Current Diabetes Reports (2019) 19:110
https://doi.org/10.1007/s11892-019-1232-4

HEALTH CARE DELIVERY SYSTEMS AND IMPLEMENTATION IN DIABETES (ME MCDONNELL AND AR SADHU, SECTION EDITORS)

Timing of Insulin with Meals in the Hospital: a Systems Improvement Approach

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Abstract

Purpose of Review Coordination of glucose monitoring, mealtimes, and insulin delivery in the hospital is complex, involving interactions between multiple key agents and overlapping workflows. The purpose of this review is to evaluate the scope of the problem as well as to assess evidence for interventions.

Recent Findings In recent years, there has been an emphasis on systems-based approaches which address multiple contributing components of the problem at once in an effort to more seamlessly integrate workflows. Technological advances, such as decision support systems and advances in automated insulin delivery, and strategies that minimize the need for complex insulin regimens hold promise for future study.

Summary Evaluation of the coordination of insulin delivery is limited by a lack of standardized metrics and systematically collected mealtimes. Nevertheless, successful efforts include system-wide multicomponent interventions, though advances in therapeutic approaches may be of value.

Keywords Hospital · Diabetes · Hyperglycemia · Inpatient · Meals · Prandial insulin

Introduction

Hyperglycemia is common in the hospital [1] and is associated with a myriad of poor outcomes, including increased length of stay, wound infection, readmission, and death [2–5]. National guidelines recommend discontinuing pre-admission therapies and using a subcutaneous insulin regimen containing basal, nutritional, and correction components in most hospitalized non-critically ill patients with diabetes or hyperglycemia [6–8]. This requires complex dosing calculations multiple times per day, potentially resulting in errors which could result in hyperglycemia or hypoglycemia. Hypoglycemia is common in insulin-treated hospitalized patients [9], and while the precise role in hospital outcomes is debated, adverse neurologic and cardiac consequences and deaths are well described [10]. Insulin is consistently considered to be a high-risk medication due to a narrow therapeutic index and frequent dosing errors [11–13]. Insulin errors may be classified as prescribing errors, dispensing errors, or administration errors (Table 1) [14•], each with possible contributing factors and solutions. The timing and coordination of insulin doses with glucose monitoring and meals is a source of administration error that is particularly challenging since it involves multiple key agents on a patient's care team. The focus of this review is to summarize the evidence surrounding the importance of timing of insulin administration and to illustrate potential solutions that hospital systems may employ.

Safe Insulin Administration Requires a Coordinated Effort

Professional organizations emphasize proper coordination of capillary blood glucose (CBG) monitoring, insulin administration, and meal delivery for the safe administration of insulin in the hospital [6, 7, 15]. Coordination of these tasks is an expectation for the Joint Commission Certificate of Distinction for Inpatient Diabetes Care, which recognizes

This article is part of the Topical Collection on *Health Care Delivery Systems and Implementation in Diabetes*

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Published online: 04 November 2019

Table 1 Types of insulin errors in the hospital

Prescribing error	Dispensing error	Administration error
• Sliding scale insulin (no basal, nutritional component) • Lack of order sets (eliminates transcription and minimizes dosing errors)	• Wrong insulin • Wrong dose (when insulin dose is dispensed by pharmacy) • Delayed delivery or omission	• Errors caused by communication of concentrated insulin doses • *Poor coordination of insulin with meals and glucose monitoring* • Lack of protocols for specific cases (enteral/parenteral nutrition, transitioning from intravenous insulin, nothing by mouth, withholding doses) • Lack of risk assessment to identify hypoglycemia or hyperglycemia risk • Improper injection technique • Wrong patient/wrong insulin • Wrong dose • Wrong glucose value

hospitals that "make exceptional efforts to foster better outcomes across all inpatient settings [16]. Coordination of these tasks is also emphasized by the Institute for Healthcare Improvement [17]. A coordinated effort involves multiple key players, including dietary personnel who control the delivery of meal trays; nurses, who administer insulin; and nursing assistants, who may assist nurses with CBG monitoring and monitoring meal delivery and intake. This may create situations where CBG monitoring, meal delivery, and insulin administration can get disjointed (Fig. 1).

Prandial Insulin Administration

A typical prandial insulin dose consists of a prandial component, which prevents postprandial hyperglycemia and a correction component, which addresses pre-existing hyperglycemia. Safe administration must consider the time-action profile of prandial insulin. Specific timing intervals include the time between CBG measurement and meals, the time between CBG measurement and insulin delivery, the time between correction doses, and the time between meals and insulin delivery (Table 2). Rapid acting insulin analogues (RAIA) may provide more flexibility for the timing of insulin administration relative to meals compared to regular human insulin. Therefore, RAIAs are frequently used in the hospital setting. The RAIA dose is ideally delivered immediately before meals, although it may be given safely post-meal (generally within 30 min of the start of the meal) [18–20]. Risks and mitigation strategies may depend upon the use of a pre-meal or post-meal dosing strategy.

Studies Assessing the Timing of Insulin Administration in the Hospital

Little is known about the impact of mistimed glucose checks, meals, and subcutaneous insulin doses in the hospital. While glucose measures and meal doses are often time-stamped, a major obstacle for evaluating coordinated insulin delivery in the hospital is the ability to systematically capture mealtimes. Moreover, even if the time of tray arrival is known, the duration and completeness of its consumption may vary.

Freeland et al. performed a prospective observational study among 33 nurses and 39 patients who recorded the start of their meal time [21]. Using meter download and prescription bar code scanning data, the mean time from CBG testing to insulin administration was 46 ± 59 min, and 16% of tests fell

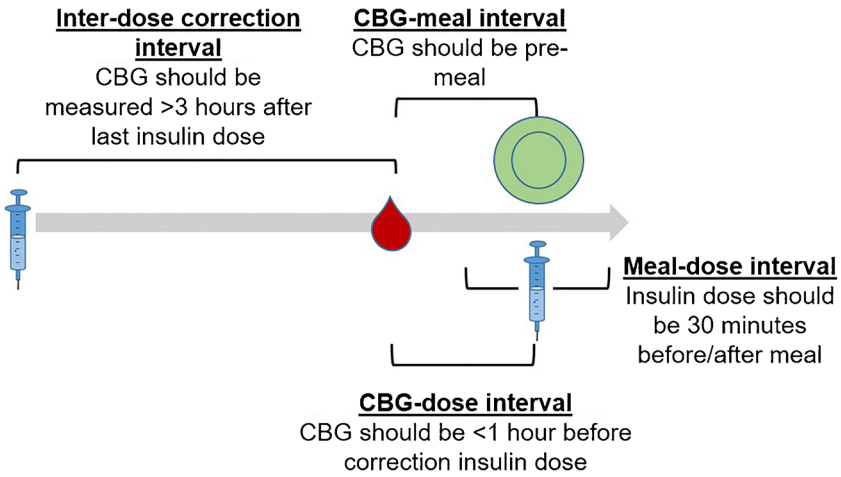

Fig. 1 Sources of error in timing and coordination of glucose monitoring, insulin dose, and meals. Elements which occur outside of appropriate windows may result in hypoglycemia or hyperglycemia. CBG—capillary blood glucose

Table 2 Errors in the coordination and timing of insulin

Timing issue	Examples	Risk	Advisory
CBG-meal interval	CBG collected post-meal	Overcorrection of hyperglycemia	The meal dose may be given but the correction component should be withheld or reduced.
CBG-dose interval	CBG collected > 1 h prior to the insulin dose.	Over/under-correction of hyperglycemia	Recheck glucose if the meal has not arrived. If patient has already begun eating the meal dose may be given but the correction component should be withheld or reduced.
Inter-dose correction interval	CBG measured less than 3 h after last dose of insulin	Insulin dose stacking	If the meal has not arrived, recheck glucose at least 3 h after the last dose. If patient has already begun eating the meal dose may be given but the correction component should be withheld or reduced.
Meal-dose interval	Insulin dose given < 30 min pre-meal	Early pre- or post-meal hypoglycemia, delayed post-meal hyperglycemia	Provide a snack if needed. Do not administer meal dose until tray is present and patient can confirm intake. Consider post-meal dosing if intake is variable. Encourage communication between dietary and nursing staff.
	Insulin dose given > 30 min post-meal	Early post-meal hyperglycemia, delayed post-meal hypoglycemia	Consider calling the prescriber for dose adjustment. Encourage communication between dietary and nursing staff and between patient and nurse.

CBG—capillary blood glucose

within the standard of 30 min. As a part was delivered on average within 21 ± 46 min of the meal, while 21% received insulin more than 60 min before or after the meal. Insulin administration and CBG testing were both within the standard in only 2 cases. Nurses had an average of over 11 years of experience and mandatory computer-based learning was conducted within the previous year, suggesting that system failures played a role. Glucose levels trended lower among those who had received timely glucose monitoring or insulin administration, but this was hampered by the small sample size and was not statistically significant.

Lampe and colleagues studied 64 mealtime events in 4 cardiology units of 2 hospitals and determined that 35% received glucose testing within 1 h prior to insulin administration and 40% within 15 min of the meal; only 14% of doses were on time with respect to both meals and glucose testing [22].

We performed a retrospective analysis of 451 hospitalized patients who were receiving prandial insulin dosed according to carbohydrate intake at breakfast [23•]. Prandial and correction insulin were ordered routinely as part of standard default order panels (1 unit per 20 [low dose], 10 [standard dose], or 5 [high dose] grams carbs and 1 unit per 100 [low], 50 [standard], or 25 [high] mg/dl > 150 mg/dl). These panels may be customized if needed. Insulin was typically dosed post-meal unless carbohydrate intake could be predicted with confidence. The time between glucose monitoring and insulin delivery was over 90 min (median 93, 25–75% 57–138 min). In addition, the median time from breakfast dose of insulin to the pre-lunch glucose measure was only 154 min (25–75% 123–181). However, mistimed glucose measurements did not impact glucose measures later in the day. Thus, it is possible that the timing of the meal is more important than the timing of glucose monitoring, or it may be possible that this flexible meal dosing strategy could have mitigated adverse effects of poorly timed insulin delivery observed with fixed meal dosing. Finally, it is possible that the timing of CBG and insulin dose is more critical in certain patients, such as those who are more insulin deficient. Among 35 nurses who completed surveys, 54% were confident delivering the correct dose all of the time while none were confident delivering the dose on time. Most cited the duration of the meal (54%), other tasks (54%), communication with patient (86%), dietary (74%), and nursing assistant (77%) as very important barriers to timely insulin delivery.

Interventional Studies

The Agency for Health Care Research and Quality recommends a systems-based approach (as opposed to an individual education approach) to reducing error [24]. In a recent systematic review, studies assessing insulin prescribing errors in non-critically ill hospitalized patients were described as heterogeneous in design, implementation, outcomes measures, and definitions of error, making it difficult to assess validity and generalizability [25•]. Unfortunately, there are few studies assessing insulin administration errors in the hospital. However, the timing of insulin delivery in particular is a complex problem, and it is likely that the orchestration of multiple stakeholders and interventions is more likely to be successful and sustainable than a single component intervention. For example, medication administration errors tend to be

addressed with educational initiatives only [26], which are important but ineffective when used in isolation [27–29].

Engle and colleagues reported an intervention in which the nurse performed all meal-related tasks, including glucose monitoring, assessment of carbohydrate intake, administering insulin, and delivering the tray, ensuring that delays between tasks would be minimized [30•]. The percentage of patients who received insulin within 30 min of a glucose check increased from 35 to 73% after the intervention and there was a trend for less hyperglycemia and hypoglycemia. Other brief reports have discussed standardized mealtimes and engagement of dietary personnel and patients, in addition to education [31, 32].

Yamamoto et al. reported the use of Lean/Six Sigma methodology to implement global institutional changes in insulin administration [33]. In a concurrent study specifically addressing the timing relative to meals and radiology testing, several process-directed solutions were identified, including a consistent mealtime on each unit, food services computer software upgrades, and restricting the number of food choices and late trays after hours [34]. New tray mats were developed to identify patients receiving insulin. With respect to radiology, recommendations included a plan to communicate insulin status while ordering the test, and scheduling of inpatient radiology tests outside of mealtimes. At post-implementation, several encouraging process measures were reported, including improvement in glucose control system-wide and estimated cost-savings. However, it was unclear whether improvements in glucose measures were due to study interventions and which interventions were successful.

Computerized clinical decision support systems (CDSS) intended for hospitalized patients with diabetes range from computerized insulin ordering templates to order sets which may include other elements such as diet orders, labwork, referrals, or discharge orders, with or without the context of a more complex system-based intervention [35]. CDSS have been shown to improve mean glucose and use of basal insulin, and have had variable effects on hypoglycemia [35]. However, interventions frequently center on computerized provider order entry (CPOE), which primarily addresses prescribing errors. Bolus calculators are becoming increasingly available and may address insulin administration errors by requiring a nurse to enter carbohydrate intake and glucose value into a medication administration record interface which then automatically calculates an insulin dose based upon a pre-specified insulin:carbohydrate ratio and insulin sensitivity factor. However, bolus calculators do not necessarily address the timing and coordination of insulin and this deserves further attention in future research. Recently, a computerized diabetes medication management system that provided immediate availability and automated handling of glucose measurements was reported to eliminate calculation errors compared to a paper-based protocol, and resulted in fewer hyperglycemic events due to omitted insulin doses [36•]. Curiously, the use of old glucose measurements for dosing calculations did not impact glucose control, though glucose measures were obtained on average of less than 1 h from the insulin dose. Further research is needed to determine whether targeted decision support may provide benefit with respect to coordinated insulin delivery.

Recommendations

AHSP recommended educating patients and caregivers to communicate with nurses when beginning a meal, though the dose may be delayed in patients with inconsistent intake [15]. It is critical that any workflow intervention includes a synchronized communication strategy and administrative/leadership support [30•]. In particular, nursing experiences need to be considered in order to optimize the efficiency of workflow with electronic decision support [37, 38]. Otherwise, existing guidelines do not provide details for addressing the timing and coordination of insulin and the following summary represents the author's recommendations. In the absence of well-designed studies, the confluence of current knowledge points to a multi-faceted intervention that can be broken down by each individual's responsibility on the patient care team.

Dietary

- Dietary orders should identify insulin-requiring patients with or without diabetes.
- Standardized mealtimes should be considered in order to standardize the workflow surrounding glucose monitoring and prandial insulin dosing.
- Patients receiving fixed meal doses should have meals with a consistent carbohydrate content. Unfortunately, this does not necessarily guarantee that a patient will eat the entire meal. A flexible (carbohydrate counting) dosing strategy may also be considered, in which case the carbohydrate content should be itemized on each meal tray.
- Dietary technicians should cross-check trays for carbohydrate-controlled diet orders, place signage on the tray, and notify nursing staff if the tray arrives outside the standard meal window. Meal tray delivery should be prioritized for insulin-requiring patients.

Patients

Patients should be encouraged to contact the nursing team at appropriate times for CBG testing and insulin delivery. In our surveys, most nurses favored low-tech approaches rather than direct patient to nurse communication (such as electronic messaging) [23•].

Nursing Assistants

Nursing staff should ensure that CBG monitoring is timed appropriately with meals and insulin doses are documented in the medical record. The nursing assistant may assist with documentation and communication of meal intake.

Nurses

The nurse should confirm that a glucose measure is a true preprandial value and was performed ideally less than 30 min and no more than 1 h prior to the insulin dose. The nurse should deliver insulin within 30 min of the meal. Further research and/or consensus is needed to determine the optimal intervals, particularly in the context of resource-constrained environment, and appropriate intervals may be more critical for specific patient groups such as type 1 diabetes. The nurse should encourage communication between members of the care team.

Laboratory

Glucose monitoring systems now provide time-stamped values which can integrate within the electronic medical record [39•]. While such timestamps are useful for evaluating workflows, many devices still need to be docked and are not immediately available to the entire care team. Nursing staff are therefore still responsible for transcribing the glucose values into the electronic medical record for immediate use. As technology advances, systems that are able to assimilate values on a real-time basis (via Bluetooth or Wi-Fi) are desirable.

Information Technology and Decision Support It is easy to imagine scenarios whereby even the best intentions would not always result in optimal timing of mealtime insulin. For example, even if a meal tray is delivered, the patient may not eat the meal in a timely fashion either because he/she is gone for a test, does not like the food, or requires additional assistance. It is possible that targeted systems support could help the nursing staff recognize situations when the timing of insulin is likely to affect glucose control. For example, best practice advisories (BPA) may be deployed that alert the nurse administering insulin that the timing with respect to the glucose measure and mealtime (via standardized mealtimes, documentation of carbohydrates by the nursing assistant or dietary staff, or previous insulin dose) is outside of the accepted window, prompting the nurse to take appropriate action, such as get an updated glucose measure (Table 2). However, implementation of BPAs requires careful assessment of nursing workflow as alert fatigue is well known [38]. In our surveys, most nurses did not endorse additional computerized alerts [23•]. Moreover, it is critical that decision support is integrated within the usual workflow in the most seamless way possible in order to maximize uptake.

While not immediately applicable to coordinated insulin delivery, insulin dosing calculators may save time, improve dosing accuracy, and provide an interface for deployment of computerized decision support to improve the timing of meal-related tasks. Dosing calculators that are integrated within the electronic medical record should be configured with an insulin-on-board feature which should protect against insulin stacking [40]. While continuous glucose monitoring systems (CGM) are not approved for use in the hospital, there is an increasing interest in their use [41•, 42•]. CGM could help to minimize the impact of mistimed insulin doses by providing real-time continuous data as well as provide a means for early detection of hypoglycemia or hyperglycemia. Future approaches may integrate glucose monitoring data and decision support into a truly closed loop insulin delivery system [43]. Further studies are needed to assess safety and effectiveness in the hospitalized patient.

Alternate Approaches Basal bolus insulin is still recommended for most hospitalized patients with hyperglycemia due in part to limited evidence to guide the use of other therapies. However, in some patients, other therapies may mitigate the need for mealtime insulin altogether. For example, a randomized study demonstrated similar glucose control with sitagliptin compared to prandial insulin, both in combination with basal and correction insulin in hospitalized patients [44•]. Recently, a pilot study demonstrated that exenatide 5 μg twice daily in combination with basal insulin resulted in a greater proportion of glucose values in target compared to exenatide alone or basal bolus insulin, though at the expense of increased risk of nausea. Patients with a lower HbA1c at admission and lower insulin requirements (< 0.5 unit/kg/day) are most likely to respond to alternative strategies [45].

While not specifically studied in the inpatient setting, newer faster-acting insulin analogues are in development or already in use and may offer an advantage with respect to insulin delivery in the hospital [46•]. For example, when administered 20 min post-meal, faster-acting aspart (Fiasp) resulted in a higher 1-h but similar 2-h glucose increment compared to pre-meal aspart [47•]. More study is needed to assess safety in the hospital, where the timing of insulin with meals can be even more delayed.

Conclusions

The timing and coordination of insulin delivery is considered an important safety issue in the hospital, though the magnitude of the issue, relative contribution of contributing factors, and safety implications have not been adequately described. There is a need for well-defined metrics addressing each component of coordinated insulin delivery, including CBG monitoring, meal delivery and intake, and insulin administration. The

complexity of the issue mandates a multifactorial, systems-based approach which should incorporate input from key stakeholders. Further research assessing the possible role of computerized decision support systems and glucose management strategies is needed.

Compliance with Ethical Standards

Conflict of Interest Kathleen Dungan reports research support from Eli Lilly, Sanofi Aventis, and Novo Nordisk; consulting activities with Eli Lilly, Mannkind; and royalties from UptoDate, DKBmed, and Elsevier.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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