently, tofacitinib, an oral small molecule that is an inhibitor of the Janus kinase signal transduction pathway, was proven efficacious for inducing and maintaining remission in adult patients with moderate to severe UC in three global Phase III studies. The purpose of this review is to summarize existing data on the efficacy, safety, and quality of life issues related to use tofacitinib as well as highlight recent real-world experience with this drug among patients with UC.

Key words: Ulcerative colitis; Tofacitinib; Review; Inflammatory bowel disease; Treatment

Core tip: Tofacitinib is a small molecule that is an inhibitor of the Janus kinase signal transduction pathway, and it is the first oral medication approved for chronic use among adults with moderately to severely active ulcerative colitis (UC). Three large phase III trials have shown overall efficacy and safety; however, long-term results and real-world data are lacking in the literature. Our objective is it consolidate the current literature to better understand what is currently known about efficacy, safety, quality of life, and real-world experience with this medication among patients with UC.

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INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory condition that primarily affects the colon, due to an abnormal dysregulation of the immune system. The pattern of disease activity is most often described as relapsing and remitting, with some patients experiencing persistent disease activity despite diagnosis and medical therapy. Therapeutic decisions are subcategorized into induction and maintenance modalities, with a primary treatment endpoint of obtaining and maintaining both endoscopic healing and symptomatic remission. The current therapeutic armamentarium for UC treatment includes corticosteroids, immunosuppressants, aminosalicylates, immunomodulators, anti-tumor necrosis factor (TNF) agents, as well as anti-integrins. Recently, tofacitinib, an oral small molecule that is an inhibitor of the Janus kinase (JAK) signal transduction pathway, was found to be effective in both inducing and maintaining remission in adult patients with moderate to severe UC in three global Phase III studies[1,2]. Tofacitinib has been used for the treatment of adults with moderate-to-severe rheumatoid arthritis (RA) since its initial Food and Drug Administration (FDA) approval in 2012, and in 2018 the FDA expanded this approval to include treatment of adults with moderate to severe UC. It should be noted that this medication has not been FDA approved for the use in pediatric populations. It is unique in that it is the first of its kind oral medication with FDA approval for treatment of moderate to severe UC.

Given its status as a relative newcomer in the treatment of UC, there is limited evidence of the long-term safety and efficacy of tofacitinib in this patient population. The purpose of this review is to summarize existing data on the safety, efficacy, and quality of life issues related to the use of tofacitinib as well as highlight recent real-world experience with this drug among patients with UC.

REVIEW OF THE LITERATURE

Data on efficacy

In a phase 2 double-blind, randomized, placebo-controlled trial by Sandborn *et al*[1] involving patients with moderate-to-severe UC, a significantly higher rate of response at 8 wk was found among those who received tofacitinib at a dose of 15 mg twice daily than among those who received placebo and also a significantly higher rate of remission with tofacitinib at doses of 3 mg, 10 mg, and 15 mg twice daily than with placebo.

Subsequently, Sandborn *et al*[2] reported the results of phase 3 trials of tofacitinib as induction therapy (OCTAVE Induction 1 and 2) and maintenance therapy (OCTAVE Sustain) in patients with moderate-to-severe UC. Enrolled patients had moderate-to-severe UC and had experienced previous treatment failure with or unacceptable side effects from glucocorticoid, thiopurine, or anti-TNF therapy. For all three trials, the primary end point was remission, which was based on Mayo scores. The rate of remission at 8 wk was significantly higher in the 10-mg tofacitinib group than in the placebo group in the OCTAVE Induction 1 trial (18.5% *vs* 8.2%, $P = 0.007$) and in the OCTAVE Induction 2 trial (16.6% *vs* 3.6%, ($P < 0.001$)). The rate of remission at 52 wk was significantly higher in the 5-mg and 10-mg tofacitinib groups (34.3% and 40.6%, respectively) than in the placebo group (11.1%) in the OCTAVE Sustain trial.

Although there have been no head-to-head clinical trials comparing tofacitinib to biologics, meta-analyses have been conducted to address this important question. A recent systematic review and network meta-analysis by Bonovas *et al*[3] aimed to comparatively assess efficacy of tofacitinib and biologics (infliximab, adalimumab, golimumab and vedolizumab) in adult patients not previously exposed to anti-TNF agents. In terms of clinical response, clinical remission, and mucosal healing, each drug demonstrated superiority over placebo. However, no indirect comparisons between tofacitinib and biologics reached statistical significance.

A recent network meta-analysis found that tofacitinib has the highest rank for induction of clinical remission among patients with prior anti-TNF exposure. In an effort to analyze the comparative safety and efficacy of differing therapies as first line (biologic-naïve) and second line (previous exposure to anti-TNF agents) therapies for moderate-severe UC, Singh *et al*[4] conducted a systematic review and network meta-

analysis. They found that while infliximab and vedolizumab were ranked highest for induction of clinical remission amongst biologic-naïve patients, among patients with prior anti-TNF exposure, tofacitinib was ranked highest for induction of clinical remission [OR: 11.88 (2.32-60.89)] and mucosal healing.

Safety and adverse events

Tofacitinib has been associated with an increased risk of infections among patients with RA[5] and psoriasis[6]. In the OCTAVE trials[2], there were higher rates of infections with tofacitinib as compared to placebo, and the rate of serious infection was found to be increased with tofacitinib in the induction trials, but similar across treatment groups in the maintenance trial. Overall, 2.9% of subjects suffered at least one serious infection compared with 1.0% of the placebo controls, including anal abscess, pneumonia, herpes zoster (HZ) infection, Clostridium difficile infection, and cytomegalovirus colitis.

In OCTAVE Sustain, HZ infections occurred in 14 patients total, 3 (1.5%) in the 5 mg group, 10 (5.1%) in the 10 mg group and 1 (0.5%) in the placebo group. An analysis of the safety of tofacitinib for the treatment of moderate to severe UC based on more than four years of data from global clinical trials by Sandborn *et al*[7] again suggest what appears to be a dose-dependent relationship with HZ infection, with those taking 10 mg BID at highest risk. For the overall cohort, the incident rate of HZ infection was 4.1 (95%CI: 3.1-5.2). Winthrop *et al*[8] conducted an analysis specifically examining the risk of HZ in patients with UC using tofacitinib. They found that among HZ incidence was 4.07 per 100 person-years among all patients with UC treated with tofacitinib, and again found a dose-dependent risk. It should be noted that the majority of HZ events were uncomplicated and mild to moderate in severity. Independent risk factors for HZ in these patients with UC included advanced age and prior anti-TNF failure[9]. In addition, patients with Asian race (IR: 6.49; 95%CI: 3.55-10.89), oral corticosteroid use at baseline (IR: 5.14; 95%CI: 3.56-7.18), history of diabetes mellitus (IR: 8.06; 95%CI: 2.96-17.55), and those who received the 10 mg twice daily dosing (IR: 4.25; 95%CI: 3.18–5.65) were at higher risk for HZ infection.

The new recombinant HZ subunit vaccine (RZV) could decrease the risk of HZ from tofacitinib; it is currently only recommended for immunocompetent adults aged ≥ 50 years. However, given the known risk of this infection, it remains to be seen whether it may be warranted to administer the RZV vaccine to all inflammatory bowel disease (IBD) patients of all ages treated with tofacitinib, including those younger than 50. A recent study by Caldera *et al*[10] attempts to further clarify this question by calculating the number needed to harm (NNH) in order to quantify the risk of HZ in patients treated with tofacitinib as compared to those with alternative treatments for UC, including infliximab and vedolizumab. They found that the higher 10 mg twice a day dosing of tofacitinib had the highest risk for HZ infection when compared to placebo with an NNH of 22 patients; the combined NNH for both treatment groups (5 mg and 10 mg) combined was 36 patients. The information gathered from these studies can collectively inform our clinical approach towards addressing the potential risk of HZ. Currently suggested approaches for lowering the risk of HZ include potentially vaccinating younger patients including those less than 50 years old on tofacitinib, who demonstrate risk factors for HZ including steroid use, Asian race, or diabetes mellitus. Moreover, educating patients to recognize early symptoms of HZ, and closely monitoring patients with UC during induction therapy in order to maintain the lowest effective dose – or, to withdraw the drug entirely in non-responders are other approaches. Of note, it is recommended to avoid the use of live vaccines concurrently with this medication[11]. Further research is needed both on understanding risk factors for HZ as well as regarding the safety and efficacy of the RZV series in patients receiving tofacitinib for treatment of UC.

Among RA patients, gastrointestinal perforations have been observed with the use of tofacitinib[5]. Across the OCTAVE trials, one intestinal perforation occurred with tofacitinib; in the OCTAVE Induction 1 trial, 1 patient in the 10-mg tofacitinib group had a serious adverse event of intestinal perforation. In the OCTAVE Induction 2 trial, a single patient in the placebo group had a serious adverse event of intestinal perforation. No patients in the OCTAVE Sustain trial experienced intestinal perforation[2].

There is some data to suggest an increase in malignancy risk among RA patients treated with tofacitinib. In a worldwide, 3-year, post-marketing surveillance study on tofacitinib in patients with RA[12], the relative risk per 100 patient-years for neoplasms was 0.45, with the most common neoplasms being nonmelanoma skin cancers (NMSCs). Fifteen cases of lymphoma were documented over approximately 34000 patient-years of exposure, and the risk of lymphoma was not found to increase over time. The data on malignancy risk among UC patients using tofacitinib is much more limited. In an integrated analysis of tofacitinib UC clinical trials, eleven patients had

malignancies (excluding NMSC), all during OCTAVE Open[7]. There 1 case reported for each of the following cancers: Cervical cancer, hepatic angiosarcoma, cholangiocarcinoma, cutaneous leiomyosarcoma, Epstein-Barr-virus-associated lymphoma, renal cell carcinoma, essential thrombocythemia, acute myeloid leukemia, adenocarcinoma of colon, lung cancer, and breast cancer. In the overall cohort, IR of malignancy (excluding NMSC) including all 11 patients with events was 0.7 (95%CI: 0.3-1.2).

Additional studies have analyzed other important safety-related questions regarding tofacitinib. Cases of maternal and paternal exposure to tofacitinib (defined as parental exposure to tofacitinib before or at the time of conception and/or during the course of pregnancy) were identified in the Pfizer safety databases in a study by Mahadevan *et al*[13] Of 1157 patients enrolled in the UC interventional studies, 11 cases of maternal exposure and 14 cases of paternal exposure to tofacitinib (doses of 5 mg or 10 mg twice daily) before or at the time of conception or during pregnancy were identified. Outcomes included 15 healthy newborns, no fetal deaths, no neonatal deaths, no congenital malformations, 2 spontaneous abortions, and 2 medical terminations. Overall, they found that outcomes across other tofacitinib studies and post-marketing cases were consistent, with a healthy newborn being the most common outcome and no fetal deaths. However, it is important to note that tofacitinib has been found to be teratogenic in animal models and is contraindicated in patients who are attempting to become pregnant[11].

There has been interest in understanding the association between tofacitinib and lipid profiles since an early pooled analysis demonstrated dose-dependent increases in total cholesterol, LDL-C, and HDL-C among patients with RA[14]. In the OCTAVE trials, as compared with placebo, tofacitinib was associated with increased lipid levels as well[2]. More recently, Sands *et al*[15] analyzed lipid concentrations and incidence rates of major adverse cardiovascular (CV) events (MACEs) in patients with UC who received and found that after 8 weeks of therapy, there were greater increases from baseline in total cholesterol, HDL-C, and LDL-C in patients on tofacitinib compared with placebo. Four MACEs were reported; the incidence rate was 0.24 (95%CI: 0.07-0.62), and 3 of these patients had 4 or more CV risk factors. Overall, they did not find clinically meaningful changes in lipid ratios or CV risk scores, and MACEs were found to be infrequent and not dose-related.

Importantly, an association between thromboembolic events and higher doses of tofacitinib was recently noted. Early results from the RA Study, an ongoing open-label clinical trial of patients over the age of 50 with at least one cardiac risk factor, show an increased risk of pulmonary embolism and overall mortality among study participants receiving tofacitinib at 10 mg twice daily as compared to 5 mg[16]. Currently, the European Medicines Agency's safety committee is recommending against the use of 10 mg twice daily dose of tofacitinib in patients who are at high risk of thromoembolic disease including pulmonary embolism, as well as those with heart failure, cancer, history of blood clots, or taking combined hormonal contraceptives[17]. Given that the recommended induction dosage for UC is 10mg twice daily, more data is needed to evaluate this potentially serious association.

Quality of life

Paschos *et al*[18] conducted a systematic review with network meta-analysis aiming to compare the impact of interventions for moderate-to-severe UC on health-related quality of life (HRQL); they found that induction therapy with tofacitinib improves quality of life of patients with moderate-to-severe UC, the beneficial effect of which is maintained during maintenance therapy. This was supported by Panés *et al*[19] who found that tofacitinib 10 mg twice daily induction therapy significantly improved HRQL versus placebo at week 8. These improvements were persistent through 52 wk' maintenance therapy with tofacitinib 5 mg and 10 mg twice a day.

Real-world experience

Recently, Weisshof *et al*[20] published their real-world experience with tofacitinib used for treatment of patients with moderate-to-severe IBD. In this retrospective, observational study, 58 patients (including 53 with UC) completed at least 8 wk of treatment with tofacitinib. Clinical response and adverse events were assessed at 8 wk (induction), at 26 wk (maintenance), at 52 wk, and at the last available follow-up. They found that at 8 wk of treatment, 21 patients (36%) achieved symptomatic improvement, and 19 (33%) achieved clinical remission. Steroid-free remission at 8 wk was achieved in 15 patients (26%). Of the 48 patients followed for 26 wk, 21% had clinical, steroid-free remission. Of the 26 patients followed for 12 mo, 27% were in clinical remission and remained steroid-free.

Rapid clinical response has been suggested in several studies. Hanauer *et al*[21] assessed the timing of symptom improvement in post-hoc analyses of data from 2

phase 3 trials of induction therapy with tofacitinib in patients with UC (OCTAVE Induction 1 and 2); they found significant improvements in symptoms among patients given tofacitinib compared with placebo within 3 d, indicating a rapid onset of effect of this drug in patients with UC. In a case study by Griller *et al*[22], tofacitinib and infliximab were used as combination rescue therapy to avoid colectomy in a hospitalized patient with severe UC. The patient received intravenous steroids and 2 loading doses of infliximab with minimal improvement and then started on 10 mg tofacitinib twice daily as rescue therapy; the patient improved dramatically within 48 hours and subsequently achieved clinical remission.

In an off-label use of tofacitinib, Berinstein *et al*[23] presented the first reported use of tofacitinib in 4 in patients with acute severe UC (ASUC) predicted to fail medical management, based on severe Truelove and Witt's criteria, C-reactive protein (CRP) > 100 mg/L at presentation, endoscopic features during admission, and prior failure of IV corticosteroids or infliximab therapy. After receiving tofacitinib, all 4 patients had a rapid improvement in clinical symptoms and decline in CRP. Two patients achieved clinical remission with a combination of tofacitinib and IV corticosteroids, whereas one patient achieved clinical remission with tofacitinib and budesonide only. One patient was unable to achieve clinical remission, although they did experience an initial rapid improvement in symptoms and CRP until tofacitinib was reduced. No major adverse effects directly attributable to the use of tofacitinib were reported during the induction phase of drug administration or up to 18 mo of reported follow-up.

DISCUSSION

IBD is a chronic condition affecting millions of people of all ages worldwide, with prevalence highest in Europe and North America, and rising incidence in newly industrialized countries in Africa, Asia and South America[24]. With ever-increasing targeted research on novel therapeutics, the treatment of IBD continues to evolve. Tofacitinib is currently the only JAK kinase inhibitor with FDA approval for the treatment of patients with moderate-to-severe UC.

Overall, clinical data shows that tofacitinib is effective in inducing and maintaining clinical remission, clinical response, and mucosal healing. Additionally, analysis of the OCTAVE 1 and 2 trials suggests a rapid onset of action with response as early as day 3[21]. Studies also indicate that tofacitinib has a favorable effect on quality of life[18,19].

In the OCTAVE trial, HZ reactivation was more frequent among patients under tofacitinib 10mg twice a day (5.1%) compared with other treatment groups (1.5% and 0.5% across tofacitinib 5mg twice a day and placebo, respectively). Vaccination can help lower the risk of infection, and an inactivated recombinant varicella zoster vaccine is now available, which in clinical trials has demonstrated 97% efficacy among adults ≥ 50 years of age[25]. Further research is needed both on understanding risk factors for HZ as well as regarding the safety and efficacy of the RZV series in patients on tofacitinib.

Recent safety data suggests that pulmonary embolism may potentially be a class-wide issue for JAK inhibitors; however, these data need to be confirmed by future adverse events reporting trends and clinical trials. Currently, the European Medicines Agency's safety committee is recommending against the use of 10 mg twice daily dose of tofacitinib in patients who demonstrate risk factors for thromboembolic disease.

Real-world experiences with the use of tofacitinib are lacking in the literature. Weisshof *et al*[20] published their real-world experience with the use of tofacitinib for treatment of patients with moderate-to-severe IBD; they found that at 8 wk of treatment, 21 patients (36%) achieved symptomatic improvement, 19 (33%) achieved clinical remission, and 15 (26%) achieved steroid-free remission. Overall, tofacitinib induced clinical response in 69% of the patients and 27% were in clinical, steroid-free remission by 1 year of treatment, suggesting that tofacitinib can be an effective treatment alternative for patients with anti-TNF resistant IBD. Tofacitinib has also been used as a combination rescue therapy with infliximab to avoid colectomy in a hospitalized patient with severe UC[22], as well as in inpatients with ASUC predicted to fail medical management[23] with good success.

Currently, there is an ongoing Phase III long-term extension study known as OCTAVE Open that aims to assess the safety, tolerability, and efficacy of long-term tofacitinib therapy; it includes non-responders in OCTAVE Induction 1 or 2, treatment failures in OCTAVE Sustain, and those who completed OCTAVE Sustain. OCTAVE Open will assess safety through an analysis of adverse events, clinical laboratory parameters, and physical examination, as well as efficacy as determined by clinical response and endoscopy at predetermined intervals.

Other future research directions to be pursued include head-to-head trials to determine the most optimal therapies in UC. In addition, there is currently limited data on the efficacy of combining tofacitinib therapy with biologics among patients with UC. Within the RA population, there is some data to support safety with combination therapy; a case series of 6 patients with RA treated with tofacitinib–biologic combination therapy did not find any adverse events after a mean of 14 months of treatment[26]. Le Berre *et al*[27] report a case of successful combination of vedolizumab and tofacitinib in a patient with UC and spondyloarthropathy for whom anti-TNF therapy was contraindicated; after 3 mo of treatment with this combination therapy, the patient achieved clinical remission for both gastrointestinal and rheumatologic symptoms. No adverse events were observed, including no infections. Additionally, rapid remission was achieved recently in an inpatient as described by Griller *et al*[22], when tofacitinib and infliximab were used as combination rescue therapy to avoid colectomy in a hospitalized patient with severe UC. Interestingly, as a stand-alone medication, it should also be highlighted that the economic burden to the patient for the cost of tofacitinib is likely less than compared to alternative therapies such as anti-TNFs and vedolizumab[28]. Overall, the available evidence remains limited regarding UC patients, and larger studies are needed to confirm the efficacy and safety profile of combination therapy in this patient population.

At this time, further novel subtype-selective JAK kinase inhibitors are currently being developed. Additional studies are required to better understand long-term efficacy, safety profiles, and the optimal positioning of agents like tofacitinib in management algorithms for UC.

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REVIEW

Antidiabetic agents in patients with hepatic impairment

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Abstract

Chronic liver disease (CLD) often coexists with type 2 diabetes mellitus, making diabetes management a challenge to the clinician. It is well known that liver is the major site of drug metabolism, and, therefore, its impairment affects hepatic metabolism of many antidiabetic agents. Furthermore, patients with CLD have serious comorbidities such as impaired renal function, hypoalbuminemia, lactic acidosis, hypoglycemia and malnutrition, making their treatment even more difficult. On the other hand, most of the antidiabetic agents, with the exception of insulin, need dosage titration due to alterations to their pharmacokinetics in patients with CLD. For well-established antidiabetic treatments, like metformin and sulfonylureas there are studies regarding their dosage chance in these patients. However, despite the growing problem of management of diabetes in patients with CLD the existing literature data, especially on newer antidiabetic agents, are limited and, furthermore, no direct guidelines exist. Therefore, in the present review article we try to summarize the existing literature data regarding management of diabetes in patients with CLD.

Key words: Hepatic impairment; Type 2 diabetes mellitus; Pharmacokinetics; Antidiabetic drugs

Core tip: Most of the antidiabetic agents, with the exception of insulin, need dosage titration due to alterations to their pharmacokinetics in patients with chronic liver disease (CLD). For well-established antidiabetic treatments, like metformin and sulfonylureas there are studies regarding their dosage chance in these patients. However, despite the growing problem of management of diabetes in patients with CLD the existing literature data, especially on newer antidiabetic agents, are limited and, furthermore, no direct guidelines exist. Therefore, in the present review article we try to summarize the existing literature data regarding management of diabetes in patients with CLD.

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INTRODUCTION

Liver is one of the principal organs in carbohydrate metabolism due to its important role in neoglucogenesis and glycogenolysis[1]. A link between type 2 diabetes mellitus (T2DM) and chronic liver disease (CLD) was observed for the first time before almost 100 years[1,2]. Since then it is well-known that diabetes and CLD often coexist. Even more, presence of CLD increases not only T2DM complications but it is recognized as a cause of premature mortality in patients with T2DM[3]. On the contrary, diabetes *per se* has been recognized as a risk factor for CLD and hepatocellular carcinoma (HCC). It is estimated that about 30%-60% of patients with cirrhosis have T2DM[4]. In another study, the prevalence of T2DM in patients with CLD was varied between 18%-71%[5]. On the other hand, glucose intolerance is present in the majority of patients with CLD[6]. It is obvious, that there is a two-side relationship between T2DM and CLD making the management of these patients a challenge to the clinicians.

Since liver is the major site of metabolism for most of the antidiabetic agents, management of T2DM in patients with CLD is still challenging for the reasons that are listed below. First of all, patients with CLD have serious comorbidities such as impaired renal function, hypoalbuminemia, lactic acidosis, hypoglycemia and malnutrition[7,8]. Secondly, patients with CLD are more prone to acute kidney injury leading to accumulation of either drugs or their metabolites resulting in various adverse events[9]. Finally, patients with CLD develop malnutrition as the liver plays a key role in carbohydrate, protein, lipid, vitamin, and mineral metabolism and energy balance[10,11].

Liver is the major site of drug metabolism, and its impairment affects hepatic metabolism of drugs[12]. On the other hand, hypoalbuminemia, a result of protein deficiency[13], can cause serious toxicity by highly protein bound drugs since their free plasma concentrations are increased in CLD. Furthermore, the potential hepatotoxicity of some oral antidiabetic agents (OADs) associated adverse events favored by CLD makes management of T2DM in patients with CLD even more complex[4].

Until now, only limited literature data are available yet regarding the management of T2DM in patients with CLD[3,8]. Therefore, the aim of the present review is to summarize the existing literature data on the use of OADs and injectable agents in T2DM patients with CLD.

CLASSIFICATION OF LIVER IMPAIRMENT

The Child-Pugh score is currently used to assess the overall prognosis of CLD, mainly cirrhosis[14]. The Child-Pugh score is consisted of 5 clinical characteristics of liver disease: total bilirubin level, serum albumin concentration, prothrombin or international normalized ratio value, presence of ascitis and hepatic encephalopathy. Each measure is scored from 1 to 3, with 3 indicating most severe derangement. Patients are classified into 3 Child-Pugh classes (A-C): Child-Pugh A = 5-6 points, Child-Pugh B = 7-9 points, and Child-Pugh C = 10 or more points.

ANTIDIABETIC TREATMENT

Biguanides (metformin)

Metformin, a biguanide compound, is the first-line therapy for T2DM patients for almost half a century[15]. Its action is mediated by the inhibition of gluconeogenesis and glycogenolysis in hepatocytes[15]. Metformin undergoes renal excretion and is excreted unchanged by the kidneys[16].

One of the most life threating adverse events of metformin is lactic acidosis. However, it must be noticed that metformin might cause lactic acidosis in predisposed patients (with heart, renal and liver failure), a rather rare, however, adverse event of metformin therapy. In patients with CLD, there is an increased risk

of low oxygen tension due to concurrent pulmonary or heart disease making lactic acidosis easy to happen. Even more, patients with CLD are at increased risk for sepsis or hemorrhage[17] making them vulnerable to lactic acidosis since metformin inhibits mitochondrial respiration in the liver[18]. It must be mentioned that lactic acidosis is rather a rare side effect of metformin since the incidence of lactic acidosis is 0.03-0.5 cases/1000 patient-years in metformin-treated population[19].

According to the existing studies, metformin therapy is safe in T2DM patients with cirrhosis, and further prolong patient's survival time. A study in 22 T2DM cirrhotic patients showed that metformin therapy was related to overt hepatic encephalopathy. A possible pathogenetic mechanism proposed by authors was the inhibition of glutaminase activity[20]. Another study showed that metformin was related with reduced incidence of HCC and liver-related death/transplantation in T2DM patients with cirrhosis due to hepatitis C virus[21]. It is noteworthy that metformin therapy reduced the risk of death by 57% in T2DM patients with cirrhosis[22].

The only risk of metformin therapy in patients with CLD, as it is mentioned above, is lactic acidosis. Therefore, according to the ADA guidelines, it is recommend to avoid metformin therapy in patients with severe hepatic impairment (HI) or in binge drinkers due to high risk for lactic acidosis[15] (Table 1).

Sulfonylureas

Liver is the major site of biotransformation for sulfonylureas. Sulfonylureas are metabolized into active and inactive metabolites in the liver through hepatic oxidative enzymes (CYP P450s). Then, they are extensively bound to serum proteins and excreted through renal pathway. Therefore, protein binding of sulfonylureas may be reduced in patients with T2DM and CLD due to hypoalbuminemia resulting to increased drug plasma concentrations[23-25] Therefore, sulfonylurea therapy in patients with CLD and renal failure increases the risk for hypoglycemia[26] that is more pronounced in the presence of malnutrition, a common comorbidity in CLD patients[7], and diminished gluconeogenic capacity[27]. Furthermore, in patients with alcoholic liver disease alcohol-induced enzyme degradation of sulfonylureas decreases drug's effectiveness and further increases the risk of hypoglycemia[26].

There are only a few studies examined the effect of CLD on sulfonylurea metabolism. A study examined the effect of glipizide on hepatic uptake of insulin, showed that glipizide caused an increase in the estimated uptake of insulin in T2DM patients with cirrhosis, whereas a small decrease was observed in the control group[28].

Sulfonylureas therapy in patients with HI may be challenging since they are metabolized by the liver and excreted by the kidneys not only the parent drug but it's active metabolites as well. Glimepiride and gliclazide are contraindicated in severe HI[23-25]. According to the position statement of the ADA and EASD insulin secretagogues should be avoided in severe HI due to the risk of hypoglycemia[15] (Table 1).

Meglitinides (glinides)

Glinides (nateglinide and repaglinide) have shorter half-lives than sulfonylureas and they do not have significant renal excretion[29,30]. They are extensively bound to serum albumin protein and are metabolized by oxidative biotransformation (CYP 450) and conjugation with glucuronic acid in the liver[31,32]. Repaglinide's metabolism is mainly affected by the presence of CLD while this is not the case for nateglinide.One possible explanation for this discrepancy is that repaglinide is metabolized by CYP isoform 2C8[33] and nateglinide by CYP isoform2C9[30].

Repaglinide clearance is significantly reduced in patients with HI and should be used with caution while in T2DM patients with severe HI the drug is contraindicated[34]. On the other hand, nateglinide pharmacokinetics (PK) is not affected in patients with HI and, therefore, no adjustment of nateglinide dosage is needed in patients with mild to moderate HI[35], There are no data available in patients with severe HI (Table 1).

Alpha-glucosidase inhibitors (Acarbose)

Acarbose acts locally within the gastrointestinal tract by inhibiting enzymes (glycoside hydrolases) needed to digest carbohydrates[36]. The lack of intestinal absorption and hepatic metabolism, makes acarbose a safe choice in CLD patients with a good tolerability and absence of toxic effects[38], well-compensated non-alcoholic cirrhosis[39], and low-grade hepatic encephalopathy[40]. However, there may be a possibility of hyperammonemia when acarbose is prescribed to T2DM patients with advanced HI[37]. The effect of acarbose in hepatic encephalopathy was studied in 107 cirrhotic patients with T2DM. Acarbose therapy was related with decreased ammonia blood levels. However, no change in biochemical parameters of liver function was observed at the end of the study[40]. The findings of another study with

Table 1 Use of antidiabetic agent according to the degree of hepatic impairment

Antidiabetic agent	Degree of hepatic impairment (HI)
Metformin	Avoid in severe HI
Sulfonylureas	
Glimepiride	Avoid in severe HI
Gliclazide	Avoid in severe HI
Glinides	
Repaglinide	Avoid in severe HI
Nateglinide	No adjustment of dosage in mild to moderate HI
Alpha-glucosidase inhibitors	
Acarbose	Well tolerated
Thiazolidinediones	
Pioglitazone	Safe in Child-Pugh Class A patients. Should be avoided in Class B and C patients
DPP-4 inhibitors	
Sitagliptin	Well tolerated
Vildagliptin	Well tolerated
Saxagliptin	Well tolerated
Alogliptin	Well tolerated
Linagliptin	Well tolerated
GLP-1 receptor agonists	
Exenatide	Well tolerated
Liraglutide	Well tolerated
Lixisenatide	Well tolerated
SGLT-2 inhibitors	
Canagliflozin	Safe in Child-Pugh Class A patients. Caution is needed in Class B patients. Should better be avoided in Class C patients
Dapagliflozin	Safe in Child-Pugh Class A patients. Caution is needed in Class B patients. Should better be avoided in Class C patients
Empagliflozin	Safe in Child-Pugh Class A patients. Caution is needed in Class B patients. Should better be avoided in Class C patients
Insulin	Safe in use

the use of acarbose showed that T2DM associated with HI might be safely and effectively treated with acarbose except for a small increase in ammonia blood levels. Therefore, acarbose treatment in T2DM patients with cirrhosis might increase the risk ofhyperammonemia[37]. According to the position statement of the ADA acarbose is safe, useful, and well tolerated in CLD patients[15,16] (Table 1).

Thiazolidinediones

Pioglitazone: Pioglitazone is the only drug available in the market of this class; it is extensively metabolized by hydroxylation and oxidation and it is metabolized mainly by CYP2C8[41]. It is excreted primarily as metabolites and their conjugates in bile and feces[41]. Hepatic safety of pioglitazone was evaluated in a large observational study in T2DM patients in Japan where no case of HI was reported and no alanine aminotransferase (ALT) abnormalities with pioglitazone therapy in different dosages[42].

In a study, where the hepatic safety profile of pioglitazone (compared to glibenclamide) was examined in pioglitazone-treated patients, there was no case of hepatocellular injury in the pioglitazone group while and four cases were observed in the glibenclamide group. No case of hepatic dysfunction or HI was reported in the pioglitazone group[43]. However, in another study, the case-fatality rate of liver failure associated with rosiglitazone or pioglitazone was 81%, while only 14% of the patients recovered[44]. On the contrary, a large-scale study in Japan, in 24993 patients (28008 patient-years), no case of HI was found[42]. The above finding was confirmed in a retrospective data analysis of 1.12 patients with T2DM, where pioglitazone therapy was not associated with increased risk of HI or hepatitis compared to other OADs[45].

According to the position statement of the ADA in case of chirrosis or serum ALT level exceeding 2.5 times of upper normal limit (ULN), pioglitazone should be avoided[15]. Pioglitazone should be used with caution in CLD patients. It should be avoided in patients whose liver enzymes are > 3 times ULN range. Pioglitazone may be used in Child-Pugh Class A patients. However, it should be avoided in Class B and C patients[15] (Table 1).

DPP-4 inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin, vildagliptin, saxagliptin, alogliptin and linagliptin) belong to the incretin-based glucose-lowering agents[46]. Sitagliptin is primarily excreted by the kidney and only a small percentage of the drug undergoes hepatic metabolism (mainly through the CYP3A4 isoenzyme and less through CYP2C8 isoenzyme)[47]. Vildagliptin is metabolized *via* hydrolysis and its inactive metabolites show renal excretion[47]. Saxagliptin is metabolized in vivo to form an active metabolite, and both parent drug and metabolite are excreted primarily via the kidneys[48]. Saxagliptin is primarily metabolized by CYP3A4 and CYP3A5 isoforms and eliminated through renal and hepatic routes. Alogliptin is metabolized into M-I, an N-demethylated active metabolite *via* CYP2D6, and M-II, an N-acetylated inactive metabolite and it is excreted primarily *via* the kidneys[48,49]. In contrast to other DPP-4 inhibitors, approximately 80% of administered dose of linagliptin[50] is eliminated through enterohepatic recycling[48].

The safety of DPP-4 inhibitors in T2DM patients was examined in a systematic review and meta-analysis, whereas no adverse events of hepatotoxiticy were reported[51]. Regarding sitagliptin, a few cases of drug-induced hepatic injury[52] and of elevated hepatic enzymes[53] have been reported. However, the causal pathogenetic relationship is still unclear[54]. Despite the initial concern about a possible hepatotoxicity of vildagliptin a pooled analysis of 38 controlled trials showed that there in not any significant increase of liver enzymes with vildagliptin therapy[55]. The safety of vildagliptin was confirmed in another pooled analysis in clinical trials with duration more than two years[56]. Sitagliptin PK is not affected by moderate HI[57]. Similarly, vildagliptin PK is not affected in patients with mild, moderate or even severe HI[58].

According to the already conducted studies, there is no liver safety issues for saxagliptin[59]. In the placebo-controlled SAVOR-TIMI 53 cardiovascular outcome trial, no signal of liver toxicity was found in the saxagliptin group[60]. Saxagliptin PK is affected only in a small degree in patients with HI[61,62].

A meta-analysis of 8 placebo-controlled trials confirmed the hepatic safety of linagliptin[63]. In a study in patients with mild and moderate HI, linagliptin was well tolerated without any adverse events[64]. There is only one case report described a probable linagliptin-induced liver toxicity[65]. One study[64] reported that mild, moderate or severe HI did not affect linagliptin PK compared to normal hepatic function.

According to the already conducted studies, there is no concern for hepatoxicity for alogliptin[66]. The large cardiovascular outcome study EXAMINE showed no signal of hepatotoxicity in the alogliptin group[67]. There is only one observational study coming from Japan where hypoglycemic symptoms under alogliptin therapy were reported and associated with liver disease and alcohol consumption[68]. Finally, in patients with moderate HI alogliptin PK is not affected[69].

Summary of product characteristic of sitagliptin, saxagliptin, and linagliptin recommends no dosage adjustments in patients with CLD[70-72], while vildagliptin should not be used in patients with CLD, including patients with

ALT or aspartate aminotransferase (AST) > 3x the ULN[73]. Therefore, DPP-4 inhibitors may be used in Child-Pugh Class A patients while their use requires caution in Class B patients. On the contrary, DPP-4 inhibitors are not preferred in Class C patients (Table 1).

GLP-1 receptor agonists

Glucagon-like peptide-1 receptor agonists (GLP-1RA) (exenatide, liraglutide, lixisenatide and dulaglutide) belong to the incretin-based glucose-lowering agents and offer new opportunities for the management of T2DM[15]. Renal excretion is the main pathway for the elimination of exenatide. Liraglutide and dulaglutide are metabolized into their component amino acids by general protein catabolism pathways[74-76].

The existing literature data regarding the effect of GLP-1RAs therapy in patients with CLD is limited. Therefore, until nowadays, clinical experience with liraglutide, exenatide and lixisenatide in CLD patients is limited. However, since exenatide is primarly excreted by the kidney, blood concentrations of the drug are not affected in patients with HI[77]. Regarding liraglutide it seems that drug concentrations are not affected by HI[78].

According to the SPC of exenatide and lixisenatide no dosage adjustment is required regarding their administration to patients with HI, whereas for liraglutide the therapeutic experience in patients with CLD is limited. On the basis of available evidence, GLP-1RAs should be used with caution without dose modification in CLD patients. Drugs of this class can be administered to Child-Pugh Class A patients. However, GLP-1RAs should be avoided in Class B and C patients (Table 1).

SGLT-2 inhibitors

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors (canagliflozin, dapagliflozin, and empagliflozin) is a new class of antidiabetic agents acting through the inhibition of glucose reuptake in the kidney[79]. They undergo hepatic metabolism through glucuronidation, and small proportions of the parent drug are eliminated through renal route[79].

The safety of empagliflozin in patients with HI has been confirmed in a study investigating the effect of various degrees of HI on the PK of empagliflozin. In patients with HI empagliflozin PK was affected in a very small degree and, therefore, no dose adjustment of the drug is required in patients with HI[80]. The same pattern was observed in a canagliflozin trial, where the canagliflozin PK was not affected by the presence of mild or moderate HI. Therefore, no dose adjustment of canagliflozin is required for these patients[81]. Finally, a study on the PK and safety profile of dapagliflozin in patients with HI showed that systemic exposure to dapagliflozin was correlated with the degree of HI[82]. Therefore, dapagliflozin should be used with caution in these patients.

On the basis of available evidence, SGLT-2 inhibitors can be used with caution and lower doses should be considered during initiation of therapy in CLD patients. These agents are contraindicated in severe HI. The risk of dehydration and hypotension is associated with the use SGLT-2 inhibitors; hence, caution is required. Precisely, SGLT-2 inhibitors are safe in Child-Pugh Class A patients; however, they should be used with caution in Class B patients. Agents of this class should better be avoided in Class C patients (Table 1).

Insulin therapy

Liver is the major site of insulin metabolism. Almost half of the insulin produced by the pancreas is metabolized by the liver[83]. Hyperinsulinemia is a common finding in T2DM patients with cirrhosis, due to higher insulin secretion rate and reduced hepatic clearance. However, insulin requirement may vary in patients with CLD as a result of the reduced capacity for gluconeogenesis and hepatic breakdown of insulin. Therefore, daily dose requirements of exogenous administrated insulin can vary in a high degree and, therefore, is difficult to control blood glucose levels in these patients[7,16].

Insulin therapy is the safest and most effective therapy in patients with CLD. However, there is still the limitation of the increased risk of hypoglycemia[84]. Newer insulin analogs are preferred in CLD patients as their PK is unaltered and possesses low risk of hypoglycemia. However, it is suggested that frequent glucose monitoring and dose adjustments are required to minimize the risk of hypoglycemia or hyperglycemia in these patients[85-88]. The ADA guidelines highlight the importance of insulin therapy and suggest frequent dose adjustment and careful glucose monitoring in T2DM patients with CLD[15] (Table 1).

CONCLUSION

Management of T2DM in patients with CLD is still a challenge for the clinician. Most of the antidiabetic agents are either contradicted or need dosage titration due to alterations to their pharmacokinetics in patients with CLD. Insulin therapy seems to be the safest choice in patients with CLD. The existing literature data regarding the management of T2DM in patients with CLD are limited[89] and only small studies and meta-analyses exist showing the effect of CLD on PK of the OADs. However, the need for the development of guidelines for the management of T2DM in patients with CLD is growing following the high prevalence of HI that characterizes T2DM.

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REVIEW

Preventive strategies for anastomotic leakage after colorectal resections: A review

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Abstract

Anastomosis is a crucial step in radical cancer surgery. Despite being a daily practice in gastrointestinal surgery, anastomotic leakage (AL) stands as a frequent postoperative complication. Because of increased morbidity, mortality, combined with longer hospital stay, the rate of re-intervention, and poor oncological outcomes, AL is considered the most feared and life-threatening complication after colorectal resections. Furthermore, poor functional outcomes with a higher rate of a permeant stoma in 56% of patients this could negatively affect the patient's quality of life. This a narrative review which will cover intraoperative anastomotic integrity assessment and preventive measures in order to reduce AL. Although the most important prerequisites for the creation of anastomosis is well-perfused and tension-free anastomosis, surgeons have proposed several preventive measures, which were assumed to reduce the incidence of AL, including antibiotic prophylaxis, intraoperative air leak test, omental pedicle flap, defunctioning stoma, pelvic drain insertion, stapled anastomosis, and general surgical technique. However, lack of clear evidence of which preventive measures is superior over the other combined with the fact that the decision remains based on the surgeon's choice. Despite the advances in surgical techniques, AL remains a serious health problem associated with increased morbidity, mortality with additional cost. Many preventative measures were employed with no clear evidence supporting the superiority of stapled anastomosis over hand-Sewn anastomosis, coating of the anastomosis, or pelvic drain. Defunctioning stoma, when justified it could decrease the leakage-related complications and the incidence of reoperation. MBP combined with oral antibiotics still recommended.

Key words: Anastomotic leakage; Colorectal; Resection; Anastomosis; Cancer; Anastomotic disruption

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Core tip: Although the most important prerequisites for the creation of anastomosis is well-perfused and tension-free anastomosis, surgeons have proposed several preventive measures, which were assumed to reduce the incidence of anastomotic leakage, including antibiotic prophylaxis, intraoperative air leak test, omental pedicle flap, defunctioning stoma, pelvic drain insertion, stapled anastomosis, and general surgical technique. However, the decision remains based on the surgeon's choice. This review found that many preventative measures were employed with no clear evidence supporting the superiority of stapled anastomosis over hand-Sewn anastomosis, coating of the anastomosis, or pelvic drain. Defunctioning stoma, when justified it could decrease the leakage-related complications and the incidence of reoperation. Mechanical bowel preparation combined with oral antibiotics still recommended.

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INTRODUCTION

Anastomosis is a crucial step in radical cancer surgery. Despite being a daily practice in gastrointestinal (GI) surgery, anastomotic leakage (AL) stands as a frequent postoperative complication[1]. A recent analysis of the National Surgical Quality Improvement Program (NSQIP) database reported that rectal anastomoses were associated with the greatest incidence of AL attributing this to lacking serosa, the under tension anastomoses, technical difficulties in working in the deep pelvis, and easily compromised blood supply[2,3].

Because of increased morbidity, mortality, combined with longer hospital stay, the rate of re-intervention, and poor oncological outcomes, AL is considered the most feared and life-threatening complication after colorectal resections. Furthermore, poor functional outcomes with a higher rate of a permeant stoma in 56% of patients this could negatively affect the patient's quality of life[4-6].

Rojas-Machado *et al*[7] in a trial to develop a prognostic index for colorectal AL, they found that 54 potential risk factors were present in the literature. The two most common factors associated with a significantly higher risk of AL were anastomotic height, followed by male sex[8,9]. So, the incidence of AL following colorectal resections varies according to the anastomotic level, being 1% to 19% in colorectal or coloanal anastomoses; 0% to 2% in colocolic anastomoses; 0.02% to 4.0% in ileocolic anastomoses; and around 1% in ileoileal anastomoses[10-14].

Surgeons advocated several surgical measures in order to reduce the incidence of AL, including antibiotic prophylaxis, intraoperative leak test, omental pedicle flap, defunctioning stoma, pelvic drain insertion, stapled anastomosis, and general surgical technique. Controversy still exists, which preventive measure is superior over the other combined with the fact that the decision remains based on the surgeon's choice[15,16].

This review will cover intraoperative anastomotic integrity assessment and preventive measures in order to reduce AL.

INTRAOPERATIVE ANASTOMOTIC INTEGRITY

Nachiappan *et al*[17] in a systematic review of intraoperative tests for the assessment of colorectal anastomotic integrity, they testified a reduction in the AL rate when these tests were applied and they divided these tests into: (1) Mechanical patency assessment including air or dye leak testing competence of the doughnuts, it tests the anastomosis by occluding proximal to the anastomosis followed by transanal filling with air or dye to assess any leaking point into the peritoneal cavity without permitting direct anastomotic inspection; (2) Endoscopic visualization which permits direct inspection with the possibility of therapeutic intervention; and (3)

Microperfusion methods permitting blood flow analysis or tissue perfusion showing oxygenated and deoxygenated hemoglobin and the properties of feeding vessels which in turn may modify the planned anastomotic site or reinforce it if needed[4].

Intraoperative anastomotic air leak testing

Wu *et al*[18] in a systematic review of the value of intraoperative leak test in prevention of colorectal AL they testified variable methods for performing air leak test (ALT) with variable volume of inflated gas/dye, while ALT group had a lower AL rate compared to the non-ALT group, however, this was non-significant. Patients with positive-ALT had a significantly higher clinical AL rate compared to those with negative-ALT. Additional sutures or diversion were applied to positive-ALT patients. Despite it does not reduce AL, they recommended the routine performance of ALT as it at least predicts high-risk anastomosis and allows additional repairs.

Evaluation of anastomotic perfusion "Microperfusion"

Traditionally, surgeons rely on active mucosal bleeding, the bright coloration, and palpable mesenteric pulses as indicators of adequate perfusion. The search for a reliable objective method to determine tissue perfusion intraoperatively was warranted in order to reduce the incidence of AL, different modalities were applied, however, none has been used routinely in clinical practice[19].

Recently, Near-Infrared (NIR) Fluorescence Angiography using Indocyanine Green (ICG) which is a tricarbocyanine molecule when it is injected intravenously, it remains confined to the intravascular space due to its hydrophobic properties allowing it to bind strongly to the plasma proteins. It also fluoresces when excited by light of a particular frequency due to its fluorophoric properties, so it can be used intraoperatively for LN mapping with higher sensitivity and specificity[20] as well as in intraoperative perfusion assessment using NIR light technology[21].

Mizrahi and Wexner[22] in a review about the role of NIR of the colorectal anastomosis using ICG they reported 3.7%-19% change in the intraoperative decision with further proximal resection for the hypo-perfused anastomoses. They found 6 series with more than 100 patients showed a lower incidence of AL by 4%-12% compared to 75% published case-control series. Jafari *et al*[23] in the PILLAR II trial using NIR ICG in distal colorectal resections, they concluded its safety and feasibility. Degett *et al*[24] in a systematic review of the role of ICG Angiography for intraoperative perfusion assessment of GI anastomoses they testified regarding the colorectal anastomoses after colorectal cancer, that ICG Fluorescence Angiography had a significant lower AL rate compared to those without assessment. Similar results were reported by studies[25,26].

PREVENTIVE MEASURES

Although the most important prerequisites for the creation of anastomosis is well-perfused and tension-free anastomosis[27], surgeons have proposed several preventive measures, which were assumed to reduce the incidence of AL, including antibiotic prophylaxis, intraoperative ALT, omental pedicle flap, defunctioning stoma, pelvic drain insertion, stapled anastomosis, and general surgical technique. However, the decision remains based on the surgeon's choice[1,28].

Mechanical bowel preparation

Traditionally, mechanical bowel preparation (MBP) through the last century was believed to be an important factor within the control of surgeons in order to reduce AL rate and infectious complications in elective colorectal surgery[29]. MBP was proposed to has a few theoretical advantages; decreasing the fecal bacterial count, which in term decrease infectious complications, easier bowel manipulation, decrease the risk of unwanted spillage into the abdomen, decrease the chance of mechanical disruption of the anastomosis[30].

Slim *et al*[31] in a meta-analysis of RCTs comparing colorectal surgery with or without prophylactic bowel preparation, they reported a significant AL rate in bowel preparation group. Furthermore, they recommended what was mentioned 40 years ago by Hughes[32], "Omission of enemas and bowel washes from the preoperative procedures will be welcomed by both patients and nursing staff".

Güenaga *et al*[33] in a Cochrane systematic review including a total of 5805 patients, there was not a significant evidence support the use of both MBP or rectal enemas. Additionally, bowel preparation can be omitted safely from colonic surgery, while few studies suggested its selective application in rectal surgery without known significant value. Anastomosis below the peritoneal reflection and laparoscopic rectal surgery still warranted further research[33].

Oral antibiotics

The concept of the use of oral antibiotics in order to reduce the AL was shown by Cohn and Rives[34] in 1955 in the animal model with a complete devascularization of the anastomotic site, the dogs which received oral antibiotics completely recovered with both serosa and mucosa were normal grossly and microscopically, while the control dogs died rapidly from perforated devascularized segment and fecal peritonitis.

Roos *et al*[35] in a systematic review and meta-analysis of RCTs about the selective decontamination of the digestive tract (SDD) using a combination of oral antibiotics in addition to intravenous antibiotics compared to intravenous antibiotics alone in elective GI surgery. They testified a significantly lower rate of AL in SDD, a further subgroup analysis for both upper and lower GI surgeries with SDD associated with reduced the incidence of AL in both subgroups.

Recently, data from the NSQIP by Scarborough *et al*[36] in a study aimed to determine the association between preoperative bowel preparation status and 30-d outcomes in including AL after elective colorectal resection, with a total of 4999 patients; 1494 patients received combined MBP and oral antibiotic preparation (OAP), 2322 MBP only, 91 OAP only, and 1092 no preoperative preparation. Patients in the combined MBP and OAP group had significantly the lowest incidence of postoperative AL (2.8%) compared to 5.7% of no preparation group, this significance was maintained after adjustment. Patients receiving MBP only or OAP only did not differ significantly from those did not receive preparation[36]. Similar results from NSQIP testified by Kiran *et al*[37] a total of 8442 patients, 3822 received MBP only, 2324 combined MBP and antibiotic, 2296 no preparation. On multivariate analyses, MBP with antibiotics compared to no preparation was independently associated with lower AL.

A recent pan-European study contacted by the European Society of Coloproctology collaborative group on 3676 patients from 343 centers across 47 countries who underwent left-sided colorectal resections. In this study 29.9% of the patients received no MBP, 52.9% received MBP only, and 16.8% received MBP plus oral antibiotics (Abx). In the multivariate analysis, MBP plus Abx was the only group with a lower risk of AL (OR 0.52, 0.30-0.92, $P = 0.02$)[38].

Creation of the anastomosis

Creation of an anastomosis is a hallmark of surgical practice, decades of practice and research brought a large variety of techniques which made it difficult when trying to conclude about the safest method[39].

Stapled *vs* hand-sewn anastomosis: Stapled anastomoses were believed to have a better healing and less operative complications in comparison to hand-sewn anastomoses, this was explained by less tissue manipulation and better blood supply[40]. MacRae *et al*[41] in a meta-analysis found no significant difference in total, clinical, and/or radiological AL between stapled and hand-sewn colorectal anastomoses. Lustosa *et al*[42] in a systematic review and meta-analysis of RCTs comparing stapled and hand-sewn anastomoses, irrespective the level of colorectal anastomosis they were not able to address any superiority of stapled over hand-Sewn anastomosis. The same conclusion was reported by Neutzling *et al*[43] in a Cochrane Systematic Review.

Slieker *et al*[39] in a systematic review of evaluating the technique of colorectal anastomosis with the clinical AL as the outcome measure, they found a level 1A evidence that there was no superiority between stapled and hand-sewn anastomoses. They also concluded that the hand-sewn anastomoses were constructed following an undefined technique, while the stapled anastomoses were much more uniform.

Compression anastomoses: Stapled or hand-sewn anastomoses both are characterized by the use of foreign material; the persistent existence of these foreign materials can be avoided by the use of compression anastomosis with a resultantly reduced inflammation which in turn decrease the duration of the lag phase of anastomotic healing[44]. A revolution took place starting from a silver ring by Denans in 1826, then in the Murphy button in 1892 by Murphy. In the 1980s, the Valtrac™ in colorectal anastomoses with the use of biofragmentable anastomotic ring by Hardy *et al*[45] in 1984, AKA-2 and subsequently the AKA-4 modification for transanal application in the lower rectal anastomoses using non-absorbable metal pins by Kanshin and colleagues in Russia. Recently in colorectal anastomose using nickel-titanium either a clip alloy (Compression Anastomosis Clip-CAC) or a ring compression device (Compression Anastomosis Ring-ColonRing)[44,45]. Slieker *et al*[39] testified a level 1B evidence similarity between hand-sewn and compression anastomoses.

The colonic J-pouch: A lower incidence of AL was testified between colonic J-pouch anastomosis and straight anastomosis[46-48]. Justifications of this difference in AL came from the idea that creation of the J-pouch necessitates the full mobilization of the splenic flexure and the obliteration of the pelvic dead space by the colon[49]. Later, Hallböök *et al*[46] considered the microcirculation difference at the anastomotic site between straight coloanal anastomosis and colonic J-pouch anal anastomosis. They settled a favorable healing anastomosis in the colonic J-pouch compared to colonic end in the straight coloanal anastomosis, due to unaffected blood flow at the anastomotic site of the pouch, whereas became relatively ischemic at the colonic end in the straight coloanal anastomosis.

Brown *et al*[50] in a Cochrane systematic review of the reconstructive techniques after rectal resection for rectal cancer they testified that colonic J-pouch leads to better bowel function and similar rates of postoperative complications when compared to the straight coloanal anastomosis. While there is limited literature comparing the transverse coloplasty procedure to the colonic J-pouch, three small RCTs suggested that bowel function was similar in patients reconstructed with either procedure. However, there is some evidence that the transverse coloplasty procedure results in more AL. Liao *et al*[51] in a meta-analysis comparing colonic J-Pouch vs transverse coloplasty pouch after AR for rectal cancer, they found no significant difference in the incidence of AL. Hüttner *et al*[52] in a meta-analysis of the reconstruction techniques after LAR for rectal cancer they reported that there is no significant difference between straight or side-to-end coloanal anastomosis, colonic J pouch, and transverse coloplasty.

Coating of the anastomosis

It was proposed that external coating of the anastomosis with various materials may reduce clinical AL, especially for high-risk anastomoses as the coating material will seal off the defect. Pommergaard *et al*[1] in a systematic review to evaluate the external coating of colonic anastomoses, they reported variable materials had been used with contradictory results, this may be due to the fact that most of these series were studied in experimental animals of different species and of different designs, so their role remains unclear. Only fibrin sealant, omental pedicle graft, and hyaluronic acid/carboxymethylcellulose have been testified in humans.

Fibrin sealant: Vakalopoulos *et al*[53] in a systematic review of the use of tissue adhesive in GI anastomoses they found it difficult to draw a conclusion on the effects of the tested tissue adhesives on each level of GI anastomosis due to too much heterogeneity in the animal model, absence of details of the amount or the method of applied sealant, and the anastomotic technique was not standardized. They reported 9 studies in rats on fibrin sealant showed to decrease the incidence of AL. The only report on human by Huh *et al*[54] in a non-randomized trial of patients who underwent laparoscopic LAR for rectal cancer without diversion, they compared 104 patients in whom fibrin sealant was applied to intracorporeal stapled anastomosis to 119 patients without the use of fibrin sealant was not found to decrease the incidence of AL. They did not describe the amount of the sealant. Nordentoft *et al*[55] in a systematic review to access the potential effect of fibrin sealant on the healing of GI anastomoses, they indicated that it is a physical and mechanical effect neither due to improving the healing power of the anastomosis.

Omental pedicle graft (Omentoplasty): A controversy still exists over the use of omentoplasty to decrease the AL rate after colorectal resection[56]. Wrapping the anastomosis with intact or pedicled omentum has been designated since 1977 in order to reduce the rate or the severity of AL after colorectal resections, however, insufficient randomized controlled trials exist with conflictive results such as necrosis of the wrap and anastomotic stricture[56,57]. Theoretically, when resections are performed for cancer, omentoplasty patients are exposed to further risks of radiation necrosis and local recurrence which was described recently in the animal model[57].

Hao *et al*[58] in a meta-analysis of the role of omentoplasty in the prevention of AL after colorectal resection found that there is no supportive evidence to use or not to use omentoplasty as a measure to reduce AL after colorectal resection. Wiggins *et al*[59] in a systematic review and meta-analysis in GI anastomoses, they testified on three RCTs of colorectal anastomoses, there was no significant difference in the incidence of AL nor the in-hospital mortality.

The defunctioning stoma

The value of defunctioning stoma is still controversial, the debate is still present, whether AL rates are lower in diverted anastomoses in comparison to non-diverted anastomoses or both are similar[60-62]. Many surgeons delineated the routine use of

proximal diversion for poor patient general condition, narrow male pelvis, neoadjuvant chemoradiotherapy, intraoperative complications related to the anastomosis, low-lying rectal cancer with total mesorectal excision (TME), the goal was to divert the fecal stream from the anastomotic site, which in turn could reduce the incidence of AL and its related morbidity[63,64].

Tan *et al*[65] in a meta-analysis about the role of the defunctioning stoma in LAR for rectal cancer testified that value conferred by defunctioning stoma in decreasing the rate and in mitigating the severity of AL. Hüser *et al*[60] in a systematic review and meta-analysis of the role of the defunctioning stoma in low rectal cancer surgery, they reached the same conclusion with a significantly lower AL and reoperation rates, whereas mortality rates remained comparable between the groups. These results also were verified by Montedori *et al*[61] in a Cochrane systematic review about the use of covering stoma in anterior resection for rectal cancer. Matthiessen *et al*[9] in a study of risk factors of AL after rectal resection concluded that in the presence of intraoperative adverse events, defunctioning stoma did not decrease the risk of symptomatic AL. Despite many surgeons delineates a concept of diverting colorectal anastomosis, a controversy still stands whether the best defunctioning could be achieved by loop ileostomy or loop colostomy to address this controversy Güenaga *et al*[62] in a Cochrane systematic review found it is not possible to express a preference for use of either loop ileostomy or loop colostomy[62].

However, these benefits must be justified by the fact that routine stoma creation will reduce the quality of life in patients in whom leakage will not occur, the stoma itself is a source of high morbidity reach up to 30%[66]. Moreover, the stoma reversal is associated with a mortality of up to 2.3%, requires a second reintervention and hospital readmission[60,67-69]. Chow *et al*[70] in a systematic review about the morbidity of the reversal of defunctioning ileostomy, they testified that an underestimation of the consequence of stoma reversal. They recommended a selective use of defunctioning ileostomy with patient counseling about the possible complications of reversal at the time of the initial operation. Lindgren *et al*[5] in a multicenter RCT about the risk of permeant stoma after LAR for rectal cancer, 234 patients randomly assigned to defunctioning stoma (n = 116) or a group without defunctioning stoma (n = 118), they testified that 19% of patients their stoma became permanent and this risk was significant for those who developed AL 56% compared to 11% for those without AL.

Pelvic drainage

The purpose of pelvic drainage is to obliterate the pelvic dead space preventing the accumulation of fluid or blood which in turn may form a pelvic abscess or infected pelvic hematoma, both may erode through the anastomosis. Pelvic drainage also may permit the early detection of AL. Some surgeons adopted the use of routine pelvic drainage, other surgeons place drain only in case of doubt about the quality of the anastomosis[71]. Pelvic drainage was believed not to prevent AL, nevertheless, the drain serves as "an eye" into the pelvis, allowing for early detection of silent leakage of feculent, pus, or air. It also may contribute to the conservative management of AL[3].

Tsujinaka and Konishi[72] in a review article about the usage of drainage in colorectal surgery, they testified that the use of drain should be justified against its own related complications like drain-site infection (up to 2.5%), pain, bleeding, bowel evisceration or injury (0.1%-0.5%), and omental herniation (up to 1.0%). Placing the drain may even disrupt the anastomosis itself. Smith *et al*[73] in the animal model showed the danger of placing latex drains near to a colonic anastomosis, as this was associated with a significantly higher incidence of AL, they assumed that latex seems to have a local inhibitory effect on anastomosis healing process. Urbach *et al*[74] in meta-analysis and systematic review testified that the use of prophylactic drain has no benefit in prevention of AL or even controlling it if occurs. Jesus *et al*[71] in a Cochrane systematic review of RCTs about the role prophylactic anastomotic drainage for colorectal anastomoses they testified this practice devoid evidence. Petrowsky *et al*[75] in a systematic review and meta-analysis testified that AL was not significantly different between drained and no drained anastomoses. Rolph *et al*[76] reported the same results in another Cochrane review.

On the other hand, Zhang *et al*[77] in a systematic review of the use of prophylactic pelvic drainage in colorectal anastomosis to reduce postoperative complications. They testified that no statistically significant difference between the drain and the no drain groups in term of clinical or radiological AL. An unclear value of draining extraperitoneal anastomosis was testified by Rondelli *et al*[78] in a meta-analysis, they revealed a lower incidence of AL in drained anastomosis than in the non-drained anastomosis, furthermore, a significantly lower rate of reintervention was found in the drained group than in the non-drained. Karliczek *et al*[79] in a systematic review and a meta-analysis on RCTs generally testified that there is no significant difference in the occurrence of clinical or radiological AL. According to the anastomotic level,

they reported no benefit of extraperitoneal anastomosis drainage, but this was based on 2 RCTs.

Transanal tube drainage

The transanal tube drainage may potentially lower the incidence of AL and its clinical consequences this may be attributed to direct drainage, decreasing the intraluminal pressure and promotion of motility[80]. Lee *et al*[81] investigated the impact of using a transanal tube drainage after LAR without defunctioning stoma on the incidence of AL, when a propensity score matching was applied the incidence of AL in patients with transanal tube drain had a lower incidence of AL with a reduced number of patients with peritonitis, however, all these difference did not a reach significant level.

Shigeta *et al*[82] in a meta-analysis tested that transanal tube drainage was associated with a significantly lower rate of AL and reoperation compared with those without. Wang *et al*[83] recently in a systematic review and meta-analysis based on three observational studies and one RC, they testified that transanal tube drainage associated with a significantly lower incidence of AL and reoperation with unknown mechanism may be attributed to the reduced intraluminal pressure. Ha *et al*[84] in a systematic review and meta-analysis about the role of transanal tube placement after LAR for rectal cancer in RCTs of 475 patients they testified no difference between both groups, while in non-randomized studies of 643 patients the placement of transanal tube was associated with a lower incidence of AL.

CONCLUSION

Despite the advances in surgical techniques, AL remains a serious health problem associated with increased morbidity, mortality with additional cost. Many preventative measures were employed with no clear evidence supporting the superiority of stapled anastomosis over hand-Sewn anastomosis, coating of the anastomosis, or pelvic drain. Defunctioning stoma, when justified it could decrease the leakage-related complications and the incidence of reoperation. MBP combined with oral antibiotics still recommended.

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MINIREVIEWS

Blood glucose control in the intensive care unit: Where is the data?

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Abstract

Blood glucose control, including hyperglycemia correction, maintaining glucose at optimal level and avoiding hypoglycemia, is a challenge clinicians face every day in intensive care units (ICUs). If managed inadequately, its related mortality can increase. Prior to 2001, no relevant data from randomized, controlled studies assessing glucose control in the ICU were available. In the past 18 years, however, many clinical trials have defined criteria for managing abnormal blood glucose levels, as well as provided suggestions for glycemic monitoring. Point-of-care blood glucose monitors have become the preferred bedside technology to aid in glycemic management. In addition, in some institutions, continuous glucose monitoring is now available. Cost-effectiveness of adequate glycemic control in the ICU must be taken into consideration when addressing this complex issue. Newer types of glycemic monitoring may reduce nursing staff fatigue and shorten times for the treatment of hyperglycemia or hypoglycemia. There are a variety of glycemic care protocols available. However, not all ICU clinicians are aware of them. The following minireview describes some of these concepts.

Key words: Blood glucose control; Critical illness; Intensive care unit; Insulin therapy; Critical care

Core tip: Blood glucose control in the intensive care unit has remained a controversial topic since 2001, with many clinical trials attempting to elucidate which method provides the best option in terms of cost-effectiveness and in providing good clinical outcomes. As technology plays an important role in this matter, this minireview

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compiles the many features of state-of-the-art glycemic monitoring in the intensive care unit and treatment strategies for blood glucose control.

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INTRODUCTION

Critically ill patients present a special challenge when dealing with glycemic control, as they require correcting hyperglycemia while avoiding hypoglycemia and keeping blood glucose (BG) at optimal levels. This can have significant repercussions on the prognosis of these patients[1]. In the last 2 decades there have been a series of studies and added recommendations for glycemic control in the intensive care unit (ICU) setting[2-5]. For example, Van den Berghe *et al*[2,3] conducted a study among patients in the surgical ICU, who were managed with a rigorous glucose control protocol (maintenance of BG between 80-110 mg/dL) versus conventional treatment (infusion of insulin if BG > 215 mg/dL). They showed an increased survival rate and better prognosis, overall decrease in the mortality rate by 34%, as well as by sepsis (46%), polyneuropathy (44%) acute kidney injury (41%), and a significant decrease in blood transfusion requirements (50%)[2]. That particular study elicited some controversies, and additional randomized controlled trials were conducted. In 2009, the Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation study (known by its acronym, NICE-SUGAR) revealed an increased mortality rate in those patients that underwent the tight glucose control (TGC) of 81-108 mg/dL, while moderate glucose control target of 140-180 mg/dL was associated with a higher survival rate[6]. This multicenter study emphasized the significant risk of hypoglycemic episodes with TGC due its proximity to the lower limit of the BG levels and other similar studies followed[6-8].

Independent of diabetes mellitus, there are many other clinical scenarios that may cause alterations in BG level among critically ill patients, although diabetics are most susceptible to these alterations[9-11]. Indeed, critically ill patients are usually admitted to the ICU with stress-induced hyperglycemia (50%-85%)[5,12]. For that reason, it is important to identify adequate BG monitoring methods. Continuous BG monitoring would be ideal but can be complex to interpret and treat. Current glucose monitoring devices are rudimentary, and laboratory results may take longer periods of time[13]. In this review, we present some aspects regarding the diagnosis, monitoring and management of glycemia in the ICU and discuss some of the newer technological advances that are at the forefront of continuous care of BG.

Complications

Hyperglycemia has been an important issue when dealing with glucose control in critically ill patients. Krinsley *et al*[9] conducted a retrospective study evaluating 1826 patients admitted to the ICU and reported a significant increase in mortality related to glycemic levels, reaching 42.5% in patients with higher mean glucose levels (> 300 mg/dL). These results are consistent with those from other studies, which also have shown that hyperglycemia is a marker of mortality in the ICU[1,14].

Hypoglycemia, on the other hand, is also an important contributing factor for mortality in critically ill patients. Many trials have tested the effectiveness of TGC and have shown it to be a risk factor for developing hypoglycemia (BG < 40 mg/dL) as well as a powerful marker for mortality; it was also found to be superior to hyperglycemia[6-8,15]. For example, hypoglycemia in intensive insulin therapy (IIT) was found to be 6-fold more common in patients with more liberal glycemic control[2,16].

MATERIALS AND METHODS

The authors independently searched an electronic database (PubMed™) using MeSH identifiers with the terms "blood glucose" and "intensive care unit" to identify articles published up to December 2018 with relevancy to glycemic care in the ICU. This search yielded 309 articles. Of those articles, after independent manual review, 160

potential articles were identified and reviewed. As the topic of this search was narrowed to the care of the critically ill patients, only 49 articles were included in this review. Abstract-only, posters, duplicate information, comments and conference papers were excluded. All data acquired were discussed later between the authors, and any disagreements were resolved (Figure 1).

GUIDELINE RECOMMENDATIONS ON GLUCOSE CONTROL

Several different guidelines recommend certain parameters for glycemic control, with slight differences between the reference values, but a common denominator is the minimization of TGC. In 2011, the American College of Physicians recommended the use of the moderate range of 140-200 mg/dL and did not recommended TGC of 80-110 mg/dL, in order to avoid hypoglycemia and glucose variability (similar to the conclusive results from NICE-SUGAR)[17]. The following year, the American Diabetes Association recommended a very similar glycemic control, ranging from 140-180 mg/dL[18]. These recommendations are consistent with current critical care guidelines that support the use of insulin infusions in values that exceed 150 mg/dL, with the aim of maintaining a glycemia of 180 mg/dL in an attempt to avoid hypoglycemic episodes[19,20]. The Society of Critical Care Medicine guidelines recommended to keep a BG between 150 mg/dL and 180 mg/dL[19].

Despite these recommendations, some studies have reported results that have different outcomes. For example, the COIITSS study investigators ran a multicenter randomized clinical trial involving 509 adult patients with septic shock, revealing no significant mortality difference in patients with a target BG of 80-110 mg/dL compared to those with a target BG of 150 mg/dL[21].

In many studies, preexisting diabetes mellitus has remained a significant cause for bias in terms of glucose management, as prior studies have shown variability in the response to therapy and different mortality from other patients in the ICU[10]. These diabetic patients can develop resistance to glucose fluctuations and can actually benefit from higher BG ranges, avoiding BG variability and hypoglycemic episodes. Marik *et al*[22] suggested the necessary target BG ranges based on the hemoglobin A1c (referred to commonly as HbA1c; 160-220 mg/dL in patients with HbA1c > 7%, and 140-200 mg/dL in patients with HbA1c < 7%). Table 1 summarizes some of these guidelines and recommendations for critically ill patients.

INSULIN THERAPY IN CRITICALLY ILL PATIENTS AND NEWER TECHNOLOGIES FOR BG MONITORING

Prior to 2001, no randomized controlled trials had assessed specific BG targets among critically ill patients. More recently, a variety of studies have focused on management criteria for BG in critically ill patients via glycemic monitoring, use of IV insulin, and computerized processes. Krinsley *et al*[23], in a study of 1600 critically ill patients managed with insulin therapy, reported a 75% reduction in acute kidney injury, 19% decrease in the number of patients transfused with packed red blood cells, 11% decrease in length of ICU stay, and a drop of 29% in mortality. This study aimed to decrease glucose levels to < 140 mg/dL with IIT. However, in a systematic review and meta-analysis by Marik *et al*[15] reviewing TGC (80-110 mg/dL) in ICU patients and including seven randomized controlled trials with more than 11000 patients, no reduction was found in 28-d mortality, blood stream infections, or requirement for renal replacement therapy. These investigators concluded that there is no evidence to support the use of IIT in ICU patients. These findings have since been replicated by other studies[3,24]. In one such, continuous insulin infusion via central venous catheter led to hypoglycemia[24].

Other studies have shown less of a risk of hypoglycemia. In 2014, Amrein *et al*[25] conducted a nurse-driven trial with the Space Glucose Control System™ involving 40 critically ill patients and utilizing a computer-assisted device combined with an infusion pump for glycemic control. The target values were set at 80-150 mg/dL and it was noted that the adherence to the given insulin dose advised by the computer program was 98.2%; only one severe hypoglycemic episode occurred (0.03% of glucose readings)[25]. In a similar study of 210 patients in four different ICUs, monitoring BG was followed by management with a computerized insulin infusion program that had been programmed to a moderate glycemic range of 120-160 mg/dL in surgical ICUs and 140-180 mg/dL in medical ICUs[26]. The mean BG was 147 mg/dL in the surgical ICUs and 171 mg/dL in the medical ICUs. Only 17% had one or more glycemic episodes between 60-79 mg/dL and 9.8% < 70 mg/dL[26].

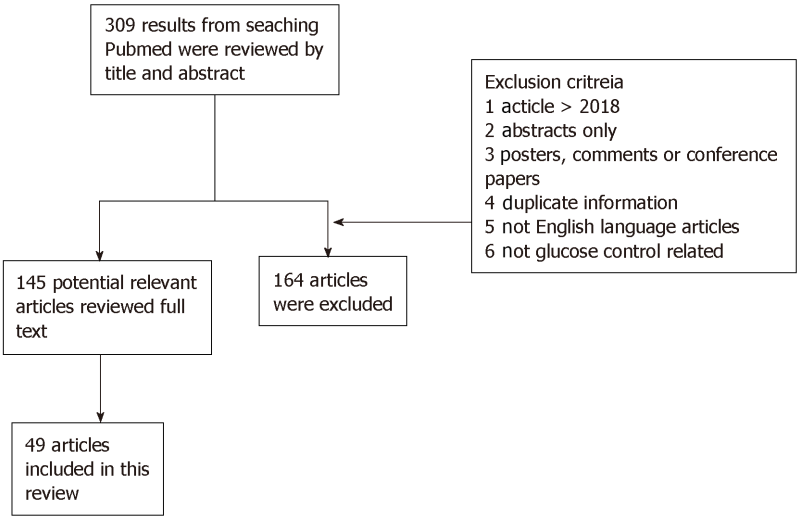

Figure 1 Flowchart describing the methodology for this review.

The Food and Drug Administration (commonly known as the FDA), in 2014, recommended that the use of point-of-care (POC) BG monitors were not suitable for critically ill patients[27]. In addition, the Centers for Medicare and Medicaid Services indicated that "off-label" use of such glucometers in the ICU could be subject to citations and fines during site evaluations[28]. The main reasons for the FDA and Centers for Medicare and Medicaid Services concerns was that ICU patients are unstable and that might cause erroneous BG readings.

In general, POC glucose monitors cost less, require smaller blood samples, and provide almost instant results. For years, they have been the preferred bedside glucose monitoring devices for glycemic management[29]. In a study of a large academic hospital, POC showed significant accuracy[30]. Results from glycemic POC paired to results of central laboratory testing of samples drawn no more than 60 min and passed the FDA's 98% criteria[30].

New software incorporating current guidelines may be just as beneficial for glycemia control[31]. Some studies have used the Clinical Notification System that relies on specific criteria and notifies nursing staff of imminent hypoglycemia and persistent hyperglycemia, defined as two consecutive readings > 150 mg/dL[32,33]. The sensitivity and specificity of this system are excellent, being 98.1% and 99.1% respectively[32,33].

Continuous BG monitoring is now available[34-36]. In a single-center study comparing the benefits of continuous with intermittent glucose monitoring, a peripheral venous catheter was inserted with the GlucoClear™ probe[35]. These monitors were flushed with heparin, calibrated, and began BG monitoring every 5 min using a glucose oxidase-based method. Target glycemic ranges for this study were between 90-150 mg/dL. The number of patients with BG < 70 mg/dL in continuous versus the intermittent groups was 8/39 (20.5%) and 15/38 (39.5%) respectively. The time spent with BG < 70 mg/dL was calculated with a continuous glucose monitoring device, and resulted in 0.4% + -0.9% versus 1.6%+ -3.4% ($P < 0.05$) in intermittent glucose monitoring group[35].

In a study by Flower *et al*[36], utilizing a novel intravascular continuous glucose monitoring with chemical fluorescence sensing mechanism, 92.4% (404/437) were in target glycemic control (108-180 mg/dL), with no values < 72 mg/dL.

There are now subcutaneous continuous glucose monitoring sensors in case intravenous access is not available[37]. In a small cohort of 14 surgical ICU patients, the Sentrino continuous glucose monitoring glucometer (Medtronic, Dublin, Ireland) was used[38]. The study showed that the sensor provided good accuracy, overestimating glycemia by only 1.5 mg/dL[38].

BG CONTROL IN DIABETIC PATIENTS IN THE ICU

The glycemic control protocols vary among different institutions and according to whether the patient has preexisting diabetes mellitus or not. The effects of IIT, for example, have been more noticeable in nondiabetic critical patients[39,40]. In one study, the mortality rates for nondiabetic patients undergoing IIT was 36.8%, as compared to

Table 1 Glycemic range recommendations

Study	Glycemic range	Ref.	Comments
American College of Physicians	140-200 mg/dL	Qaseem *et al*[17], 2014	Recommend use of moderate glucose control to avoid hypoglycemic episodes
American Diabetes Association	140-180 mg/dL	American Diabetes Association[18], 2012	Intensive insulin therapy in TGC can cause severe hypoglycemia
Society of Critical Care Medicine	150-180 mg/dL	Jacobi *et al*[19], 2012	Recommend the use of moderate use of glucose control
COIITSS study	80-110 mg/dL	Annane *et al*[21], 2010	No significant mortality in patients with TGC compared to MGC
Standards of medical care in diabetes	Nondiabetic HbA1c < 7% 140-200 mg/dL HbA1c > 7% 160-220 mg/dL	Marik *et al*[22], 2014	Different approach between diabetics and nondiabetics, due to glucose variability in tolerance

MGC: Moderate glucose control; TGC: Tight glucose control.

40.9% in the control group[39]. In addition, when compared to patients with diabetes, the interventional group mortality was 39.6% versus 36.8% in the diabetic group[39]. In fact, some authors have also suggested that diabetes may be "protective" in the ICU[40].

Mortality is lower for the ICU diabetic population when it comes to hyperglycemia and glucose variability, as compared to nondiabetics. However, hypoglycemia and severe hypoglycemia have an equal mortality rate for both types of patients[10,41]. In a study evaluating both nondiabetic patients and diabetic patients with tight and moderate glycemic control (80-110 mg/dL and 90-140 mg/dL), nondiabetic mortality was 11.9% in the moderate glycemic control group when compared to 8.1% in the TGC group[42]. In contrast, patients with diabetes had a 12.3% mortality with TGC compared to 9.8% for the moderate glycemic control group[42].

COST-EFFECTIVENESS

Cost analysis in the ICU remains an important topic. In one study, an economic analysis reported a cost-saving of 2638 Euros per patient in the group that was treated with intensive glycemic control[43]. Some have suggested that blood gas analyzers capable of monitoring continuous BG levels are the best option for accuracy and cost-saving, if they are in proximity to the ICU, even when the cost per device is $40000. The single test cost is very similar to a POC meter ($100) and the accuracy is equal to a central laboratory device[44]. It is clear that euglycemia and avoidance of hypoglycemia decreases the length of stay in the hospital (from 29 d to 24 d) and has a lower health-care cost (mean $5847), showing a notable amount of money-saving in 5 d[45].

Another factor to consider when analyzing cost savings is the role of TGC in reducing blood stream infections. Some studies have reported that decreasing 5% of hospital-acquired infections could improve cost savings considerably; in fact, one of these studies showed a cost-saving of $1580 per patient, driven by the decreased length of stay in the ICU[46,47]. Such goals can be achieved by attempting to control BG with avoidance of hypoglycemia.

FUTURE APPROACHES

As noted above, dysregulation of glycemia is a significant factor in the poor prognosis of an ICU patient[48]. There are other contributing factors that can change the glycemic status, such as age (older), underweight condition, and type of feeding that is managed in the ICU, since these are labile and can create fluctuations in a more noticeable way compared with the rest of the patients. Critical care clinicians may not be fully aware of these findings. Indeed, some survey studies have shown that clinicians vary significantly in how they manage glycemic index in the ICU and very few are aware that hypoglycemia is associated with an increased hospital mortality[49]. Educational programs aimed at understanding these important risk factors are needed. The development of professional awareness of current guidelines and introduction of new technologies are the first step for improving patient care outcomes.

We believe that computerized, protocol-driven and continuous BG monitoring will become the standard of care in ICUs across the world.

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