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INTEGRATIVE REVIEW ARTICLE

RECOMMENDATIONS FOR THE GLYCEMIA MEASUREMENT OF CRITICAL PATIENTS RECEIVING INTRAVENOUS INSULIN THERAPY: INTEGRATIVE REVIEW

RECOMENDAÇÕES PARA A MENSURAÇÃO GLICÊMICA DO PACIENTE CRÍTICO COM INSULINOTERAPIA INTRAVENOSA: REVISÃO INTEGRATIVA

RECOMENDACIONES PARA LA MENSURACIÓN GLUCÉMICA DEL PACIENTE CRÍTICO CON INSULINOTERAPIA INTRAVENOSA: REVISIÓN INTEGRADORA

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ABSTRACT

Objective: to analyze the factors influencing the accuracy of glycemia measurements in critical patients receiving intravenous insulin. **Method:** integrative review with a time frame of five years (2008-2013) aiming to answer the guiding question << *What factors influence the accuracy of glycemia measurements in patients receiving intravenous insulin?* >> The following databases were used: MEDLINE, Science Direct and Scopus and a total of 15 papers were identified and analyzed. **Results:** the main factors affecting accuracy were capillary blood samples, lack of knowledge concerning the technical specifications of glucose meters and the clinical conditions of patients. **Conclusion:** nurses should pay special attention to patients with anemia, hypoperfusion, peripheral edema, or using vaso amines, given the risk of acquiring imprecise glycemia measurements, especially with capillary blood samples. **Descriptors:** Insulin; Glycemia; Intensive Therapy.

RESUMO

Objetivo: analisar os fatores que influenciam a acurácia das mensurações glicêmicas em pacientes críticos que utilizam insulina intravenosa. **Método:** revisão integrativa com recorte temporal de cinco anos (2008-2013) a fim de atender à questão norteadora << *Quais fatores influenciam a acurácia das mensurações glicêmicas em pacientes que utilizam insulina intravenosa?* >> nas bases de dados MEDLINE, Science Direct e Scopus. Foram selecionados 15 artigos, analisados buscando respostas à questão norteadora. **Resultados:** os fatores redutores da acurácia predominantes foram as amostras de sangue de origem capilar, o desconhecimento das especificações técnicas dos glicosímetros e as condições clínicas dos pacientes. **Conclusão:** os enfermeiros devem ter especial atenção com pacientes que apresentam anemia, hipoperfusão, edema periférico e uso de vasoaminas pelo risco de uma medida glicêmica imprecisa, principalmente se a amostra for de origem capilar. **Descritores:** Insulina; Glicemia; Terapia Intensiva.

RESUMEN

Objetivo: analizar los factores que influyen en la exactitud de las mediciones glucémicas en pacientes críticos que utilizan insulina intravenosa. **Método:** revisión integradora con recorte temporal de cinco años (2008-2013) para atender a la pregunta orientadora << *¿Cuales factores influyen en la exactitud de las medidas de glucosa en pacientes que reciben insulina intravenosa?* >> Los siguientes bases de datos fueron utilizados: MEDLINE, Science Direct y Scopus y, al total, fueron identificados y analizados 15 artículos. **Resultados:** los principales factores que influyen en la exactitud fueron las muestras de sangre capilar, el desconocimiento de las especificaciones técnicas de los glicosímetros y las condiciones clínicas de los pacientes. **Conclusión:** los enfermeros deben prestar atención especial a pacientes con anemia, hipoperfusión, edema periférico y uso de vasoaminas, debido al riesgo de una medida glucémica imprecise, principalmente con muestras capilares. **Descriptores:** Insulina; Glucemia; Terapia Intensiva.

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INTRODUCTION

The use of insulin in hospitals to treat patients with diabetes mellitus is common, especially via subcutaneous injections, though continuous intravenous insulin infusion (CIII) has been used in Intensive Care Units (ICUs) to treat even patients without diabetes mellitus.

This use is justified given the fact that critical patients experience physiopathological changes accruing from the pathologies that motivated their hospitalization and from consequent adaptive processes. These patients present hypermetabolic state characterized by increased consumption of energy, cell resistance to insulin action, and increased glycemia levels.¹ This hyperglycemia is common in acute diseases showing an association with worse clinical outcomes, identified in 38% of inpatients, one third of which without previous history of diabetes.^{1,2}

There are studies addressing the treatment of these patients given the need to consider how insulin should be administered in terms of dosage, indications, routes of administration, therapeutic objectives, and associated risks. The study that is considered pioneer tested the hypothesis that the normalization of blood glucose with IV insulin or intensive glucose control would reduce the mortality and morbidity of critical patients, and reports that insulin reduced mortality from 8% to 4.6%.³

Despite reduced mortality, the incidence of hypoglycemia increased six times in a group of patients with intense glycemic control receiving CIII, so that diverse authors consider hypoglycemia the only adverse event related to CIII.^{1,3} Hence, protocols guiding the implementation of IV insulin and the monitoring of its effects were developed. These protocols indicate the concentration of the infusion solution, its initial dosage, how to monitor the therapeutic effect, and how to establish subsequent dosages. They seek to correct hyperglycemia and avoid hypoglycemia. In general, nurses are the main agents implementing these protocols.

Glycemia measurement to establish insulin solution is mostly performed with portable glucose meters using capillary blood samples obtained through the use of lancets. One study showed that blood glucose measurements acquired from digital devices may not be exact among critical patients due to impaired peripheral perfusion caused by the use of vasoactive drugs, the presence of edema or microcirculation disorders, which possibly lead to inappropriate changes in the flow of insulin.^{3,4}

In Brazil, nurses are responsible for preparing and administering CIII and monitoring the action of insulin to avoid severe hypoglycemia. This surveillance is centered on the measurement of glycemia performed by the nursing staff so that the control of insulin flow is based on glycemia levels that are adjusted in accordance with protocols intended to maintain glycemia levels within the established target range, minimizing the risk of hypoglycemia.

When providing care to patients in ICUs the nursing staff follows insulin protocols establishing the flow of insulin according to glycemia levels that are generally measured by using capillary blood samples. Nonetheless, these protocols do not standardize the collection of blood samples in terms of what is the best route to collect blood or the best method, whether by using glucose meters or arterial blood gas analyzers in a central laboratory. The nursing staff collects blood through the most accessible route and it is the role of the professional to judge what is the best route at the time and use the glucose meter, even though laboratory analysis is known to be the gold standard method to be used with critical patients.⁵

This study is justified by the fact that insulin may be considered a potentially dangerous medication, i.e., a medication with high potential to harm patients and is related to most drug-related adverse events in hospital environments.^{4,5} This study is expected to contribute with information that increase the safety of critical patients who receive IV insulin and are monitored by nurses through glycemic measurement.

Based on the previous discussion, we developed a search, the objective of which was:

♦ To analyze the factors that influence accuracy of glycemia measurements in critical patients receiving intravenous insulin.

METHOD

An integrative review was performed following six stages⁶: establishment of a guiding question; establishment of inclusion criteria and descriptors; search in the literature of studies that would compose the sample; assessment of studies; presentation of results; and synthesis of knowledge acquired from the final sample of papers.

The guiding question was: << ***What factors influence the accuracy of glycemia measurements in patients receiving intravenous insulin?*** >>

The following inclusion criteria were established: papers addressing glycemia measurement during continuous intravenous infusion of insulin; addressing adult inpatients in ICUs; written in Portuguese, English or Spanish; full-text available on line; and published between 2008 and 2013. This last criterion was established due to the increased use of CIII in the last five years.

The following databases were searched using the Capes portal: Science Direct, Scopus and MedLine through standardized descriptors available at Descriptors Health Sciences (DeCS): “insulin” [AND] “blood glucose” [AND] “intensive care”.

The analysis included reading the selected papers using a tool based on a review protocol, which addressed: paper’s title, author(s), periodical, year of publication, objectives, methodology, results and conclusion.⁶

To help defining the best evidence possible we propose a hierarchy of evidence reported in the papers⁶: level I- evidence resulting from meta analysis of multiple randomized and controlled clinical trials; level II- evidence obtained in individual studies with experimental design; level III- evidence from quasi-experimental studies; level IV- evidence

of descriptive (non-experimental) studies or with a qualitative approach; level V- evidence arising from case reports or experience reports; level VI- evidence based on experts’ opinions.

Through thematic or category analysis, which is a type of content analysis⁶, the texts were broken down into units (categories) according to analogic systematic groupings.

The papers selected are described in the results session according to chronological order, from the newest to the oldest, seeking to identify the factors that influence the accuracy of glycemia measurement. The discuss session presents, by categories, the synthesis of content obtained with the analysis of results and factors that influence the accuracy of glycemia measurement.

RESULTS

A total of 15 studies were selected, the characteristics of which are presented in table 1.⁷⁻²¹ Most studies were reviews (60%), which characterizes level IV of evidence; also, the authors of two studies were nurses (13.3%).^{15,21} In terms of time frame, most studies were published in 2013 (26.7%) and most were North-American studies (86.7%) published in American journals.^{7,8,10-12,14-21}

Source/ Year	Title	Method	Level of evidence
Scopus 2013	Accuracy of blood-glucose measurements using glucose meters and arterial blood gas analyzers in critically ill adult patients: systematic review ⁷	Bibliographic review	IV
MedLine 2013	Consensus recommendations on measurement of blood glucose and reporting glycemic control in critically ill adults ⁸	Bibliographic review	IV
Science 2013	Monitoring Glycemic Control ⁹	Bibliographic review	IV
MedLine 2013	Blood Glucose Measurement in the Intensive Care Unit: What Is the Best Method? ¹⁰	Bibliographic review	IV
Scopus 2012	Relative accuracy of arterial and capillary glucose meter measurements in critically ill patients ¹¹	Prospective observational	III
MedLine 2012	The accuracy of point-of-care glucose measurements ¹²	Bibliographic review	IV
Science 2011	Comparison between arterial and capillary blood glucose monitoring in patients With shock ¹³	Prospective Case-control	III
MedLine 2011	Intensive insulin therapy in critically ill hospitalized patients: making it safe and efecctive ¹⁴	Bibliographic review	IV
MedLine 2010	International recommendations for glucose control in adult non diabetic critically ill patients ¹⁵	Bibliographic review	IV
MedLine 2009	Glycemic control in the burn intensive care unit: focus on the role of anemia in glucose measurement ¹⁶	Bibliographic review	IV
MedLine 2009	Computerized intensive insulin dosing can mitigate hypoglycemia and achieve tight glycemic control when glucose measurement is performed frequently and on time ¹⁷	Retrospective Observational	III
Science 2009	Bedside capillary blood glucose measurements in critically ill patients: Influence of catecholamine therapy ¹⁸	Case-control	III
Science 2008	Comparison of POCT and central laboratory blood glucose results using arterial, capillary, and venous samples from MICU patients on a tight glycemic protocol ¹⁹	Prospective observational	III
Scopus 2008	Continuous Intravenous Insulin: Ready for Prime Time ²⁰	Bibliographic review	IV
Scopus 2008	Accuracy of Glycemic Measurements in the Critically Ill ²¹	Prospective Observational	III

Table 1. Papers addressing glycemic measurement. Rio de Janeiro, Brazil 2008-13.

One more recent study was a review addressing the accuracy of glycemia measurement with glucose meters in comparison to having glycemia measured in central laboratories. The conclusion was that accuracy is greater when arterial blood is analyzed instead of capillary either using glucose meters or arterial blood gas analyzers.⁷ Research established guidelines to manage glycemia control in critical patients. In regard to the glycemia measurement, the use of ascorbic acid or paracetamol, low hematocrit levels, and errors committed by professionals, were considered factors that reduce accuracy when glucose meters are used.⁸ One study mentions that peritoneal dialysis solutions containing icodextrin may lead to falsely elevated glycemia when glucose meters using the glucose dehydrogenase enzyme are employed.⁹ One study compared accuracy, response time and

costs of glycemia measurement performed by glucose meters and by central laboratories (gold standard). It considered that glucose meters are not accurate given diverse patient-related circumstances such as changed levels of hematocrit, hypotension, hemodynamic instability, increased levels of oxygenation, and the use of icodextrin.¹⁰

One study assessed the sensitivity of capillary and arterial measurements to detect hypoglycemia (less 80 mg/dL) and hyperglycemia (more than 180 mg/dL). Accuracy was verified based on the ISO 15197 guidelines, which standardize accuracy of glucose meters in comparison to laboratory results. The study reports that 25.2% of the results from capillary samples and 11.3% of the results concerning arterial samples were inaccurate. The conclusion was that arterial samples enable more accurate glycemia measurements, when using glucose meters, in

comparison to capillary samples in critical patients.¹¹

One review verified the precision of glycemia measurement with the use of glucose meters. It mentions that microcirculation changes, hypotension, the use of vaso amines, the presence of peripheral edema, gasometrical changes, hematocrit changes, and the origin of blood samples are factors that may interfere in the measurement. Its conclusion is that glucose meters are not very reliable for extreme (either too low or too high) levels of glycemia.¹²

One study compared the accuracy of glycemia measurements performed with capillary and arterial samples using bedside glucose meters in two groups of 100 patients, one group with shock (G1) using vaso amines and another group not in shock and without vaso amines (G2). It reports 18% of inaccurate measures in G1 and only 3% in G2. The conclusion is that blood glucose measurements are only reliable among patients not in state of shock.¹³ Another research lists the factors that may influence the accuracy of portable glucose meters used in ICUs, such as the fact that the strips are manufactured only for capillary samples. Its conclusion is that new technologies should be developed to enable greater accuracy for monitoring glucose in ICUs.¹⁴

The results of one study show that glycemia measurements in critical patients should be performed with arterial samples in central laboratories (gold standard) or blood gas analyzers. The study emphasizes that capillary blood samples are the least reliable, whose error sources include vasoconstriction, state of shock, ischemia, or edema. In such cases, approximately 15% of the measurements are above 20% in comparison to 'gold standard', and are greater in cases of hypoglycemia. The conclusion was that glucose meters provide inaccurate measurements in critical patients.¹⁵

One study indicates that the lower the level of hematocrit, the greater is the effect on the accuracy of glucose meters, possibly reaching up to 30% of inaccuracy with falsely elevated glycemia. It proposes a

mathematical correction of hematocrit levels because when glucose meters analyze a blood sample, it assumes 40% of hematocrit and the development of new technologies is needed to improve the safety and clinical usefulness of glucose meters.¹⁶

Another study observed 254 episodes of severe hypoglycemia that occurred in 195 of 4,588 patients receiving CIII. There was, in 66.9% of the cases, a delay in the glycemia measurement. It concludes that delays in glycemia measurements of more than 12 minutes may contribute to the occurrence of hypoglycemia events.¹⁷ One study compared accuracy between glycemia measurements using capillary samples and venous samples in two groups of patients, with and without vaso amines. Overestimation of glycemia levels was verified in 40% of the capillary measurements in the group of patients with amines. The conclusion is that capillary blood samples do not enable precise measurements in critical patients with intravenous amines using bedside glucose meters.¹⁸

Another study compared the results of bedside glucose measurements using capillary, arterial and venous blood samples with analyzes performed in a central laboratory. Overestimated glycemia was observed in 11.3% of the arterial samples, 6.1% of the venous samples, and in 17.4% of the capillary samples measured with bedside glucose meters. Thus, the conclusion was that arterial and venous blood samples should be used in ICUs while the use of capillary blood samples is discouraged in critical patients given the risk of masking the occurrence of severe hypoglycemia.¹⁹

One review verified that the accuracy of glycemia measurements is affected by glucose meters inadequate calibration, incorrect coding of test strips, and inadequate handling of test strips.²⁰

One study assessed samples of both capillary and arterial origin and the tests performed in glucose meters and in a central laboratory. It concluded that extreme levels of hematocrit (<25% and >60%) may lead to inaccurate results as well as variations in the partial pressure of oxygen (PaO₂) affect devices using glucose oxidase enzyme.²¹

Code	Results	Papers
A1	Capillary blood samples should be avoided in patients with edema or microcirculation disorders and the glucose meter is a method the reliability of which is questionable among ICU patients. Glucose overestimation from 25.2% to 11.3% was found when capillary blood samples were used; 11.3% overestimation was found in arterial blood samples, and 6.1% in venous blood samples; which are situations that may mask hypoglycemia. Data show that the most accurate method to measure glucose in severely ill patients is laboratory analysis.	7, 11,13,19
A2	The studies show that the accuracy of measurements were affected by the use of vaso amines, the presence of hypoperfusion, hypotension, peripheral edema, shock, increased lactate levels, change of hematocrit and arterial blood gas levels, the use of other sugars such as maltose or medications such as ascorbic acid or acetaminophen.	8,9,10,12,14,15,16,20,21

Table 2. Synthesis of Results.

DISCUSSION

The discussion presents analytical categories that emerged from the attentive reading of papers and descriptive analysis of results, and after identifying that the blood samples origin as well as the physiopathology of patients influence measurement.

♦ Influence of the origin of blood samples and method

Data show that collecting capillary blood samples should be avoided among patients with edema or microcirculation disorders while glucose meters are not reliable to be used in ICUs. The most accurate method to measure glycemia is by performing laboratory analysis. Overestimated glycemia from 25.2% to 11.3% was found when capillary blood samples were used; overestimation of 11.3% was found in arterial blood samples; and 6.1% in venous blood samples; situations that may mask hypoglycemia.^{7, 11,13,19}

These data show that venous blood samples should preferably be collected from critical patients followed by arterial blood samples, and lastly, capillary blood samples. This recommendation, however, presents the possibility of blood contamination given the handling of the venous system when collecting blood. Nurses are supposed to be attentive to potential inaccurate measurements when patients present extreme glycemic levels with a tendency to hypoglycemia. Thus, we suggest in these cases, measuring glucose using a capillary blood sample with a glucose meter and then comparing it with an arterial blood sample analyzed in a central laboratory. In case of a difference greater than 20 mg/dl, we recommend the measurements be performed in laboratory with arterial blood samples.²²

Likewise, whenever hypoglycemia is verified at bedside measurement, we

recommend checking glucose using arterial blood and laboratory testing.

In regard to the glucose meters, which became popular given its practicality, most of these portable devices use strips containing glucose oxidase reagent (reagents are rarely peroxidase or hexokinase). This reagent changes color when there is blood on the strip. This reaction is interpreted by the photometric or amperometric method and translated into a numerical value that corresponds to the level of glycemia.²³

Glucose meters use technologies that are supposed to meet international guidelines establishing accuracy for systems of blood glucose measurements, i.e. International Organization for Standardization, more specifically ISO 15197.^{10-12,14,15,20,21}

This standard determines that glucose meters are reliable when 95% of the results are ± 15 mg/dl when the reference value is below 75 mg/dl (less than 4.2 mmol/l) verified in central laboratories. Concentrations $\pm 20\%$ are also considered reliable when the reference value is equal to or greater than 75 mg/dl (greater than or equal to 4.2 mmol/l).²³

Ideally, this is the recommendation to be complied with, but in practice, an interval of ± 15 mg/dl may increase the risk of hypoglycemia in critical patients since a patient with 80mg/dl of glycemia could in reality have 70mg/dl of glycemia (nevertheless, according to ISO 15197, the glucose meter would still be considered reliable).²⁴

Most CIII protocols, however, recommend that when glycemia is 80mg/dl, the insulin dosage should be maintained the same. The patient, however, may present hypoglycemia in the subsequent hour and its detection is not foreseen given glucose meters' technical specificities. Glycemia of 70mg/dl, however, implies in the interruption of CIII.

The selected papers present restrictions concerning which is the best glucose meter to be used in ICUs considering the inaccuracy of these in the glycemic measurement of hospitalized critical patients. The papers took into account that glucose meters were initially developed to be used at home to monitor diabetes outpatients using capillary blood samples and meeting specificities such as the need for calibration and inserting a code before measurement, maintaining the device and using a standardized technique to collect blood samples.^{14,15,20}

In this sense, the recommendation is to calibrate the device at least once a day, store the strips in the temperature recommended by the manufacturer and avoid moisture while hand washing is required to refrain from contaminating the strips with food residues or dyes. The fact that glucose meters do not detect problems accruing from poor strips storage, manufacturing defects, or enzymatic coverage loss, is emphasized. Additionally, the strips that require less amounts of blood are less accurate and may lead to the underestimation of glycemic levels.²³

The use of arterial blood gas analyzers in ICUs aiming a more accurate and safer measurement of CIII is recommended. Despite the apparent increase in workload and response time, there was not increase in the costs involved in this type of procedure.^{10,21}

Intensive care nurses should be familiar with the applications and limitations of glucose meters used in the routine care of critical patients to properly implement CIII protocols.

♦ Influence of patients' physiopathological characteristics

The studies show that the accuracy of measurements were influenced by the use of vaso amines, hyperfusion, hypotension, peripheral edema, shock, increased lactate level, changes in hematocrit levels and arterial gas levels, increased triglycerides levels, the use of other sugars, e.g. maltose, and medications such as ascorbic acid or acetaminophen.^{7,9,10,12,14,15,16,20,21}

Hypoperfused patients in state of shock, with peripheral edema, or using vasoconstrictive drugs, may present false low glycemia levels given the poor quality of capillary blood samples, therefore, the collection of arterial blood is recommended.²²

The effect of abnormal levels of hematocrit on the accuracy of portable glucose meters is long known. The instructions to operate these devices suggest that hematocrit levels must be between 25% and 55% to enable a reliable measurement of capillary glycemia. Currently,

many glucose meters compensate for hematocrit levels, reducing errors. Still, the use of glucose meters among individuals with very low levels of hematocrit is not recommended because the authors observed more than 5% of errors in patients whose hematocrit levels were much lower than 34% as it causes falsely elevated levels of glucose.^{21,23} In daily practice, however, nurses do not seem to be attentive to hematocrit levels as a factor with potential to change the results of glucose measurements. The papers also mention that hypertriglyceridemia (>1000 mg/dl) or hyperuricemia (> 7 mg/dl) may interfere on the reaction of oxidase glucose (the reagent most commonly used in glucose meters), thus devices based on the dehydrogenase glucose method should be indicated.²³

Additionally, icodextrin, which is used in some peritoneal dialysis fluids, does not change the glucose measurement by devices based on glucose oxidase.²³

The use of acetaminophen, L-Dopa, tolazamide or ascorbic acid (vitamin C) generally slightly changes the readings of amperometric or photometric glucose meters that use glucose oxidase reaction. It was not possible, however, to determine whether this influence is significant for the management of CIII protocols.

Note that only one study found that delay in performing glucose measurement led to severe hypoglycemia in critical patients. Nevertheless, it is not clear whether this result can be generalized to all protocols currently applied.¹⁷

The routine established for critical patients is verifying glucose by the hour. It seems, though, that no consensus was reached in literature while some authors recommend other intervals for measuring glucose.^{22, 25-27}

The suggestion to consider longer intervals when measuring glucose refers to cases in which patients reach the glucose target range, that is, patients who stay within the expected target range may have their glucose levels measured every 2h, 4h or even every 6h. These suggestions, however, do not take into account the ideal interval to measure glucose so to not expose patients to the risk of hypoglycemia.^{22,27}

CONCLUSION

This study identified that factors that can influence the accuracy of glucose measurement in critical patients are those related to the origin of blood samples. The most reliable blood samples to be used in glucose meters were venous blood sample

followed by arterial blood sample and then capillary blood sample. Other factors equally important are those related to the physiological conditions of patients while nurses should pay special attention to patients with low hematocrit levels, hypoperfusion, peripheral edema and the use of vaso amines, given the risk of imprecise glucose measurement, especially if the sample is of capillary origin, which may lead to inappropriate adjustments of insulin infusion.

It is recommended that nurses confirm extreme values, hypoglycemia or hyperglycemia, with laboratory tests. There are, however, difficulties in performing laboratory tests such as lack of availability on the part of the central laboratory to respond promptly and the establishment of which glycemia level will indicate the need for a laboratory confirmation. Thus, repeating glycemia measurements with a blood sample of different origin when glycemia is below 60 mg/dl or above 250 mg/dl using arterial blood gas analyzers is a more viable measure to be used in Brazilian ICUs.

This review indicates the need to develop intervention studies to identify existing deviations from the gold standard for glycemia measurement and which may compromise its accuracy through observational studies.

There are gaps in the development of nursing studies addressing the glycemia measurement technique, which is considered a routine procedure used among ICU patients, and verifying its real influence on potentially less reliable results.

Further studies are needed to establish which glycemia levels measured using bedside glucose meters require laboratory confirmation; what specificities glucose meters should meet to ensure accurate measurements in critical patients; what factors signalize the risk of glycemia measurements not detecting hypoglycemia; and what conditions indicate patients with greater or lesser susceptibility to the occurrence of adverse events during CIII.

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