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Subcutaneous fast-acting insulin analogues, alone or in combination with long-acting insulin, versus intravenous regular insulin infusion in patients with diabetic ketoacidosis: protocol for an updated systematic review and meta-analysis of randomised trials

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ABSTRACT

Introduction Diabetic ketoacidosis (DKA) is traditionally managed using intravenous regular insulin infusion (RII) in intensive care unit (ICU)/high dependency unit (HDU). Subcutaneous fast-acting insulin analogues (FAIAs) may help to manage DKA outside ICU/HDU. Furthermore, combining subcutaneous long-acting insulin (LAI) with subcutaneous FAIAs may accelerate ketoacidosis resolution. The latest (2016) Cochrane review was inconclusive regarding subcutaneous FAIAs versus intravenous RII in DKA. It was limited by small sample sizes, unclear risk of bias (RoB) in primary trials and did not examine subcutaneous FAIAs with subcutaneous LAI versus intravenous RII in DKA. We report the protocol for an updated meta-analysis on the safety and benefits of subcutaneous FAIAs with/without subcutaneous LAI versus intravenous RII in DKA.

Methods and analysis We will search Medline, Embase, CINAHL and Cochrane Library, from inception until December 2022, without language restrictions, for randomised trials on subcutaneous FAIAs with/without subcutaneous LAI versus intravenous RII in DKA. We also search ClinicalTrials.gov, ClinicalTrialsRegister.eu and reference lists of included trials. Primary outcomes include all-cause in-hospital mortality, time to DKA resolution, in-hospital DKA recurrence and hospital readmission for DKA post-discharge. Secondary outcomes include resource utilisation and patient satisfaction. Safety outcomes include important complications of DKA and insulin. Reviewers will extract data, assess overall RoB and quality of evidence using Grading of Recommendations, Assessment, Development and Evaluation. We will assess statistical heterogeneity by visually inspecting forest plots and the I^2 statistic. We will synthesise data using the random-effects model. Predefined subgroup analyses are: mild versus moderate versus severe DKA; age <20 vs ≥20 years; pregnant versus non-pregnant; infective versus non-infective DKA precipitating cause; subcutaneous FAIAs alone versus subcutaneous FAIAs and subcutaneous LAI; and high versus low overall RoB. We will also perform trial sequential analysis for primary outcomes.

Ethics and dissemination Ethics board approval is not required. Results will be disseminated through publication in a peer-reviewed journal.

PROSPERO registration number CRD42022369518.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is an updated meta-analysis that will include recent trials.
⇒ This study will include trials of subcutaneous fast-acting insulin analogues (FAIAs) with/without subcutaneous long-acting insulin (LAI) versus intravenous regular insulin infusion (RII) in diabetic ketoacidosis (DKA); combination therapy of subcutaneous FAIAs and subcutaneous LAI versus intravenous RII has not been investigated in previous reviews.
⇒ We will perform trial sequential analysis on the primary outcomes.
⇒ Other strengths include a comprehensive search strategy, predefined subgroup analyses and use of Grading of Recommendations, Assessment, Development and Evaluation methodology to assess certainty of evidence.
⇒ Limitations include the anticipated high clinical heterogeneity given the different severities of DKA, different regimens of subcutaneous FAIAs with/without subcutaneous LAI, the wide age distribution of DKA and the differences in outcome reporting across primary trials.

INTRODUCTION

Diabetic ketoacidosis (DKA) is an acute hyperglycaemic emergency that can result in serious morbidity and mortality if left untreated. The incidence of DKA ranges

from 0 to 56 per 1000 person-years in different geographical areas.[1] DKA is characterised by hyperglycaemia, metabolic acidosis and ketonaemia.[2–6] Its treatment involves the correction of fluid and electrolyte abnormalities and insulin administration. Insulin therapy is an important component of DKA management as it reduces hepatic gluconeogenesis and suppresses ketogenesis.[2]

Intravenous regular insulin infusion (RII) is often used to treat DKA and is historically recommended by the American Diabetes Association (ADA)[5] and Joint British Societies[3] guideline for DKA management. In many institutions and for decades, DKA has been treated with intravenous RII in the intensive care unit (ICU) or high dependency unit (HDU). The main reasons for ICU/HDU care requirements had been cited as the need for frequent monitoring of blood sugar during intravenous RII and vital signs in DKA.[7]

Intravenous RII has a rapid (15 min) onset of action and allows for titratable drug administration to match changing glucose levels in DKA.[8] Commonly available forms of regular insulin include Humulin R, Novolin R and Actrapid. In the past two decades, fast-acting insulin analogues (FAIAs) have been developed. These analogues include insulin lispro, insulin aspart, insulin glulisine and fast-acting insulin aspart (faster aspart). Subcutaneous administration of these FAIAs has an onset of action of ≈5–15 min, a peak action of 1–3 hours and duration of action of 3–5 hours.[9] These pharmacological properties suggest that subcutaneous FAIAs may produce clinical benefits comparable with intravenous RII in DKA and may be useful to manage some DKA cases outside the ICU/HDU, which are scarce and costly hospital resources.

In the latest Cochrane review (n=201 in five trials) published in 2016[10] and based on low-quality to very low-quality evidence, the authors concluded that there were neither advantages nor disadvantages when comparing the effects of subcutaneous FAIAs versus intravenous RII for treating mild-to-moderate DKA. However, this review has important limitations. The primary studies had small sample sizes (n=20–60), were mainly (four out of five) single-centre trials and only one trial recruited paediatric patients (n=60). The risk of bias (RoB) across several domains was unclear in the majority of primary studies including random sequence generation, allocation concealment and various aspects of blinding.

Since this Cochrane review, there has been a further trial involving paediatric patients (n=50) published that compared subcutaneous insulin aspart with intravenous RII in DKA.[11] It increased the pooled sample size of paediatric patients (from 60 to 110) and this might allow better examination of the effects of subcutaneous FAIAs versus intravenous RII in DKA among paediatric patients.

This review also did not investigate the effects and safety of combination therapy of subcutaneous FAIAs and subcutaneous long-acting insulin (LAI) in DKA compared with intravenous RII. Common examples of LAI include insulin glargine, insulin detemir and insulin degludec. Subcutaneous LAI provides a basal insulin component, and its concomitant administration with intravenous RII in DKA accelerates ketoacidosis resolution and prevents rebound hyperglycaemia especially during transition from intravenous RII to subcutaneous insulin.[12] The benefits of subcutaneous LAI and subcutaneous FAIAs may be similar in DKA. In a recent large retrospective pre- and post- cohort study (n=7989), combination therapy with subcutaneous insulin lispro and subcutaneous insulin glargine reduced rates of ICU admission and 30-day hospital readmission but with no increase in hypoglycaemic or 30-day mortality rates when compared with intravenous RII.[13]

Results from meta-analyses often suffer from overestimation (type 1 errors) or underestimation (type 2 errors) of intervention effects due to inclusion of too few patients and multiple and sequential testing.[14 15] Trial sequential analysis (TSA) has been developed and increasingly used recently to reduce false positive and negative results in meta-analyses. TSA provides updated monitoring and futility boundaries with the chronological addition of each new trial result to allow early detection or rejection of intervention effect when the required cumulative meta-analytical information size has not been reached.[16] TSA may be useful to provide more conclusive interpretations of the effects of subcutaneous FAIAs versus intravenous RII in DKA on important outcomes as sufficient meta-analytical information size is unlikely to be reached with small primary trials.

The aim of this systematic review and meta-analysis is to update, by including recent data and TSA, on whether subcutaneous FAIAs, alone or in combination with subcutaneous LAI, improve important patient-centred outcomes and are safe in patients with DKA compared with intravenous RII by reviewing randomised controlled trials (RCTs).

METHODS AND ANALYSIS

Study design and registration

This systematic review and meta-analysis protocol has been prospectively registered in the International Register of Systematic Reviews (PROSPERO; CRD42022369518). We will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement for reporting the study findings.[17] We have followed the guidance of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols checklist in reporting the present protocol (online supplemental appendix 1).

Eligibility criteria

We will include randomised trials investigating the effectiveness and safety of subcutaneous FAIAs (alone or combined with subcutaneous LAI) versus intravenous RII among patients presenting with DKA across various hospital settings, that is, emergency department (ED), medical/surgical general ward, obstetric ward, perioperative care, ICU and HDU.

We will include trials that recruited patients with DKA of any age with type 1 or 2 diabetes mellitus (DM) including

pregnant women with pre-existing or gestational DM (GDM).

Diagnostic criteria for DM and GDM change over the years and might differ between major national and international bodies (eg, ADA vs WHO). For this review, we will use the primary authors' definition or their quoted diagnostic criteria of DM or GDM valid at the trial commencement date. Similarly, we will also use the primary authors' definition or their quoted diagnostic criteria for DKA at trial commencement.

In addition, it is unlikely that subcutaneous FAIAs (alone or combined with subcutaneous LAI) will be able to replace intravenous RII for DKA across all severities, and the most critically ill patients with DKA with airway and circulation issues will still require intravenous RII in the ICU/HDU. Hence, it is important to have a reliable DKA severity classification system to better characterise the appropriate severity subgroup(s) of patients with DKA who may potentially be managed using subcutaneous FAIAs (alone or combined with subcutaneous LAI). We will use the ADA criteria for DKA severity,[2] which are as follows:

- Mild DKA: plasma glucose >250 mg/dL (13.9 mmol/L), arterial pH 7.25–7.30, serum bicarbonate 15–18 mEq/L, urine and serum ketones positive, anion gap >10, alert.
- Moderate DKA: plasma glucose >250 mg/dL (13.9 mmol/L), arterial pH 7.00–7.24, serum bicarbonate 10–<15 mEq/L, urine and serum ketones positive, anion gap >12, alert/drowsy.
- Severe DKA: plasma glucose >250 mg/dL (13.9 mmol/L), arterial pH <7.00, serum bicarbonate <10 mEq/L, urine and serum ketones positive, anion gap >12, stupor/coma.

The comparator arm will include intravenous RII. There will likely be variations in intravenous RII regimens across studies conducted at different time periods (use of intravenous bolus, differences in dosage, frequency and duration). We will accept all intravenous RII regimens. Intervention arm(s) will include subcutaneous FAIAs (alone or combined with subcutaneous LAI). Subcutaneous FAIAs will include subcutaneous insulin lispro, insulin aspart, insulin glulisine and fast-acting insulin aspart (faster aspart) in dosage regimens as listed by the primary authors. Subcutaneous LAI will include subcutaneous insulin glargine, insulin detemir and insulin degludec in dosage regimens as listed by the primary authors.

Concomitant management of DKA in both intervention versus comparator arms will have to be similar to allow fair comparisons. These management steps will include correction of fluid and electrolytes, addressing of precipitating factors of DKA, and monitoring of sensorium, vital signs, fluid status and laboratory parameters like blood sugar, blood gas and important electrolytes.

Primary outcomes are important patient-centred outcomes including all-cause in-hospital mortality, time to resolution of DKA, in-hospital recurrence of DKA and hospital readmission for DKA post-discharge. We will use the resolution criteria for DKA and time frame stated by the primary authors to examine the time to resolution of DKA and hospital readmission for DKA post-discharge, respectively.

Secondary outcomes will include resource utilisation and patient satisfaction. Resource utilisation outcomes will include length of hospital stay, total hospitalisation costs and total dose of insulin administered until DKA resolution.

Safety outcomes will be important complications associated with DKA and/or its management (including insulin therapy). These will include rates of hypoglycaemia, hypokalaemia, cerebral oedema,[18] hypophosphataemia, secondary infections, renal replacement therapy and cardiorespiratory complications like pulmonary embolism and oedema.

Search strategy

We will search Medline, Embase, CINAHL and Cochrane Library from inception until December 2022 without language restrictions. We will seek help from relevant native speakers if we encounter potentially relevant studies that are published in a language not spoken by the authors. We will review reference lists for eligible new trials and search ClinicalTrials.gov as well as Clinical TrialsRegister.eu for ongoing or unpublished trials and for additional data from published trials. The search strategy will include the following keywords: diabetic ketoacidosis, hyperglycemic crisis, intravenous regular insulin infusion, intravenous continuous regular insulin, intravenous short-acting insulin infusion, intravenous continuous short-acting insulin, subcutaneous fast-acting insulin, subcutaneous rapid-acting insulin, subcutaneous long-acting insulin, intravenous Humulin R, intravenous Novolin R, intravenous Actrapid, subcutaneous Insulin Lispro, subcutaneous Insulin Aspart, subcutaneous Insulin Glulisine, subcutaneous fast-acting Insulin Aspart (Faster Aspart), subcutaneous Insulin Glargine, subcutaneous Insulin Detemir, subcutaneous Insulin Degludec, mortality, resolution of diabetic ketoacidosis, recurrence of diabetic ketoacidosis, re-admission for diabetic ketoacidosis, humans and randomized clinical trials. Medical Subject Heading (MeSH) terms will include diabetic ketoacidosis, insulin, insulin; short-acting, insulin; long-acting, Insulin Lispro, Insulin Aspart, Insulin Glargine, Insulin Detemir, mortality and humans.

Proposed search strategies using Medline, Embase, CINAHL and Cochrane Library are attached as online supplemental appendix 2.

If we detect additional keywords or MeSH terms during our electronic or other searches, we will modify the electronic searches to incorporate these changes and document the changes in the search strategy.

Study selection

Reviewers (BLL, WFL, BL and YELC) will, independently and in duplicate, screen the titles and abstracts of all

identified studies to generate a list of eligible trials from which full texts will be obtained. Subsequently, the same reviewers will, independently and in duplicate, assess the eligibility of these full texts of published trials and search the reference lists of these publications to decide on the final included studies.

Discrepancies between reviewers will be resolved through discussion and consensus, or if needed by adjudication from an external reviewer and/or contact with authors of the original trials for clarification.

Data extraction

Two pairs of reviewers (BLL and WFL; BL and YELC) will extract data from included studies using a predesigned data extraction form adapted from the Cochrane Collaboration.[19] The data collection form is attached as online supplemental appendix 3. Data extracted will include the following: general study information (authors, publication year and study location(s)); study population details (clinical setting—ED vs other hospital settings, adult (including pregnant patients with pre-existing DM or GDM) vs paediatric patients, spectrum of DKA severity); details of the intervention arm(s) (differing regimens of subcutaneous FAIAs with/without subcutaneous LAI); control arm(s) (differing regimens of intravenous RII with/without intravenous RI bolus(es)) as well as the primary, secondary and safety outcomes as listed above.

In randomised trials that included >one arm of subcutaneous FAIAs with/without subcutaneous LAI and/or >one control arm of intravenous RII with/without intravenous regular insulin bolus(es), we will extract data from the comparison between intervention versus control arm(s) in the primary trial that is closest to that in other primary studies to be used for pooled main or planned subgroup analyses.

Discrepancies in data extraction will be resolved through discussion and consensus or, if needed, via consultation with an external reviewer and/or contact with authors of the original trials for clarification.

RoB assessment

We will assess the RoB for each outcome of the individual studies using a modified Cochrane RoB instrument.[20] The instrument assesses biases in the following five domains: selection bias (random sequence generation and allocation concealment); performance bias (blinding of participants and researchers); detection bias (blinding of outcome assessment); attrition bias (incomplete outcome data) and reporting bias (selective reporting). Within each domain, we will classify the RoB as high, low or unclear. Reviewers will also judge to determine whether any particular domain is logistically challenging to achieve in any of the primary studies (like blinding when comparing subcutaneous FAIAs with/without subcutaneous LAI and intravenous RII) and whether this limitation is likely or unlikely to affect the reported effect size of the outcome.

Primary studies will be classified as having an overall high RoB when they have at least one domain that is rated as having high risk after exclusion of certain domain that is judged to be logistically challenging to achieve and unlikely to affect the reported outcome effect size. The overall RoB for a primary trial will be considered low if RoB is judged to be low in all domains and unclear if RoB is judged to be unclear in any of the domains. A primary trial will be classified as having high overall risk of RoB if it has at least one domain rated as high risk and unclear risk simultaneously.

Quality of evidence

We will also assess the quality of evidence (QoE) for each outcome using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach that classifies evidence as high, moderate, low or very low quality based on considerations of RoB, consistency, directness, precision and publication bias.[21] We attach a summary of findings table (online supplemental appendix 4) which is adapted using the GRADEpro software to demonstrate how we will present our GRADE assessment for the main outcomes.

Assessment of the individual and overall RoB categories as well as the QoE will be performed independently by the two pairs of reviewers (BLL and WFL; BL and YELC) with any discrepancies resolved by discussion and consensus or if necessary, via consultation with an external reviewer.

Data analysis

All analyses will be performed using RevMan V.5.3 (Cochrane Collaboration, Oxford, UK) software. We will use DerSimonian and Laird random-effects model a priori to conduct the data analysis and meta-analysis. We choose the random-effects model as it produces more conservative CIs and it considers both within-study and between-study variability.[17]

For continuous outcomes, we will calculate the mean difference and its corresponding 95% CIs whenever possible. When primary studies reported continuous outcomes using median, range and IQR, we will convert them into mean and SD. We will adopt a modified conversion method which considers the effects of sample size,[22] an important limitation of the Hozo *et al*'s[23] and Bland's[24] methods. For dichotomous outcomes, we will calculate relative risk and its 95% CIs.

We will generate forest plots to demonstrate individual and pooled effect sizes for the outcome of interest if there are at least two studies. We will assess for heterogeneity between studies by first visual inspection of the forest plots and then using the I^2 statistic. I^2 measures the percentage of the total variation in estimated effects of the outcome across studies that is due to heterogeneity rather than to chance.[25] An I^2 value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity.

Regardless of the observed statistical heterogeneity (I^2 values), we plan to conduct the following a priori subgroup analyses for each outcome when each subgroup is represented by at least two studies. These subgroup analyses will be: mild versus moderate versus severe DKA; age <20

(childhood to adolescence) vs ≥20 years (adult); pregnant versus non-pregnant; infective versus non-infective precipitating cause of DKA; subcutaneous FAIAs alone versus subcutaneous FAIAs and subcutaneous LAI, as well as high versus low overall RoB. We will test for subgroup interaction using χ^2 significance test.[26]

We will address missing data in several ways. We will evaluate for efforts within the study design to prevent missing data, rates of and reasons for missing data in the primary studies. We will contact primary authors for clarification if necessary. We will also assess whether primary authors attempted to identify potential bias due to missing data by comparing participants with and without missing values and explain how they handled missing data using ways like imputation and performing sensitivity analyses such as best-case and worst-case scenario analyses to investigate how missing data affect their reported outcome effect sizes. We will then judge independently, through consensus and/or consultation with an external reviewer whether the reported outcome effect sizes by the primary authors are likely/unlikely to be affected by missing data. We will perform sensitivity analyses in our meta-analysis that include and exclude those primary studies that are judged to be affected by missing data. These sensitivity analyses will allow us to investigate how pooled effect sizes in our meta-analysis are affected by missing data. The steps mentioned above are important in our address of attrition bias during RoB and GRADE assessments of the primary studies.

Meta-analyses often suffer from overestimation (type 1 errors) or underestimation (type 2 errors) of intervention effects due to inclusion of sparse data and repeated significance testing when they are updated with data from new trials.[14 15] We will perform TSA using a random-effects model for the primary outcomes (all-cause in-hospital mortality, time to resolution of DKA, in-hospital recurrence of DKA and hospital readmission for DKA post-discharge) whenever possible. In the TSA, we will use α=0.05, β=0.20 (80% power), estimated effect sizes and control rates obtained using several means. These estimates can be derived from sample size calculations in the largest primary trial with low overall RoB or the magnitude of effect and control rate reported from pooled analysis (empirical estimates). If such information is unavailable, we will use the control rate in pooled analysis and a clinically significant effect size based on our consensus. Our consensus represents our expectations of clinically relevant effect sizes. TSA can guide interpretation of observed effect sizes in several ways. TSA generates the required information size calculated as diversity-adjusted information size (DIS) needed to support valid conclusions on the observed effect size and provides important information on how many more patients need to be included in further trials.[16] In addition, TSA also creates adjusted and restricted thresholds for statistical significance (trial sequential monitoring boundaries (TSMBs)) when the DIS and the corresponding number of required trials for the meta-analysis are not reached.[16] The cumulative Z curve, which includes the selected primary trials, if it crosses the TSMB for benefit (before DIS is reached) will make it likely that the observed treatment effect size is true.[16] However, if the Z curve crosses the TSMB for futility (before DIS is reached), the observed treatment effect size is likely to be absent.[16] If the Z curve crosses neither the TSMB for benefit or futility (before DIS is reached), there is inconclusive evidence to support the presence or absence of the observed treatment effect size.[16]

TSA will be performed using TSA V.0.9.5.10 Beta (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark, www.ctu.dk/tsa).

Patient and public involvement

None.

ETHICS AND DISSEMINATION

Ethics board approval is not required. Results will be disseminated through publication in a peer-reviewed journal.

DISCUSSION

DKA is the most common hyperglycaemic emergency among patients with diabetes and is associated with significant morbidity and healthcare costs.[18 27] Intravenous RII is often used to treat DKA; and in many institutions and for decades, DKA has been treated with intravenous RII in the ICU or HDU. The ICU and HDU are scarce resources that are often critically strained especially in pandemics like COVID-19.[28] There is constant pressure to identify emergencies traditionally managed in the ICU/HDU to be managed outside these settings by incorporating newer management strategies. DKA has been identified by critical care specialists as a diagnosis suitable for treatment in a non-ICU/HDU setting if the right patient selection, appropriate treatment and monitoring can be put in place.[29 30]

Subcutaneous FAIAs, with their rapid onset time (≈5–15 min) and greater peak serum insulin concentrations,[9] may offer treatment alternatives in selected patients with DKA outside the ICU/HDU. Furthermore, subcutaneous LAI provides a basal insulin component, and its concomitant administration with intravenous RII in DKA accelerates ketoacidosis resolution and prevents rebound hyperglycaemia during transition from intravenous RII to subcutaneous insulin.[12] Combination therapy with subcutaneous FAIAs and subcutaneous LAI in DKA may produce similar benefits.

In the latest Cochrane review in 2016[10] and based on low-quality to very low-quality evidence, the effects of subcutaneous FAIAs versus intravenous RII in mild-to-moderate DKA were inconclusive. The limitations of the review are mainly small sample sizes (n=20–60) of largely single-centre primary trials with unclear RoB in several domains in the majority of these trials. Our study protocol

aims to provide an updated review by including new data, investigating the effects of subcutaneous FAIAs either alone or with subcutaneous LAI versus intravenous RII in DKA and performing TSA on our primary outcomes. Our TSA for the primary outcomes will generate DIS, TSMBs for effect and futility to reduce type 1 and 2 errors in our meta-analysis.

The strengths of our protocol include a comprehensive search strategy of published and unpublished literature, a priori clinically relevant subgroup analyses and using GRADE methodology to assess certainty of evidence.

Limitations of our protocol include the anticipated high clinical heterogeneity given the different severities of DKA, different regimens of subcutaneous FAIAs with/without subcutaneous LAI, the wide age distribution of DKA and the differences in outcome reporting across included primary trials. We will address clinical heterogeneity by evaluating for statistical heterogeneity, explore predefined clinically important subgroup analyses and to account for inconsistencies in our GRADE evaluation. To address differences in outcome reporting across included trials, we will include a spectrum of relevant primary and secondary outcomes.

In conclusion, this protocol describes the details and methodology of a planned systematic review and meta-analysis addressing the effects and safety of subcutaneous FAIAs with/without subcutaneous LAI versus intravenous RII in DKA. This review will provide a timely update on this important clinical topic to inform daily practice and clinical practice guidelines, and guide areas of investigation in future RCTs.

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Contributors BLL, WFL and BL conceived the study. BLL and WFL also wrote the study protocol to be registered with PROSPERO. All authors (BLL, WFL, BL, YELC and KVL) contributed to protocol development. BLL and WFL drafted the study protocol and this manuscript. All authors (BLL, WFL, BL, YELC and KVL) contributed to refinement of the study protocol and manuscript as well as approved the final manuscript.

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