REVIEW

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Hospital management of diabetes: Beyond the sliding scale

ABSTRACT

A growing body of evidence suggests that there is a close correlation between good glucose control and improved clinical outcomes in hospitalized diabetic patients. Until recently, however, no established standards have existed for caring for people with diabetes in the hospital. At a recent consensus conference, experts from around the world studied the evidence and recommended new glycemic targets for hospitalized patients (*Endocr Pract* 2004; 10:77–82). The challenge now is to implement these targets.

KEY POINTS

Studies have found tight glycemic control improves outcomes for patients hospitalized for myocardial infarction or for cardiac surgery and for patients in intensive care.

Insulin, given either intravenously as a continuous infusion or subcutaneously, is the most effective agent for achieving glycemic control in hospitalized patients.

To prevent and treat hypoglycemia, it is critical that communication be clear between nursing and ancillary services, that glucose levels be monitored frequently, and that clear algorithms and protocols be in place for ordering insulin and for treating hypoglycemia.

To implement the new glycemic targets safely and effectively, standard protocols and algorithms need to be developed by multidisciplinary teams.

The author has indicated that she is on the speakers' bureaus of the GlaxoSmithKline, Novo Nordisk, and Pfizer corporations.
This paper discusses therapies that are experimental or are not approved by the US Food and Drug Administration for the use under discussion.

DIABETIC PATIENTS need good glycemic control when they are in the hospital just as much as they do at home, or perhaps even more, considering the stresses of illness and surgery in hospitalized patients. In fact, recent evidence suggests that, regardless of whether the patient even has a known history of diabetes, hyperglycemia in the hospital is associated with increased mortality and morbidity, and that meticulous glycemic control can improve clinical outcomes.

Yet, although multiple organizations have developed glycemic targets for diabetic outpatients, no such targets have existed for hospitalized patients.

Until now. At a recent consensus conference, the American Association of Clinical Endocrinologists brought together the key investigators of major interventional studies as well as multiple organizations to examine the relationship between hyperglycemia and hospital outcome and to recommend glycemic targets for hospitalized patients. In a subseqent position statement,[1] the following targets were recommended:

- In the intensive care unit: 110 mg/dL (6.1 mmol/L)
- In noncritical care units, preprandial: 110 mg/dL (6.1 mmol/L)
- In noncritical care units, maximal: 180 mg/dL (10.0 mmol/L).

For many patients this will mean insulin therapy, tailored to meet physiologic requirements. Gone is the sliding scale of old. Instead, some patients will receive continuous intravenous insulin infusions; others will receive subcutaneous doses of a long-acting insulin for basal coverage, preprandial doses of a rapid-acting insulin for prandial coverage,

and "correction" doses when the blood glucose concentration exceeds goal levels.

The challenge facing each institution now is to implement the new glycemic targets safely and effectively. Standardized protocols, developed by multidisciplinary teams, are necessary to ensure safety and efficacy.

This paper reviews the rationale for tight glycemic control in the hospital and offers practical advice on how to achieve it.

DIABETES IS COMMON IN THE HOSPITAL

Diabetes remains a major cause of mortality and morbidity and is increasing in prevalence at an alarming rate.[2] Chronic complications of diabetes, especially cardiovascular disease, result in hospitalization in many patients with diabetes. In addition, diabetic patients stay in the hospital on average 1 to 3 days longer than patients without diabetes.

The exact prevalence of diabetes among hospitalized patients is not known. However, in the year 2000, 12.4% of hospital discharges in the United States listed diabetes as a diagnosis. Among cardiac surgery patients, the prevalence of diabetes is as high as 29%.

One third of patients with hyperglycemia did not have a history of diabetes

In a retrospective review of 2,030 consecutive hospital admissions, Umpierrez et al[3] found that 718 (38%) of the 1,886 patients who had blood glucose measurements recorded in their charts had hyperglycemia. Of the patients with hyperglycemia, 495 had a known history of diabetes, but the other 223 did not. Of interest is that the patients with newly diagnosed hyperglycemia were more likely to require admission to the intensive care unit, had longer hospital stays, and were less likely to be discharged straight home.

RATIONALE FOR TIGHT CONTROL

In acute myocardial infarction

Patients with diabetes are at a higher risk of coronary artery disease and have worse outcomes. In a meta-analysis of 15 studies in patients with acute myocardial infarction, Capes et al[4] compared the risk of in-hospital mortality and congestive heart failure in hyperglycemic patients with and without a history of diabetes. In subjects without a known history of diabetes, the risk of death was significantly higher if the blood glucose concentration at admission was more than 109.8 mg/dL. The threshold for patients with a known history of diabetes was over 180 mg/dL.

The DIGAMI study (Diabetes Insulin Glucose in Acute Myocardial Infarction)[5] provides convincing evidence that giving insulin intravenously improves outcome in hyperglycemic patients with acute myocardial infarction. In this study, 620 patients with acute myocardial infarction and hyperglycemia (with or without a history of diabetes) were randomly assigned to an insulin infusion group or a control group. The infusion group received insulin intravenously for 24 hours and then multiple subcutaneous doses of insulin for 3 months or longer; the control group received standard therapy.

The mean blood glucose concentration for the first 24 hours in the insulin infusion group was 172.8 mg/dL; in the control group it was 210.6 mg/dL.

At 1 year, the mortality rate was 18.6% in the insulin infusion group and 26.1% in the control group, a 28% difference. At 3.4 years, the mortality rate was 33% in the infusion group and 44% in the control group, a 25% difference (P = .011). The difference was even more impressive in the 272 patients considered at low risk and who had never received insulin before. In these patients, those in the insulin infusion group had a 58% lower mortality rate at discharge (P < .05), a 50% lower rate at 12 months, and a 45% lower rate at 3.4 years (P = .004).

The DIGAMI study underscores the importance of early and aggressive glucose control regardless of a prior history of diabetes.

In critically ill patients

Van den Berghe et al[6] performed a landmark study of 1,548 adults who were admitted to a surgical intensive care unit and were on mechanical ventilation.

Patients were randomized to receive either intensive insulin therapy to maintain the blood glucose concentration at 80 to 110 mg/dL or conventional therapy to maintain blood glucose between 180 to 200 mg/dL. An insulin infusion was started in the conventional therapy group only if blood glucose exceeded 215 mg/dL.

In 60% of cases the reason for admission to the intensive care unit was cardiac; the admissions in the remaining cases were for multiple trauma, abdominal surgery, burns, and neurologic conditions.

Mortality and morbidity rates were significantly lower in the intensive therapy group. The mortality rate in the intensive care unit was 4.6% in the intensive therapy group vs 8% in the control group ($P < .04$). Overall in-hospital mortality was reduced by 34%. In addition, compared with the conventional therapy group, the incidence of sepsis in the intensive therapy group was 46% lower, need for dialysis 41% lower, need for blood transfusion 50% lower, and incidence of polyneuropathy 44% lower; all differences were statistically significant.

Krinsley[7] found a close correlation between blood glucose levels and in-hospital mortality rates in 1,826 consecutive patients admitted to a medical-surgical intensive care unit. In the patients who died in the hospital, the mean blood glucose level was 172.0 mg/dL; among survivors it was 137.9 ($P < .001$). Mortality rates increased progressively as blood glucose levels increased, from 9.6% in patients with mean glucose levels of 80 to 99 mg/dL to 42.5% in those with levels greater than 300 mg/dL ($P < .001$ for the trend).

Krinsley[8] then analyzed the outcomes of 800 consecutive patients admitted to the same medical-surgical intensive care unit immediately after a protocol for intensive glucose control was instituted, and compared them with those of 800 consecutive patients admitted before the protocol was instituted.

The protocol was designed to keep the blood glucose level lower than 140 mg/dL, with frequent testing, subcutaneous insulin injections, and, if the blood glucose level exceeded 200 mg/dL on two consecutive readings, insulin infusions. Results:

- Mean blood glucose levels: 152.3 mg/dL before the protocol vs 130.7 with the protocol ($P < .001$)
- In-hospital mortality: 20.9% before the protocol vs 14.8% with the protocol—a 29.3% reduction ($P = .002$)
- Median length of stay in the intensive care unit: 1.9 vs 1.6 days—a 10.8% reduction ($P = .01$)
- Incidence of new renal insufficiency: 12 patients vs 3 ($P = .03$)
- Need for packed red blood cell transfusions: 25.2% vs 20.5%—an 18.7% reduction ($P = .04$)

These two studies clearly demonstrate the benefit of tight glycemic control in medical and surgical patients in intensive care.

In cardiac surgery patients

Hyperglycemia is an independent risk factor for surgical infection for diabetic patients undergoing cardiac surgery.[9]

Furnary et al,[10] in a nonrandomized interventional study, examined the effect of hyperglycemia on the outcome of cardiac surgery patients. A historical control group (N = 968) consisted of diabetic patients who underwent surgery between 1987 and 1991 and who received subcutaneous insulin injections every 4 hours with a blood glucose goal of less than 200 mg/dL. The intensive therapy group (N = 1,499) underwent surgery between 1992 and 1997 and received insulin infusions with a glycemic target of 150 to 200 mg/dL. In the later group, the incidence of deep surgical wound infection was reduced to 0.8%, vs 2% in the control group ($P = .01$).

In addition, in a recent analysis,[1] the investigators reported that the intravenous insulin infusion during the first 3 postoperative days resulted in a 50% reduction in the risk-adjusted hospital mortality rate.

In surgical ICU patients, tight glucose control reduced mortality by 34%

Lazar et al[11] randomized 141 diabetic patients undergoing coronary artery bypass graft surgery to receive either an intravenous infusion of glucose, insulin, and potassium, with a target glucose concentration of 125 to 200 mg/dL; or standard therapy with subcutaneous insulin, with a target glucose concentration of less than 250 mg/dL.

Compared with the standard therapy group, the infusion group had a lower mean glucose concentration (138 vs 260 mg/dL), a lower incidence of atrial fibrillation (16.6% vs 42%), a shorter hospital stay (6.5 vs 9.2 days), a lower incidence of recurrent ischemia (5% vs 19%), and a lower incidence of wound infection (1% vs 10%).

In stroke patients

In the area of stroke, the evidence is mostly observational, but studies suggest a correlation

between glucose level and clinical outcomes.

Capes et al[12] performed a meta-analysis of 26 studies published between 1996 and 2000 and found that patients with no known history of diabetes whose glucose levels were above 110 mg/dL had a threefold higher risk of death and a higher risk of poor functional recovery compared with those with lower glucose levels.

This finding highlights the need for interventional controlled studies to evaluate the impact of glycemic control on the outcome of stroke patients.

ARE BETTER OUTCOMES DUE TO GLUCOSE CONTROL OR INSULIN?

An intriguing question is whether the better outcomes are due to lowering the blood glucose level or, rather, to some effect of insulin per se.

Insulin suppresses free fatty acids, inflammatory cytokines, and inflammatory growth factors, all substances that may be detrimental to critically ill patients. In addition, insulin stimulates nitric oxide synthesis, which promotes vasodilatation. It also improves cell membrane stability, myocardial contractility, and endothelial function, all of which may contribute to the better clinical outcomes observed with intravenous insulin infusions.

With insulin infusions, blood glucose must be checked frequently

Further research is needed to delineate the exact contributions of insulin therapy and the blood glucose level in the clinical outcome.

ATTAINING GLUCOSE TARGETS IN HOSPITALIZED PATIENTS

Insulin, given either intravenously as a continuous infusion or subcutaneously, is the most effective agent for achieving glycemic control in hospitalized patients. A number of protocols for continuous insulin infusion have been published.[13–20] No large studies have compared the effectiveness and safety of different protocols, however.

Indications for intravenous insulin therapy

According to the American College of Endocrinology position statement,[1] indications for intravenous insulin therapy in hospitalized diabetic patients are:

- Prolonged fasting (> 12 hours) in type 1 diabetes
- Critical illness
- Before major surgical procedures
- After organ transplantation
- Diabetic ketoacidosis
- Total parenteral nutrition therapy
- Labor and delivery
- Myocardial infarction
- Other illnesses requiring prompt glucose control.

Caveats about insulin infusions

Intravenous insulin infusions have been used for many years and have a proven track record for efficacy and safety. Several caveats should be kept in mind, however.

- Enough glucose must be provided to avoid starvation ketosis and prevent hypoglycemia: most authors suggest 5 to 10 g/hour of glucose.
- The blood glucose level must be checked frequently at the bedside to ensure safety. The ideal frequency has not been studied, but most authorities recommend that it be tested every hour until it is stable.
- The protocol should include some mechanism for changing the infusion rate to reach glucose targets and to avoid hypoglycemia.

Intravenous insulin protocol

As mentioned above, many protocols are used in different hospitals. **TABLE 1** shows a protocol devised by Trence et al.[17]

The ideal intravenous insulin protocol should be easy to order (it should require a signature only), effective (patients should achieve goal glucose levels quickly), safe, and easy to follow.

A multidisciplinary effort is needed to implement such a protocol, with support from administration and pharmacy staff. Order forms should be printed up and available in the hospital units, and nurses and physicians should undergo training in the protocol.

According to the American College of Endocrinology position statement,[1] the hospital should assess its systems and routines to make sure the protocol can be safe and effective. Adjustment may be required for appropriate provision of diabetes care, including timely delivery of meal trays, point-of-care blood glucose testing, and administration of insulin.

TABLE 1

Protocol for intravenous insulin infusion

General guidelines

- Goal blood glucose level = _____ (usually 80–180 mg/dL, 80–110 for intensive care patients)
- Standard drip: 100 units/100 mL 0.9% NaCl via an infusion device (1 unit/1 mL)
- Surgical patients who have received an oral diabetes medication within 24 hours should start when blood glucose is more than 120 mg/dL. All other patients can start when blood glucose is 70 mg/dL or higher
- Insulin infusions should be discontinued when a patient is eating AND has received first dose of subcutaneous insulin

Intravenous fluids

- Most patients will need 5 to 10 g of glucose per hour: eg, dextrose 5% in water (D5W) or dextrose 5% in water with 0.45% sodium chloride (D5W-1/2 NS) at 100–200 mL/hour or equivalent (eg, total parenteral nutrition, enteral feeding)

Initiating the infusion

- **Algorithm 1:** Start here for most patients (see table below).
- **Algorithm 2:** For patients not controlled with algorithm 1, or start here if status is post coronary artery bypass graft surgery or solid organ transplantation or islet cell transplant, receiving glucocorticoids, or for patients with diabetes receiving more than 80 units/day of insulin as an outpatient.
- **Algorithm 3:** For patients not controlled on algorithm 2. NO PATIENTS START HERE without authorization from the endocrine service.
- **Algorithm 4:** For patients not controlled on algorithm 3. NO PATIENTS START HERE.

Patients not controlled with the above algorithms need an endocrine consult.

PATIENT'S BLOOD GLUCOSE LEVEL (MG/DL)	INSULIN INFUSION RATE (U/HOUR)			
	ALGORITHM 1	ALGORITHM 2	ALGORITHM 3	ALGORITHM 4
< 60 = Hypoglycemia (see below for treatment)				
< 70	0	0	0	0
70–109	0.2	0.5	1	1.5
110–119	0.5	1	2	3
120–149	1	1.5	3	5
150–179	1.5	2	4	7
180–209	2	3	5	9
210–239	2	4	6	12
240–269	3	5	8	16
270–299	3	6	10	20
300–329	4	7	12	24
330–359	4	8	14	28
> 360	6	12	16	28

Moving from algorithm to algorithm

- **Move up to the next higher algorithm** if the blood glucose concentration is above the goal range (see above goal) and does not change by at least 60 mg/dL within 1 hour.
- **Move down an algorithm** when blood glucose is < 70 mg/dL X 2.

Patient monitoring

- Goal blood glucose = 80–180 mg/dL
- Check capillary blood glucose every hour until it is within goal range for 4 hours, then decrease to every 2 hours for 4 hours, and if it remains stable, may decrease to every 4 hours
- Hourly monitoring may be indicated for critically ill patients even if they have stable blood glucose

Treatment of hypoglycemia (blood glucose < 60 mg/dL)

- Discontinue insulin drip AND
- Give dextrose 50% in water (D50W) intravenously
  If patient is awake: 25 mL (1/2 amp)
  If patient is not awake: 50 mL (1 amp)
- Recheck blood glucose every 20 minutes and repeat 25 mL of D50W IV if < 60 mg/dL. Restart insulin drip once blood glucose is > 70 mg/dL X 2 checks. Restart drip with lower algorithm (see "Moving down")

Notify the physician

- For any blood glucose change greater than 100 mg/dL in 1 hour
- For blood glucose > 360 mg/dL
- For hypoglycemia that has not resolved within 20 minutes of giving 50 mL of D50W IV and discontinuing the insulin drip

TRENCE DL, KELLY JL, HIRSCH IB. THE RATIONALE AND MANAGEMENT OF HYPERGLYCEMIA FOR IN-PATIENTS WITH CARDIOVASCULAR DISEASE: TIME FOR CHANGE. J CLIN ENDOCRINOL METAB 2003; 88:2430–2487.

Transition to subcutaneous insulin therapy

To keep blood glucose at the target level, it is important to give a dose of short-acting or rapid-acting insulin subcutaneously 1 to 2 hours before stopping the intravenous insulin infusion. Basal and prandial insulin doses must be tailored to each patient's need.

A simple formula to establish the 24-hour insulin requirement is to extrapolate from the average intravenous insulin dose required over the previous 6 to 8 hours (if stable) and to give one half as an intermediate-acting or long-acting insulin for basal coverage and one half as a short-acting or rapid-acting insulin in divided doses before meals.

For example, if the average dose of intravenous insulin was 1.0 units/hour over the past 8 hours (and stable), the total daily dose would be 24 units. Of this, 50% (12 units) would be basal: eg, Neutral Protamine Hagedorn (NPH) 12 units once a day or 6 units twice a day, or glargine 12 units once a day. The other 50% would be prandial, ie, short-acting (regular) or rapid-acting (lispro or aspart) insulin 4 units before each meal.

The insulin dose must be adjusted according to patient's stress level, oral intake, intravenous or enteral alimentation, weight, insulin sensitivity, medications (eg, steroids), and other factors.

Give a dose of short-acting or rapid-acting insulin 1–2 hours before stopping an insulin infusion

EFFECTIVE SUBCUTANEOUS INSULIN THERAPY

Effective insulin therapy must provide both basal and nutritional insulin.[13] Nutritional insulin is defined as the insulin that is needed to cover any intravenous glucose the patient is receiving, intravenous or enteral alimentation, and calories consumed in meals. If the patient is eating and is not receiving any other sources of calories, nutritional insulin would be the same as prandial insulin.

Keep in mind that hospitalized patients often require higher doses of insulin because of the stress of their illness.

In addition to basal and nutritional insulin requirements, patients often require supplemental or correction doses of insulin to treat unexpected hyperglycemia. Therefore, subcutaneous insulin can be given as a scheduled dose (basal + nutritional) and a supplemental (correction) dose to cover any hyperglycemia above target. The supplemental algorithm should not be confused with the "sliding scale" that traditionally has been used alone with no scheduled dose and that can result in poor glycemic control as well as hypoglycemia.

Insulins used for basal requirements are NPH (which is intermediate-acting) and the long-acting insulins: ultralente and the analogue insulin glargine.

To cover the nutritional need, regular insulin or rapid-acting analogues such as lispro or aspart can be used. In the outpatient setting, use of these analogues can increase flexibility, and result in lower risk of hypoglycemia and better postprandial control compared with regular insulin. Although they have not been studied in the hospital setting, we can infer that they would be as effective and as safe to use there as regular insulin, and perhaps would even be preferred.

For supplemental insulin coverage, the rapid-acting analogues are preferred. **TABLE 2** is an example of a subcutaneous insulin protocol.[15]

For patients on an intensive insulin regimen (receiving multiple daily injections or using an insulin pump) prior to admission, consultation with an endocrinologist is advisable to assist in management.

PREVENTING HYPOGLYCEMIA

Hypoglycemia is a concern in hospitalized patients with diabetes, and it has been a major barrier to aggressive treatment of hyperglycemia in the hospital. However, hypoglycemia can be predicted, and it can be prevented without allowing suboptimal treatment of hyperglycemia. Factors that increase the risk of hypoglycemia in the hospital include inadequate glucose monitoring, lack of clear communication or coordination between dietary, transportation, and nursing staff, indecipherable orders, and an unsafe work environment. Clear algorithms for insulin orders and clear hypoglycemia protocols are critical to preventing hypoglycemia.

Data from clinical trials in outpatients clearly show a lower risk of hypoglycemia with the insulin analogues, and one would expect the same for inpatients. For this reason,

TABLE 2

An example of standardized subcutaneous insulin orders

Blood glucose monitoring: ___ Before meals and at bedtime ___ at ___ hours after meals ___ 2–3 AM

Goal premeal blood glucose = 80–150 mg/dL

INSULIN ORDERS	BREAKFAST	LUNCH	DINNER	BEDTIME
Prandial	Give ___ units of: ___ Lispro ___ Aspart ___ Regular	Give ___ units of: ___ Lispro ___ Aspart ___ Regular	Give ___ units of: ___ Lispro ___ Aspart ___ Regular	
Basal	Give ___ units of: ___ NPH ___ Lente ___ Ultralente ___ Glargine		Give ___ units of: ___ NPH ___ Lente ___ Ultralente ___ Glargine	Give ___ units of: ___ NPH ___ Lente ___ Ultralente ___ Glargine

Suggested lag times for prandial insulin: aspart or lispro: 0–15 minutes before eating; regular: 30 minutes before eating

For blood glucose < 60 mg/dL

- If patient can eat or drink, give 15 grams of fast-acting carbohydrate (4 oz fruit juice/non diet soda, 8 oz nonfat milk, or 3–4 glucose tablets)
- If patient cannot eat or drink, give D50W 25 mL as IV push
- Check finger capillary glucose every 15 minutes and repeat above if < 80 mg/dL

Premeal "correction dose" algorithm for hyperglycemia ___ Lispro ___ Aspart
(to be administered in addition to scheduled insulin dose to correct premeal hyperglycemia)

Use low-dose algorithm for patients requiring < 40 units of insulin/day
Use medium-dose algorithm for patients requiring 40–80 units of insulin/day
Use high-dose algorithm for patients requiring > 80 units of insulin/day

PREMEAL BLOOD GLUCOSE (MG/DL)	ADDITIONAL INSULIN DOSE (UNITS)			
	LOW-DOSE ALGORITHM	MEDIUM-DOSE ALGORITHM	HIGH-DOSE ALGORITHM	INDIVIDUALIZED ALGORITHM
150–199	1	1	2	___
200–249	2	3	4	___
250–299	3	5	7	___
300–349	4	7	10	___
> 349	5	8	12	___

GENERAL INSULIN DOSING RECOMMENDATIONS

Patients with type 1 diabetes

This patient must have insulin to prevent ketosis. Even if the patient is not eating, he or she will need at least basal insulin (NPH, lente, ultralente, or glargine) to prevent ketosis.

When admitting a patient with type 1 diabetes, continue the basal insulin that they were taking at home at the same dose. **If the patient will be NPO, use an insulin drip rather than subcutaneous insulin.** The prandial insulin (regular, lispro, or aspart) may require adjustment depending on the patient's situation. If the patient is eating much less, the prandial insulin will need to be reduced. Many hospitalized patients are under significant metabolic stress (infection, glucocorticoids, etc) and may require larger doses of prandial insulin despite eating less.

If a patient is newly diagnosed, the usual daily insulin requirement is 0.5 to 0.7 units/kg/day. Half (or 50%) should be given as basal insulin and the remainder as prandial insulin.

Patients with type 2 diabetes

If the patient is using insulin at home, continue the outpatient regimen and adjust as needed.
If the patient has not been using insulin previously, the usual total daily insulin requirement is 0.4 to 1.0 units/kg/day.
Individual insulin doses vary widely, and adjustments should be made based on the bedside and laboratory glucose levels.

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insulin analogues are my choices for hospitalized patients while we await the results of future clinical trials.

HYPERGLYCEMIA IS AN OPPORTUNITY

When a patient develops significant hyperglycemia in the hospital, we should view it as an opportunity to revise the long-term care plan. If the hemoglobin A_{1c} level is elevated, then hyperglycemia has been going on prior to admission, and the patient's long-term therapy must be reevaluated and modified.

If a patient without a history of diabetes has an elevated blood glucose level, one must differentiate whether he or she has hospital-related hyperglycemia or undiagnosed diabetes. These patients require follow-up with a fasting glucose level and a 2-hour oral glucose tolerance test.

A team approach can improve clinical outcomes and reduce length of stay. In addition to physicians, the team may include qualified diabetes educators and nurses, who should work together in a collaborative manner. Discharge planning should be started early to evaluate community resources and arrange proper follow-up after discharge.

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