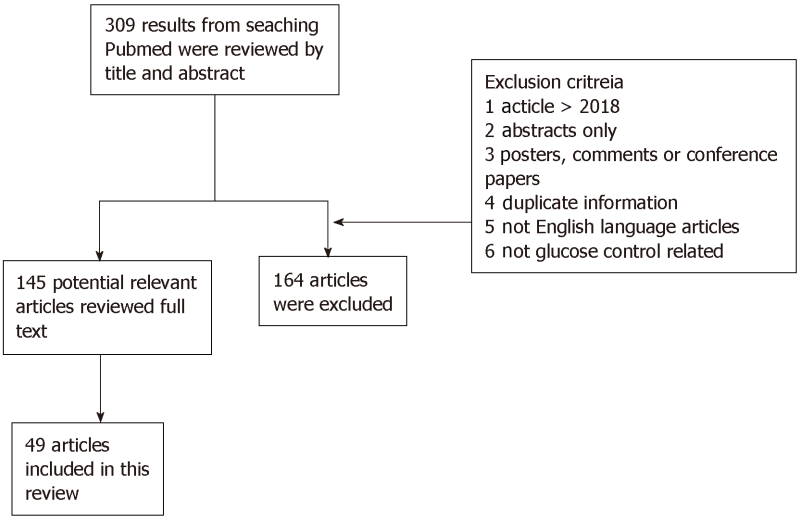

Figure 1 Flowchart describing the methodology for this review.

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.

REFERENCES

1 **Lu M**, Zuo Y, Guo J, Wen X, Kang Y. Continuous glucose monitoring system can improve the quality of glucose control and glucose variability compared with point-of-care measurement in critically ill patients: A randomized controlled trial. *Medicine (Baltimore)* 2018; **97**: e12138 [PMID: 30200106 DOI: 10.1097/MD.0000000000012138]

2 **van den Berghe G**, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; **345**: 1359-1367 [PMID: 11794168 DOI: 10.1056/NEJMoa011300]

3 **Van den Berghe G**. What's new in glucose control in the ICU? *Intensive Care Med* 2013; **39**: 823-825 [PMID: 23460140 DOI: 10.1007/s00134-013-2874-3]

4 **Preiser JC**, Chase JG, Hovorka R, Joseph JI, Krinsley JS, De Block C, Desaive T, Foubert L, Kalfon P, Pielmeier U, Van Herpe T, Wernerman J. Glucose Control in the ICU: A Continuing Story. *J Diabetes Sci Technol* 2016; **10**: 1372-1381 [PMID: 27170632 DOI: 10.1177/1932296816648713]

5 **De Block C**, Manuel-y-Keenoy B, Rogiers P, Jorens P, Van Gaal L. Glucose control and use of continuous glucose monitoring in the intensive care unit: a critical review. *Curr Diabetes Rev* 2008; **4**: 234-244 [PMID: 18690906 DOI: 10.2174/157339908785294460]

6 **Lleva RR**, Thomas P, Bozzo JE, Hendrickson KC, Inzucchi SE. Using the glucometrics website to benchmark ICU glucose control before and after the NICE-SUGAR study. *J Diabetes Sci Technol* 2014; **8**: 918-922 [PMID: 25013157 DOI: 10.1177/1932296814540871]

7 **Bersoux S**, Cook CB, Kongable GL, Shu J. RETROSPECTIVE STUDY OF GLYCEMIC CONTROL FOLLOWING TRANSITION FROM THE INTENSIVE CARE UNIT IN A NATIONAL SAMPLE OF U.S. HOSPITALS. *Endocr Pract* 2015; **21**: 986-992 [PMID: 26121449 DOI: 10.4158/EP15650.OR]

8 **Dodson CH**, Simpson J, Feinstein D. Glycemic control in a medical intensive care setting: revision of an intensive care unit nurse-driven hyperglycemia protocol. *Crit Care Nurs Q* 2014; **37**: 170-181 [PMID: 24595254 DOI: 10.1097/CNQ.0000000000000016]

9 **Krinsley JS**. Association between hyperglycemia and increased hospital mortality in a heterogeneous population of critically ill patients. *Mayo Clin Proc* 2003; **78**: 1471-1478 [PMID: 14661676 DOI: 10.4065/78.12.1471]

10 **Krinsley JS**, Egi M, Kiss A, Devendra AN, Schuetz P, Maurer PM, Schultz MJ, van Hooijdonk RT, Kiyoshi M, Mackenzie IM, Annane D, Stow P, Nasraway SA, Holewinski S, Holzinger U, Preiser JC, Vincent JL, Bellomo R. Diabetic status and the relation of the three domains of glycemic control to mortality in critically ill patients: an international multicenter cohort study. *Crit Care* 2013; **17**: R37 [PMID: 23452622 DOI: 10.1186/cc12547]

11 **Jamaludin UK**, M Suhaimi F, Abdul Razak NN, Md Ralib A, Mat Nor MB, Pretty CG, Humaidi L. Performance of Stochastic Targeted Blood Glucose Control Protocol by virtual trials in the Malaysian intensive care unit. *Comput Methods Programs Biomed* 2018; 149-155 [PMID: 29903481 DOI: 10.1016/j.cmpb.2018.03.001]

12 **Fahy BG**, Sheehy AM, Coursin DB. Glucose control in the intensive care unit. *Crit Care Med* 2009; **37**: 1769-1776 [PMID: 19325461 DOI: 10.1097/CCM.0b013e3181a19ceb]

13 **Krinsley JS**. Glycemic variability: a strong independent predictor of mortality in critically ill patients. *Crit Care Med* 2008; **36**: 3008-3013 [PMID: 18824908 DOI: 10.1097/CCM.0b013e31818b38d2]

14 **Godinjak A**, Iglica A, Burekovic A, Jusufovic S, Ajanovic A, Tancica I, Kukuljac A. Hyperglycemia in Critically Ill Patients: Management and Prognosis. *Med Arch* 2015; **69**: 157-160 [PMID: 26261382 DOI: 10.5455/medarh.2015.69.157-160]

15 **Marik PE**, Preiser JC. Toward understanding tight glycemic control in the ICU: a systematic review and metaanalysis. *Chest* 2010; **137**: 544-551 [PMID: 20018803 DOI: 10.1378/chest.09-1737]

16 **Kavanagh BP**, McCowen KC. Clinical practice. Glycemic control in the ICU. N. *Engl J Med* 2010; **363**: 2540-2546 [PMID: 21175316 DOI: 10.1056/NEJMcp1001115]

17 **Qaseem A**, Chou R, Humphrey LL, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Inpatient glycemic control: best practice advice from the Clinical Guidelines Committee of the American College of Physicians. *Am J Med Qual* 2014; **29**: 95-98 [PMID: 23709472 DOI: 10.1177/1062860613489339]

18 **American Diabetes Association**. Executive summary: Standards of medical care in diabetes--2012. *Diabetes Care* 2012; **35** Suppl 1: S4-S10 [PMID: 22187471 DOI: 10.2337/dc12-s004]

19 **Jacobi J**, Bircher N, Krinsley J, Agus M, Braithwaite SS, Deutschman C, Freire AX, Geehan D, Kohl B, Nasraway SA, Rigby M, Sands K, Schallom L, Taylor B, Umpierrez G, Mazuski J, Schunemann H. Guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients. *Crit Care Med* 2012; **40**: 3251-3276 [PMID: 23164767 DOI: 10.1097/CCM.0b013e3182653269]

20 **Clain J**, Ramar K, Surani SR. Glucose control in critical care. *World J Diabetes* 2015; **6**: 1082-1091 [PMID: 26265994 DOI: 10.4239/wjd.v6.i9.1082]

21 **COIITSS Study Investigators**. Annane D, Cariou A, Maxime V, Azoulay E, D'honneur G, Timsit JF, Cohen Y, Wolf M, Fartoukh M, Adrie C, Santré C, Bollaert PE, Mathonet A, Amathieu R, Tabah A, Clec'h C, Mayaux J, Lejeune J, Chevret S. Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial. *JAMA* 2010; **303**: 341-348 [PMID: 20103758 DOI: 10.1001/jama.2010.2]

22 **Marik PE**, Egi M. Treatment thresholds for hyperglycemia in critically ill patients with and without diabetes. *Intensive Care Med* 2014; **40**: 1049-1051 [PMID: 24859623 DOI: 10.1007/s00134-014-3344-2]

23 **Krinsley JS**. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. *Mayo Clin Proc* 2004; **79**: 992-1000 [PMID: 15301325 DOI: 10.4065/79.8.992]

24 **Maury E**, Vitry P, Galbois A, Ait-Oufella H, Baudel JL, Guidet B, Offenstadt G. Continuous insulin administration via complex central venous catheter infusion tubing is another risk factor for blood glucose imbalance. A retrospective study. *Ann Intensive Care* 2012; **2**: 16 [PMID: 22697362 DOI: 10.1186/2110-5820-2-16]

25 **Amrein K**, Kachel N, Fries H, Hovorka R, Pieber TR, Plank J, Wenger U, Lienhardt B, Maggiorini M.

Glucose control in intensive care: usability, efficacy and safety of Space GlucoseControl in two medical European intensive care units. *BMC Endocr Disord* 2014; **14**: 62 [PMID: 25074071 DOI: 10.1186/1472-6823-14-62]

26 **Sandler V**, Misiasz MR, Jones J, Baldwin D. Reducing the risk of hypoglycemia associated with intravenous insulin: experience with a computerized insulin infusion program in 4 adult intensive care units. *J Diabetes Sci Technol* 2014; **8**: 923-929 [PMID: 25172875 DOI: 10.1177/1932296814540870]

27 **Klonoff DC**. Point-of-Care Blood Glucose Meter Accuracy in the Hospital. *Setting. Diabetes Spectr* 2014; **27**: 174-179 [PMID: 26246776 DOI: 10.2337/diaspect.27.3.174]

28 **DuBois JA**, Slingerland RJ, Fokkert M, Roman A, Tran NK, Clarke W, Sartori DA, Palmieri TL, Malic A, Lyon ME, Lyon AW. Bedside Glucose Monitoring-Is it Safe? A New, Regulatory-Compliant Risk Assessment Evaluation Protocol in Critically Ill Patient Care Settings. *Crit Care Med* 2017; **45**: 567-574 [PMID: 28169943 DOI: 10.1097/CCM.0000000000002252]

29 **Seley JJ**, Diaz R, Greene R. Blood Glucose Meters in ICUs. *Am J Nurs* 2016; **116**: 46-49 [PMID: 27011137 DOI: 10.1097/01.NAJ.0000482138.89553.94]

30 **Zhang R**, Isakow W, Kollef MH, Scott MG. Performance of a Modern Glucose Meter in ICU and General Hospital Inpatients: 3 Years of Real-World Paired Meter and Central Laboratory Results. *Crit Care Med* 2017; **45**: 1509-1514 [PMID: 28640025 DOI: 10.1097/CCM.0000000000002572]

31 **Dubois J**, Van Herpe T, van Hooijdonk RT, Wouters R, Coart D, Wouters P, Van Assche A, Veraghtert G, De Moor B, Wauters J, Wilmer A, Schultz MJ, Van den Berghe G, Mesotten D. Software-guided versus nurse-directed blood glucose control in critically ill patients: the LOGIC-2 multicenter randomized controlled clinical trial. *Crit Care* 2017; **21**: 212 [PMID: 28806982 DOI: 10.1186/s13054-017-1799-6]

32 **Colpaert K**, Oeyen S, Sijnave B, Peleman R, Benoit D, Decruyenaere J. Influence of smart real-time electronic alerting on glucose control in critically ill patients. *J Crit Care* 2015; **30**: 216.e1-216.e6 [PMID: 25194590 DOI: 10.1016/j.jcrc.2014.07.030]

33 **Berger MM**, Que YA. Bioinformatics assistance of metabolic and nutrition management in the ICU. *Curr Opin Clin Nutr Metab Care* 2011; **14**: 202-208 [PMID: 21157310 DOI: 10.1097/MCO.0b013e328341ed77]

34 **Crane BC**, Barwell NP, Gopal P, Gopichand M, Higgs T, James TD, Jones CM, Mackenzie A, Mulavisala KP, Paterson W. The Development of a Continuous Intravascular Glucose Monitoring Sensor. *J Diabetes Sci Technol* 2015; **9**: 751-761 [PMID: 26033921 DOI: 10.1177/1932296815587937]

35 **Preiser JC**, Lheureux O, Thooft A, Brimioulle S, Goldstein J, Vincent JL. Near-Continuous Glucose Monitoring Makes Glycemic Control Safer in ICU Patients. *Crit Care Med* 2018; **46**: 1224-1229 [PMID: 29677007 DOI: 10.1097/CCM.0000000000003157]

36 **Flower OJ**, Bird S, Macken L, Hammond N, Yarad E, Bass F, Fisher C, Strasma P, Finfer S. Continuous intra-arterial blood glucose monitoring using quenched fluorescence sensing: a product development study. *Crit Care Resusc* 2014; **16**: 54-61 [PMID: 24588437]

37 **Yue XY**, Zheng Y, Cai YH, Yin NN, Zhou JX. Real-time continuous glucose monitoring shows high accuracy within 6 hours after sensor calibration: a prospective study. *PLoS One* 2013; **8**: e60070 [PMID: 23555886 DOI: 10.1371/journal.pone.0060070]

38 **Punke MA**, Decker C, Wodack K, Reuter DA, Kluge S. Continuous glucose monitoring on the ICU using a subcutaneous sensor. Med Klin Intensivmed. *Notfmed* 2015; **110**: 360-363 [PMID: 25676120 DOI: 10.1007/s00063-014-0453-1]

39 **Krinsley JS**, Meyfroidt G, van den Berghe G, Egi M, Bellomo R. The impact of premorbid diabetic status on the relationship between the three domains of glycemic control and mortality in critically ill patients. *Curr Opin Clin Nutr Metab Care* 2012; 151-160 [PMID: 22234163 DOI: 10.1097/MCO.0b013e32834f0009]

40 **Krinsley JS**, Fisher M. The diabetes paradox: diabetes is not independently associated with mortality in critically ill patients. *Hosp Pract (1995)* 2012; **40**: 31-35 [PMID: 22615076 DOI: 10.3810/hp.2012.04.967]

41 **Sechterberger MK**, Bosman RJ, Oudemans-van Straaten HM, Siegelaar SE, Hermanides J, Hoekstra JB, De Vries JH. The effect of diabetes mellitus on the association between measures of glycaemic control and ICU mortality: a retrospective cohort study. *Crit Care* 2013; **17**: R52 [PMID: 23510051 DOI: 10.1186/cc12572]

42 **Lanspa MJ**, Hirshberg EL, Phillips GD, Holmen J, Stoddard G, Orme J. Moderate glucose control is associated with increased mortality compared with tight glucose control in critically ill patients without diabetes. *Chest* 2013; **143**: 1226-1234 [PMID: 23238456 DOI: 10.1378/chest.12-2072]

43 **Van den Berghe G**, Wouters PJ, Kesteloot K, Hilleman DE. Analysis of healthcare resource utilization with intensive insulin therapy in critically ill patients. *Crit Care Med* 2006; 612-616 [PMID: 16521256 DOI: 10.1097/01.ccm.0000201408.15502.24]

44 **Le HT**, Harris NS, Estilong AJ, Olson A, Rice MJ. Blood glucose measurement in the intensive care unit: what is the best method? *J Diabetes Sci Technol* 2013; **7**: 489-499 [PMID: 23567008 DOI: 10.1177/193229681300700226]

45 **Macrae D**, Grieve R, Allen E, Sadique Z, Morris K, Pappachan J, Parslow R, Tasker RC, Elbourne D; CHiP Investigators. A randomized trial of hyperglycemic control in pediatric intensive care. *N Engl J Med* 2014; **370**: 107-118 [PMID: 24401049 DOI: 10.1056/NEJMoa1302564]

46 **Krinsley JS**. Is glycemic control of the critically ill cost-effective? *Hosp Pract (1995)* 2014; **42**: 53-58 [PMID: 25502129 DOI: 10.3810/hp.2014.10.1142]

47 **Krinsley JS**, Jones RL. Cost analysis of intensive glycemic control in critically ill adult patients. *Chest* 2006; **129**: 644-650 [PMID: 16537863 DOI: 10.1378/chest.129.3.644]

48 **Liu X**, Wang DF, Xiong J. [Prospective observational study exploring the relationship between the levels and variability of blood glucose and the prognosis of critical patients]. *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue* 2012; **24**: 538-540 [PMID: 22938662 DOI: 10.3760/cma.j.issn.1003-0603.2012.09.012]

49 **Liu X**, Wang DF, Liu Y, Tang Y, Xiong J. Attitudes, Knowledge, and Practices Regarding Blood Glucose Control: A Survey of Intensive Care Unit Professionals. *Chin Med J (Engl)* 2018; **131**: 622-623 [PMID: 29483401 DOI: 10.4103/0366-6999.226058]

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