Early Intervention for Diabetes in Medical and Surgical Inpatients Decreases Hyperglycemia and Hospital-Acquired Infections: A Cluster Randomized Trial

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OBJECTIVE

To investigate if early electronic identification and bedside management of inpatients with diabetes improves glycemic control in noncritical care.

RESEARCH DESIGN AND METHODS

We investigated a proactive or early intervention model of care (whereby an inpatient diabetes team electronically identified individuals with diabetes and aimed to provide bedside management within 24 h of admission) compared with usual care (a referral-based consultation service). We conducted a cluster randomized trial on eight wards, consisting of a 10-week baseline period (all clusters received usual care) followed by a 12-week active period (clusters randomized to early intervention or usual care). Outcomes were adverse glycemic days (AGDs) (patient-days with glucose <4 or >15 mmol/L [<72 or >270 mg/dL]) and adverse patient outcomes.

RESULTS

We included 1,002 consecutive adult inpatients with diabetes or new hyperglycemia. More patients received specialist diabetes management (92% vs. 15%, $P < 0.001$) and new insulin treatment (57% vs. 34%, $P = 0.001$) with early intervention. At the cluster level, incidence of AGDs decreased by 24% from 243 to 186 per 1,000 patient-days in the intervention arm ($P < 0.001$), with no change in the control arm. At the individual level, adjusted number of AGDs per person decreased from a mean 1.4 (SD 1.6) to 1.0 (0.9) days (−28% change [95% CI −45 to −11], $P = 0.001$) in the intervention arm but did not change in the control arm (1.8 [2.0] to 1.5 [1.8], −9% change [−25 to 6], $P = 0.23$). Early intervention reduced overt hyperglycemia (55% decrease in patient-days with mean glucose >15 mmol/L, $P < 0.001$) and hospital-acquired infections (odds ratio 0.20 [95% CI 0.07–0.58], $P = 0.003$).

CONCLUSIONS

Early identification and management of inpatients with diabetes decreased hyperglycemia and hospital-acquired infections.

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Hyperglycemia and hypoglycemia are common events in the hospital and are associated with adverse patient outcomes (1,2). Acute hyperglycemia is independently associated with hospital-acquired infections, longer length of stay, and greater mortality (1,3). Multiple cellular and physiological mechanisms are implicated, particularly neutrophil and endothelial dysfunction, osmotic diuresis, and proinflammatory changes (4). Treating hyperglycemia may improve clinical outcomes in the critical care (5), stroke care (6), and noncritical care settings (7). However, aggressive treatment of hyperglycemia can lead to hypoglycemia (7–9), which causes undesirable symptoms and adverse outcomes. Thus, a key target of inpatient diabetes care should be to avoid the glycemic extremes of both hyperglycemia and hypoglycemia, also described as adverse glycemia (10). Despite published guidelines on ideal blood glucose (BG) targets (11–13), glycemic control remains challenging because of multiple obstacles, and systems-based solutions are needed (14).

Because most inpatients with diabetes are managed by hospitalists or parent (admitting) teams, diabetes specialists are seldom involved in their care. Many hospitals have implemented specialized inpatient diabetes teams (IDTs) (or glycemic management teams) to develop protocols, deliver education programs, and perform clinical audits in addition to directly assisting in diabetes management. These teams usually consist of specialized diabetes nurses and diabetologists who provide management advice in response (or reactive) to referrals from the parent team (15–18). However, referrals to IDTs may be inconsistent because of clinical inertia (19).

A more proactive model of diabetes care can be delivered by a diabetes team that autonomously provides early assessment and management without referral from the admitting team (20). Availability of networked BG meters (that electronically capture capillary BG measurements) has enabled remote electronic surveillance of glycemic control. Proactive models of care using networked BG meters have demonstrated improved glycemic control in observational studies (21–23), but randomized studies are lacking (14). Therefore, we investigated the effect of early intervention, using a proactive model of inpatient diabetes care, on glycemic and clinical outcomes in a prospective cluster randomized study.

RESEARCH DESIGN AND METHODS

Study Design and Participants

The Randomized Study of a Proactive Inpatient Diabetes Service (RAPIDS) is an open-label, cluster randomized controlled study with a baseline period that was conducted over 6 months at the Royal Melbourne Hospital (tertiary referral hospital affiliated with the University of Melbourne). The intervention was implemented at the cluster level. Outcomes were assessed at both the cluster and the individual level.

There were eight wards (clusters) involved in the study that comprised four medical wards (cardiology, neurology, and two general medicine) and four surgical wards (orthopedic surgery, neurosurgery, abdominal surgery, and emergency surgery). The two general medical wards contained patients with similar characteristics and can be considered as sister (symmetrical) wards; however, the remaining six wards had unique parent teams and patient characteristics.

We included consecutive adult inpatients admitted over the study period with preexisting diabetes or new hyperglycemia (random capillary BG $>$11.1 mmol/L [$>$200 mg/dL] without a history of diabetes) and with a $>$1 day length of stay. Individuals admitted with glycemic emergencies or those admitted under endocrinology or palliative care teams were excluded. For individuals who were admitted more than once during the study period, only the first admission was included. The study was approved by the Melbourne Health Human Research Ethics Committee with a waiver of individual consent and was registered prospectively with the Australian New Zealand Clinical Trials Registry.

Procedures, Randomization, and Masking

Before commencement of the study, we implemented networked BG meters (StatStrip; Australasian Medical & Scientific Limited) on the study wards. These devices have recently become available in Australia and facilitated accurate collection of capillary BG data and remote identification of inpatients with diabetes.

At commencement of the study, and before randomization, there was a 10-week baseline period where all eight clusters received usual care. The clusters were then randomized 1:1 into control and intervention arms, stratified by type of ward (medical or surgical) using a random number generator by a blinded statistician. A 12-week active period then followed where the four clusters randomized to the intervention arm received the proactive, early management model of care, and the four clusters randomized to the control arm continued with usual care (Supplementary Fig. 1). Treating staff and patients were not masked to the allocation of clusters to intervention or control arms.

Usual Inpatient Diabetes Management (Usual Care)

Diabetes management is performed primarily by the hospital medical officers of the parent team. A specialist IDT consisting of a diabetes nurse and endocrinology fellow supervised by a diabetologist provided a consultation service in response (or reactive) to referrals from the parent unit. Our institution had guidelines and protocols on inpatient diabetes management but did not have insulin order sets or an electronic medical record for delivering inpatient care; therefore, written BG observation charts and medication orders at the bedside were used. In accordance with local practice in Australia, the U.K., and Europe, there is no standardized algorithm of discontinuing oral antidiabetic medications and routine prescription of a subcutaneous basal-bolus insulin regimen in all individuals with diabetes admitted to the hospital.

Early Intervention (Proactive Model of Care)

The specialist IDT identified all consecutive inpatients with diabetes or hyperglycemia and aimed to provide diabetes management within 24 h of admission without referral from the parent team. The IDT performed electronic surveillance of capillary BG measurements captured by networked BG meters, which enabled early identification of inpatients with diabetes and ongoing electronic surveillance of glucose control. In addition, a structured clinical escalation pathway (Melbourne Glucose Alert Pathway) (10) was implemented on the intervention wards to encourage clinical escalation of patients with dysglycemia to the IDT.

Before the intervention, the IDT participated in four training modules delivered by a senior diabetologist. Aimed at upskilling the team, the training modules included insulin initiation guidelines and case-based discussions focused on optimizing glycemic control. During consultations, the IDT prescribed subcutaneous insulin and glucose lowering medications in an individualized manner, aiming to achieve safe glycemic control while avoiding glycemic extremes. The IDT consultations occurred daily, with insulin dose titration depending on clinical need. The IDT optimized long-term diabetes control by intensifying or deescalating diabetes treatment at the time of discharge, depending on admission HbA_{1c} (24). The IDT regularly interacted with the parent teams' medical and nursing staff, providing an opportunity for ward-based education on inpatient diabetes management. A weekly audit meeting was led by a senior diabetologist to discuss patient care and monitor outcomes. The proactive IDT operated during weekdays, with an on-call endocrinologist available for advice after hours and on weekends. During the active period, the same IDT provided proactive care in the intervention wards and consultation service in response to referrals (usual care) in the control wards.

Data Collection

A researcher independent of the IDT performed surveillance of capillary BG measurements to identify eligible patients. Patient information and clinical outcomes were collected from inpatient progress notes, the pathology results system, and the patient administration database. Point-of-care BG measurements were collected by networked BG meters. BioViewer (BioAsia Diagnostics) data manager was used to obtain BG measurements from day 1 of admission until discharge. BG measurements from day 0 were excluded because glycemic control on the day of admission is influenced by treatment before admission or in the emergency department rather than by ward management. BG measurements were excluded after day 14 of admission to avoid skewing of BG data by the few individuals with a prolonged hospital stay. In addition, we applied the glucometric technique to exclude repeated measurements from a single episode of hypo- or hyperglycemia as described by Weinberg et al. (25).

Outcomes Measures

The primary outcome was adverse glycemic day (AGD) defined as a patient-day with any BG <4 or >15 mmol/L (<72 or >270 mg/dL). These pragmatic BG cutoff points were used to define AGD because the aim of this trial was for safe glycemic control rather than tight glycemic control. Although a target random BG <10 mmol/L (<180 mg/dL) is recommended in noncritical care, this target is not based on strong experimental evidence, and the target may vary depending on the individual's comorbidities (13). However, a BG >15 mmol/L (>270 mg/dL) may be associated with adverse pathophysiology (4) and should be avoided in most inpatients. Similarly, any degree of hypoglycemia (even BG <4 mmol/L [<72 mg/dL]) in inpatients with complex comorbidities and concurrent illness is undesirable and should be avoided. Therefore, the AGD outcome reflects glycemic extremes that should be avoided for safe diabetes management in the hospital (26). At the cluster level, the incidence of AGD is reported per 1,000 observed patient-days, and at the individual level, the number of AGDs per patient is reported. Because BG measurements were excluded after day 14 of admission, each individual contributed to a maximum of 14 observed patient-days.

The prespecified secondary outcomes were process-of-care measures, glucometric measures, adverse patient outcomes, and length of stay. Adverse outcomes were analyzed individually and as a composite of five items, including hospital-acquired infections, acute kidney injury, acute myocardial infarction, unplanned critical care admission, and in-hospital mortality. These outcomes were included because they were commonly associated with poor glycemic control (27). Hospital-acquired infection was defined as clinical or microbiological evidence of skin wound or surgical site infection, urinary tract infection, bacteremia, or pneumonia that developed at least 48 h after admission. Acute kidney injury was defined as a rise in serum creatinine by $>50\%$ from admission or the need for acute renal replacement therapy. Myocardial infarction was defined as new ischemic changes on electrocardiogram and a rise in troponin that developed at least 48 h after admission. The adverse patient outcomes were adjudicated by an independent assessor who was blinded to treatment group allocation.

Statistical Analysis

The primary outcome of AGD was analyzed at the cluster level (proportion of the total number of AGDs divided by the total number of observed days and reported as a rate per 1,000 patient-days) and at the individual level (the number of AGDs per patient). The number of AGDs per patient was adjusted for patient covariates (age, sex, modified Charlson comorbidity index, creatinine, HbA_{1c}, diabetes type, insulin treatment before admission) and hospital treatment covariates (number of days observed, admission unit, type of admission, type of ward) as fixed effects and wards (clusters) as a random effect using a mixed-effects Poisson regression model (Supplementary Table 1). The adjusted number of AGDs per patient was then calculated using the predict function from the regression. We expected differences in patient characteristics between control and intervention arms as a result of enrolling clusters with unique clinical services. However, we expected well-matched patient characteristics between the baseline and active periods within each treatment arm. Therefore, we planned to analyze the outcomes between treatment arms and as a change from baseline within each treatment arm. To enable this analysis, we created four distinct groups depending on treatment arm (control vs. intervention) and time period (baseline vs. active). The four groups (control-baseline period, control-active period, intervention-baseline period, and intervention-active period) were used as a factor in the mixed-effects regression model to allow simultaneous comparison between treatment arms and as a change between baseline and active periods within each treatment arm.

Hospital-acquired infections were analyzed using a mixed-effects logistic regression model adjusting for covariates (post hoc analysis). All analyses were performed using the intention-to-treat approach; therefore, if an individual crossed over treatment arms because of ward transfers, he or she was analyzed in the initial treatment arm that was in place when first admitted. If an individual was transferred from the study wards to a nonstudy ward in the hospital, subsequent

BG measurements from the time of transfer were excluded, but clinical outcomes and hospital length of stay for the entire hospitalization were analyzed.

This study was designed as a 24-week trial (the feasible duration of the study), recruiting consecutive inpatients. The power calculation was performed prospectively and estimated the minimum difference in AGDs that can be detected given the expected number of recruited patients. A previous pilot study showed that the incidence of AGDs was 300 per 1,000 patient-days at our institution (10). On the eight wards, we expected to recruit 600 individuals during the baseline period and 600 individuals during the active period, with a median of 3.5 observed days per patient. This entailed 300 patients and 1,050 patient-days per treatment arm during the active period. For four clusters in each arm, using a 0.01 intraclass correlation and a two-sided α of 0.05, this study had >80% power to detect a 33% change in AGDs. Analyses were performed using Stata 15 statistical software (StataCorp, College Station, TX).

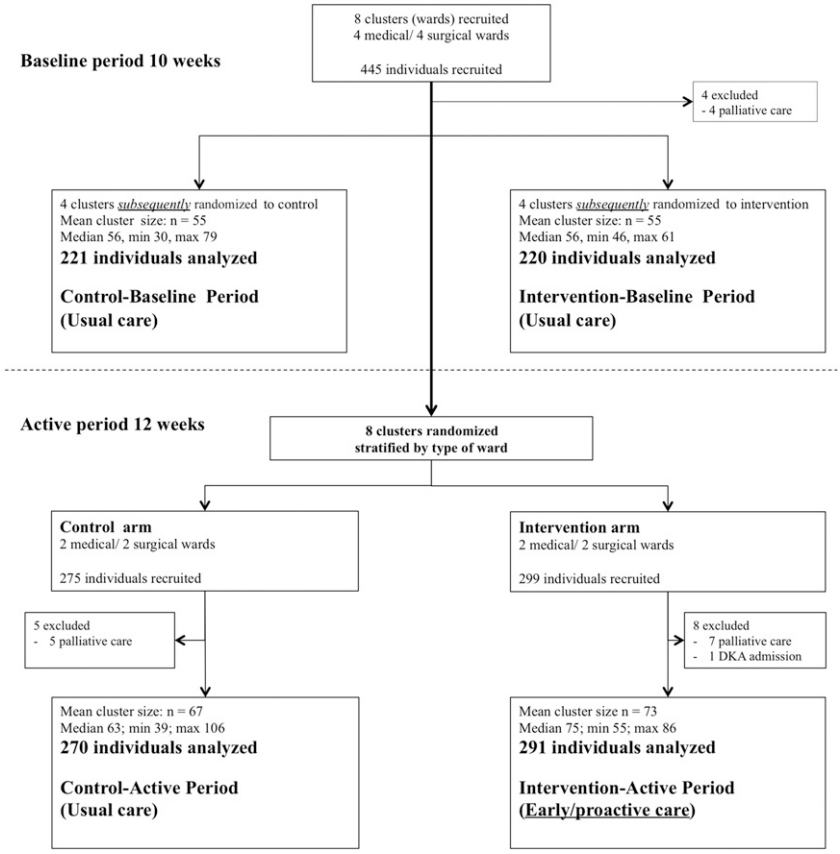

Figure 1—Patient recruitment. DKA, diabetic ketoacidosis; max, maximum; min, minimum.

RESULTS

There were 1,019 unique patient admissions to the eight study wards between March and August 2016. After exclusion, the final sample comprised 1,002 individuals equally distributed across the study arms (Fig. 1). Overall, 87% of the cohort had type 2 diabetes, with a mean HbA_{1c} of 58 (SD 18) mmol/mol (7.5% [1.7%]), and 30% were treated with insulin before admission. Patients were observed for a median of 4 (interquartile range 2, 8) days and had 3.5 (1.7) capillary BG measurements per patient-day.

There were differences in patient characteristics between control and intervention arms. Compared with the control arm, the intervention arm had a higher proportion of patients with surgical and emergency admissions. The intervention arm had a lower proportion of patients with insulin treatment before admission and a lower mean HbA_{1c} (Table 1). However, patient characteristics were well matched between the baseline and active periods within each treatment arm. There were more emergency admissions during the active period than during the baseline period in the intervention arm.

Early identification and management improved process-of-care outcomes (Fig. 2). In the intervention arm, *1*) the proportion of patients managed by the IDT increased from 8% during the baseline period to 92% during the active period ($P < 0.001$), *2*) the proportion of patients managed within 24 h of admission increased from 4% to 64% ($P < 0.001$), and *3*) insulin treatment in insulin-naive patients increased from 34% to 57% ($P < 0.001$). No changes were observed in the control arm.

Over the study period, 5,447 patient-days were observed. At the cluster level, there was a 24% decrease in the incidence of AGDs (243 vs. 186 per 1,000 patient-days, $P < 0.001$) in the intervention arm, with a nonsignificant 9% decrease observed in the control arm (291 vs. 261 per 1,000 patient-days, $P = 0.09$). The decrease in incidence in the intervention arm (57 per 1,000 patient-days) was significantly higher than that in the control arm (30 per 1,000 patient-days, $P = 0.004$).

At the individual level, the adjusted number of AGDs per patient decreased from mean 1.4 (SD 1.6) to 1.0 (0.9) days (−28% change [95% CI −45 to −11], $P = 0.001$) in the intervention arm, with a nonsignificant change in the control arm (1.8 [2.0] to 1.5 [1.8] days, −9% change [−25 to 6], $P = 0.23$) (Table 2). Comparing parallel treatment groups during the active period, the number of AGDs per patient was 23% lower (95% CI 6–40, $P = 0.008$) in the intervention arm than in the control arm (Supplementary Table 1). Comparison between the two symmetrical general medical clusters demonstrated that the cluster randomized to the intervention arm had a significant reduction in AGDs per patient (2.2 [2.3] to 1.4 [1.3] days, $P = 0.010$], whereas the cluster randomized to the control arm had no significant change (2.0 [2.5] to 2.1 [2.6] days, $P = 0.96$) (Supplementary Table 2).

On glucometric analyses, 19,060 capillary BG measurements were observed during the study period. The patient-day mean glucose decreased from 9.4 (SD 3.3) to 9.0 (2.7) mmol/L (169 [59] to 162 [49] mg/dL, $P = 0.003$) in the intervention arm but remained stable in the control arm (9.6 [3.2] to 9.5 [3.2] mmol/L [173 (58) to 171 (58) mg/dL],

Table 1—Patient characteristics

	Control arm (four clusters)			Intervention arm (four clusters)			
	Baseline period (n = 221)	Active period (n = 270)	P value‡	Baseline period (n = 220)	Active period (n = 291)	P value‡	P value (four groups)§
Age (years)	70 ± 14	70 ± 14	0.726	70 ± 15	71 ± 16	0.292	0.124
Male sex	135 (61)	166 (61)	0.929	112 (51)	156 (54)	0.545	**0.039**
Modified Charlson score*	2 (1, 3.5)	2 (0, 3)	0.476	1 (0, 3)	1 (0, 3)	0.525	0.066
Admission creatinine (μmol/L)	111 ± 57	107 ± 59	0.430	102 ± 59	104 ± 68	0.742	0.477
Type of diabetes			0.799			0.190	0.071
Type 2	193 (87)	241 (89)		190 (86)	251 (86)		
Type 1	18 (8)	19 (7)		16 (7)	12 (4)		
New hyperglycemia	10 (5)	10 (4)		14 (6)	28 (10)		
HbA_{1c}							
mmol/mol	60 ± 18	62 ± 19	0.158	57 ± 19	57 ± 18	0.590	**0.049**
%	7.6 ± 1.7	7.8 ± 1.8		7.4 ± 1.8	7.4 ± 1.7		
Diabetes treatment before admission			0.960			0.843	**0.007**
No treatment	43 (19)	55 (20)		56 (25)	79 (27)		
Oral agents and GLP-1	99 (45)	121 (45)		113 (51)	142 (49)		
Insulin (with or without oral agents and GLP-1)	79 (36)	94 (35)		51 (23)	70 (24)		
Hospital stay (days)	5 (3, 5)	4 (2, 4)	0.064	4 (2, 7)	4 (2, 8)	0.964	0.335
BG measurements/day	3.6 ± 1.9	3.5 ± 1.7	0.543	3.4 ± 1.5	3.5 ± 1.6	0.469	0.990
Capillary glucose at admission							
mmol/L	10.3 ± 4.4	10.3 ± 4.3	0.986	9.3 ± 4.0	9.2 ± 3.8	0.620	**0.001**
mg/dL	182 ± 79	182 ± 77		167 ± 72	165 ± 68		
Glucocorticoid treatment during admission†	41 (19)	38 (14)	0.179	28 (13)	30 (10)	0.395	0.062
Type of admission			0.731			**0.006**	**0.003**
Elective	31 (14)	35 (13)		26 (12)	15 (5)		
Emergency	190 (86)	235 (87)		194 (88)	276 (95)		
Admission parent unit			0.294			0.159	**<0.001**
Medicine	168 (76)	194 (72)		106 (48)	122 (42)		
Surgery	53 (24)	76 (28)		114 (52)	169 (58)		
Medical admissions by parent unit							
General medicine	54 (24)	55 (20)		56 (25)	89 (31)		
Cardiology	70 (32)	95 (35)		0	2 (1)		
Neurology	0	3 (1)		49 (23)	71 (24)		
Respiratory	21 (10)	22 (8)		0	1		
Gastroenterology	15 (6)	9 (3)		5 (2)	5 (2)		
Other medical	8 (4)	11 (5)		4 (2)	2 (1)		
Surgical admission by parent unit							
Abdominal and emergency general surgery	16 (7)	21 (8)		47 (21)	68 (23)		
Neurosurgery	0	0		43 (19)	41 (14)		
Orthopedics and trauma	37 (17)	50 (19)		10 (5)	8 (3)		
Other surgery	0	4 (1)		6 (3)	4 (1)		

Data are mean ± SD, median (interquartile range), or n (%). Boldface indicates significance at $P < 0.05$. *Modified Charlson comorbidity index excluded items related to diabetes. †Glucocorticoid treatment was defined as treatment with a supraphysiological dose of glucocorticoid medication (dose equivalent >7.5 mg of prednisolone) for ≥24 h during admission. ‡P value of difference between baseline and active periods within each treatment arm. §P value of difference among four groups.

P = 0.235). The proportion of patient-days with a mean BG >10 and >15 mmol/L (>180 and >270 mg/dL) decreased by 14% and 55%, respectively, in the intervention arm, with no change in the control arm (Table 2 and Fig. 2). The proportion of good diabetes days (patient-days with no BG <4 mmol/L [<72 mg/dL] and no more than one BG >11 mmol/L [198 mg/dL]), a U.K. metric (28), increased in the intervention arm (70% to 74%, P = 0.020) but did not change in the control arm (65% to 66%, P = 20.61). There was no change in the incidence of hypoglycemia in either treatment arm.

The proportion of individuals with hospital-acquired infections decreased from 6.4% to 2.4% (P = 0.035) in the intervention arm but did not change significantly in the control arm (8.6% to 7.0%, P = 0.61). Post hoc analyses using mixed-effects logistic regression adjusting for covariates (Supplementary Table 3) demonstrated that early diabetes management conferred a lower risk of developing hospital-acquired infection (adjusted odds ratio 0.20 [95% CI 0.07–0.58], P = 0.003). The number needed to treat to prevent one hospital-acquired infection was 25. There was a strong correlation between number of AGDs and hospital-acquired

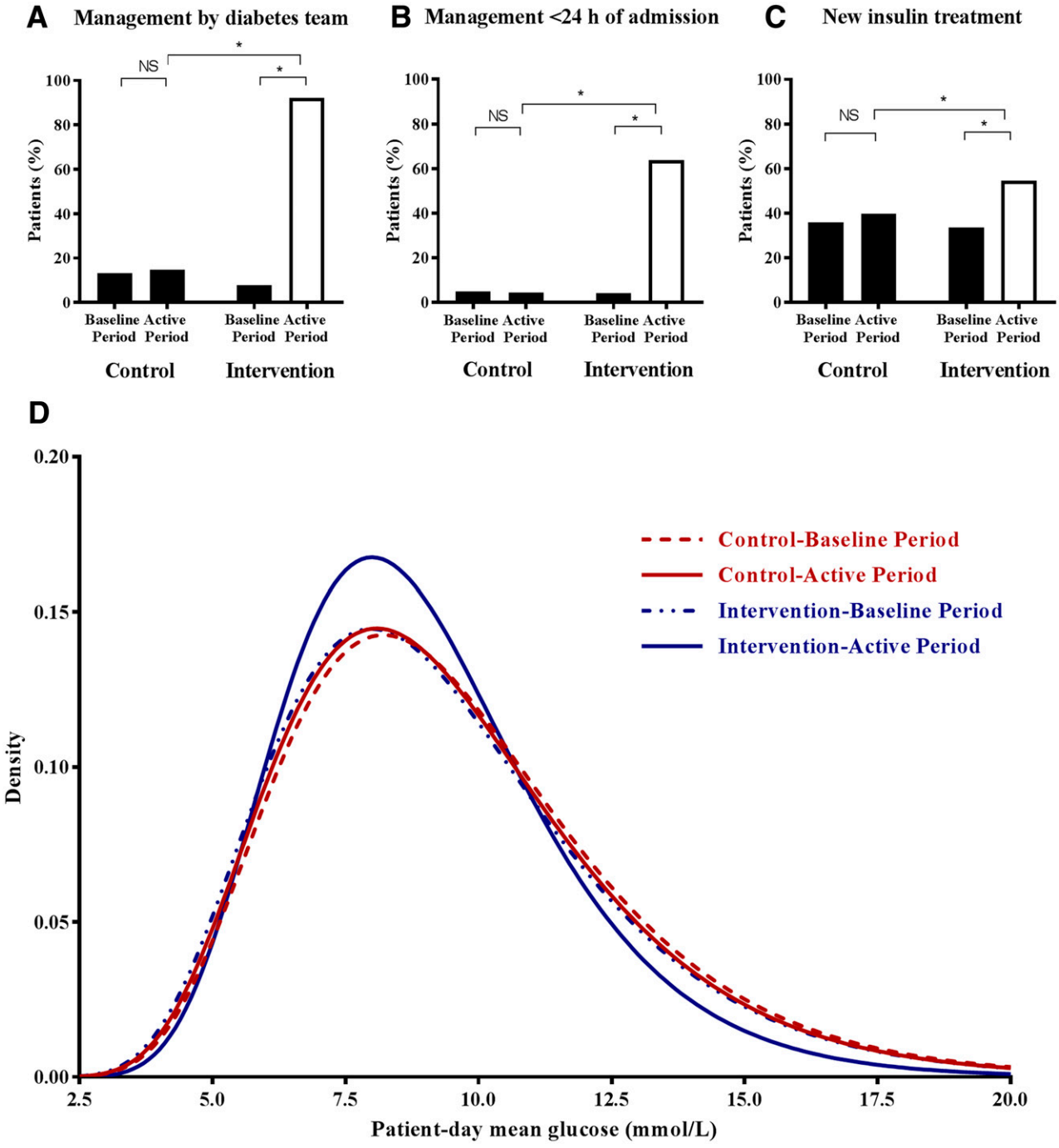

Figure 2—Process of care and glucometric outcomes. *A*: Proportion of patients who received management by the IDT during admission. *B*: Proportion of patients who had diabetes team management within 24 h of admission. *C*: Proportion of insulin-naive patients who had treatment with subcutaneous insulin during admission. Filled bars represent usual care, and open bars represent the proactive/early intervention model of care. *D*: Distribution of patient-day mean glucose. Patient-day mean glucose fits a log-normal distribution. There was no difference in the distribution in the groups that received usual care (dotted lines and solid red line). The group that received early intervention (solid blue line) had a lower mean and variance in the distribution and therefore a lower proportion of days with severe hyperglycemia. *$P < 0.001$.

infection (each day increase in AGDs conferred an odds ratio of 1.35 [1.20–1.51] for hospital-acquired infection). The reduction in infection rate remained consistent on subgroup analysis of only individuals with type 2 diabetes (Supplementary Tables 4–7). There was a higher baseline incidence of infections (hence greater reduction in infections) in medical compared with surgical patients (Supplementary Table 8). There were no differences in the remaining individual or composite clinical outcomes in either arm (Table 2).

CONCLUSIONS

To our knowledge, RAPIDS is the first randomized trial to investigate the effect of comprehensive early intervention for all consecutive patients with diabetes, consisting of early electronic identification and bedside specialist IDT

Table 2—Primary and secondary outcomes

	Control arm (four clusters)			Intervention arm (four clusters)		
	Baseline period (usual care)	Active period (usual care)	*P* value	Baseline period (usual care)	Active period (early/proactive intervention)	*P* value
Primary outcome: AGDs						
Cluster level: incidence of AGDs (per 1,000 patient-days)	291	261	0.090	243	186	**<0.001**
Individual level: adjusted number of AGDs per patient, mean ± SD*	1.8 ± 2.0	1.5 ± 1.8	0.23†	1.4 ± 1.6	1.0 ± 0.9	**0.001**†
Median (IQR)	1.2 (0.7, 1.9)	1.0 (0.6, 1.7)		0.9 (0.5, 1.7)	0.7 (0.4, 1.3)	
Secondary: glucometric outcomes						
Patient-days, *n*	1,271	1,394		1,200	1,582	
Patient-day mean BG, mean ± SD	9.6 ± 3.2	9.5 ± 3.2	0.23	9.4 ± 3.3	9.0 ± 2.7	**0.003**
Mean BG >10 mmol/L (>180 mg/dL), %	37	37	0.88	35	30	**0.010**
Mean BG >15 mmol/L (>270 mg/dL), %	6.9	6.1	0.39	7.3	3.3	**<0.001**
BG <4 mmol/L (<72 mg/dL), %	5.6	5.0	0.52	3.8	4.0	0.69
BG <3 mmol/L (<54 mg/dL), %	1.6	1.4	0.75	1.0	0.7	0.40
Secondary: clinical outcomes						
Patients, *n*	221	270		220	291	
Any hospital-acquired infection, *n* (%)	19 (8.6)	19 (7.0)	0.52	14 (6.4)	7 (2.4)	**0.035**
Skin wound and surgical site	5 (2.3)	8 (3.0)		2 (0.9)	2 (0.7)	
Urinary tract	5 (2.3)	4 (1.5)		4 (1.8)	3 (1.0)	
Bacteremia	1 (0.5)	0		1 (0.5)	0	
Pneumonia	9 (4.1)	10 (3.7)		9 (4.1)	4 (1.4)	
Acute kidney injury	15 (6.8)	22 (8.1)	0.56	11 (5.0)	11 (3.8)	0.50
Acute myocardial infarction	4 (1.8)	5 (1.9)	0.97	2 (0.9)	1 (0.3)	0.40
Unplanned critical care admission	12 (5.4)	12 (4.4)	0.61	2 (0.9)	3 (1.0)	0.89
In-hospital mortality	5 (2.3)	8 (3.0)	0.63	6 (2.7)	6 (2.1)	0.63
Composite outcome‡	39 (17.6)	51 (18.9)	0.72	28 (12.7)	26 (8.9)	0.17
Length of stay (days)	6 (3, 11)	6 (3, 11)	0.60	6 (3, 10)	6 (3, 10)	0.19

Boldface indicates significance at $P < 0.05$. IQR, interquartile range. *Adjusted for age, sex, modified Charlson comorbidity index, creatinine, HbA_{1c}, insulin treatment before admission, admission unit, admission type, ward type, days observed (fixed effects), and ward (random effect). †Mixed-model Poisson regression. ‡Hospital-acquired infection, acute kidney injury, acute myocardial infarction, unplanned critical care admission, and in-hospital mortality.

management. RAPIDS achieved its primary outcome of reducing AGDs with no concomitant increase in hypoglycemia.

This study used the primary outcome of AGD (with a more liberal glycemic target) as an index of safe glycemic control in the hospital to achieve the balance of decreasing overt hyperglycemia while minimizing hypoglycemia. This is similar to the concept of a good diabetes day used in the annual National Inpatient Diabetes Audit in the U.K. (28). Although there are no published data that investigated AGD and clinical outcomes, we propose AGD is a clinical index of both hyperglycemia and hypoglycemia events as well as a tangible concept for educating health professionals about safe glycemic control in the hospital.

Early identification and management for diabetes decreased the number of AGDs per patient by 28% in the intervention arm. There was a slight (but nonsignificant) 9% decrease in the control arm that was possibly related to contamination or a Hawthorne effect, but even after adjusting for this change, the intervention arm had a 23% lower number of AGDs per person compared with the control arm. In addition to AGD outcomes, traditional glucometric analyses also demonstrated improved glycemic control. With early identification and management, patient-day glucose was lower in both the mean (decreased by 0.4 mmol/L [7.2 mg/dL]) and the variance (SD decreased by 0.6 mmol/L [10.8 mg/dL]). There was a 55% decrease in patient-days with mean glucose >15 mmol/L. These findings are comparable to an observational study by Seheult et al. (22) wherein a proactive diabetes team achieved a 0.13 mmol/L (2.3 mg/dL) decrease in patient-day mean glucose and a 20% reduction in patient-days with mean glucose >15 mmol/L. Similarly, Rushakoff et al. (21) provided a virtual glucose monitoring service with proactive electronic consultation notes on patients with unstable diabetes, decreasing patient-day mean glucose by 0.24 mmol/L (4.3 mg/dL) and achieving a 40% reduction in patient-days with hyperglycemia (two or more BG measures >12.5 mmol/L [>225 mg/dL]).

In RAPIDS, early identification and management did not decrease hypoglycemia, in contrast to Rushakoff et al. (21). The baseline incidence of hypoglycemia in our cohort (4.7% of patient-days) was lower than the mean incidence in 635 U.S. hospitals (6.1% of patient-days) (29). A more extensive multifaceted intervention, including dedicated insulin prescription order sets, protocols, and education campaigns (16), may be required to further decrease hypoglycemia from the current relatively low rates at our institution. Nevertheless, it is encouraging that early intervention and increased tailored insulin treatment did not increase hypoglycemia and thus did not pose any safety risk for inpatients.

With early identification and management of diabetes, a 4% absolute risk reduction in hospital-acquired infection was observed. It is well known that poor glycemic control in the community (30) and in the hospital (31,32) is associated

with an increased risk for infection. There is strong evidence that intensive glycemic control decreases infections in cardiac and general surgery (33,34), critical care (35), and noncritical care (7,36). In a noncritical care study, basal-bolus insulin therapy improved a composite outcome but especially decreased wound infections and hospital-acquired pneumonia (7). A meta-analysis of noncritical care studies also demonstrated intensive glycemic control is associated with a 60% decreased risk of hospital-acquired infections (37). We found AGDs were strongly correlated with hospital-acquired infection and the decrease in hospital-acquired infections paralleled a decrease in AGDs, despite a modest change in mean glucose. This suggests that eliminating glycemic extremes may be most effective at improving clinical outcomes. In addition, RAPIDS provides further evidence to support the notion that improving inpatient glycemic control decreases hospital-acquired infection; however, as one of several prespecified secondary outcomes, this finding requires further confirmatory randomized studies.

Of various models of inpatient diabetes care (16,20–22,38–40), the strengths of our intervention included remote surveillance and identification of hyperglycemia and bedside consultations by a specialist IDT that directly prescribed insulin. The IDT used individualized treatment (rather than protocolized intensive insulin treatment) with the practical aim of decreasing both extremes of glycemia rather than aiming for "tight" glycemic control. This approach successfully decreased hyperglycemia without increasing hypoglycemia. By providing bedside management, it was also possible to recognize and address any other relevant aspects of patient care in addition to diabetes management, which may have contributed to improved clinical outcomes.

RAPIDS used a parallel cluster randomized design with a baseline period, which was necessitated by several factors. It was only practical to deliver the proactive intervention at the ward level rather than at the individual patient level. Contamination was possible as a result of movement of patients and staff across wards, although the active period occurred during one resident staff rotation. In addition, increased presence of the IDT could result in increased awareness and upskilling of inpatient diabetes care. The study design, which included baseline and active periods, allowed for comparison of the intervention against its own baseline, whereas a parallel control arm accounted for any other potential variations within the overall study period.

Limitations of this study include the relatively few clusters and some differences in patient characteristics between clusters as a result of our hospital structure with nonsymmetrical specialist medical and surgical wards. We used a mixed-effects model, which accounted for clustering and adjusted for baseline patient characteristics, but it is possible that there are residual confounders that are unaccounted for. The Hawthorne effect may also have contributed to improved glycemic outcomes. This study was relatively short; therefore, the sustainability of the improvements is yet to be determined. A longer duration study was not feasible with the available resources and would be susceptible to further contamination.

There are also limitations on the generalizability of our findings. Our hospital did not have a comprehensive electronic medical record, including electronic medication prescription and order sets, to assist with delivering inpatient care. The baseline proportion of inpatients managed by an IDT was modest. Therefore, the early intervention model may have less of an impact in a facility with state-of-the-art hospital systems already in place. Furthermore, the IDT identified and provided consultation on all consecutive individuals with diabetes or new hyperglycemia (as a proof of concept of this model of care), but this was resource intensive. However, we have since developed a risk stratification tool to identify individuals at high risk for adverse glycemia to enable a more sustainable model of care and plan to evaluate the cost-effectiveness of targeted proactive intervention models.

In conclusion, RAPIDS demonstrated early electronic identification of inpatients with diabetes, and treatment by a specialist IDT decreased hyperglycemia without increasing hypoglycemia. In addition, early management of diabetes was associated with decreased hospital-acquired infection, but this important observation requires further confirmatory studies. This study provides evidence that early intervention models of diabetes care in the hospital improve glycemia and patient outcomes. With the increasing prevalence of diabetes and complexity of hospital care, hospital clinicians should concentrate on early identification and management to improve the care of people with diabetes.

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References

1. Umpierrez GE, Isaacs SD, Bazargan N, You X, Thaler LM, Kitabchi AE. Hyperglycemia: an independent marker of in-hospital mortality in patients with undiagnosed diabetes. J Clin Endocrinol Metab 2002;87:978–982

2. Turchin A, Matheny ME, Shubina M, Scanlon JV, Greenwood B, Pendergrass ML. Hypoglycemia and clinical outcomes in patients with diabetes hospitalized in the general ward. Diabetes Care 2009;32:1153–1157

3. Frisch A, Chandra P, Smiley D, et al. Prevalence and clinical outcome of hyperglycemia in the perioperative period in noncardiac surgery. Diabetes Care 2010;33:1783–1788
4. Clement S, Braithwaite SS, Magee MF, et al.; American Diabetes Association Diabetes in Hospitals Writing Committee. Management of diabetes and hyperglycemia in hospitals [published correction appears in Diabetes Care 2004;27:856; 1255]. Diabetes Care 2004;27:553–591
5. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1359–1367
6. Middleton S, McElduff P, Ward J, et al.; QASC Trialists Group. Implementation of evidence-based treatment protocols to manage fever, hyperglycaemia, and swallowing dysfunction in acute stroke (QASC): a cluster randomised controlled trial. Lancet 2011;378:1699–1706
7. Umpierrez GE, Smiley D, Jacobs S, et al. Randomized study of basal-bolus insulin therapy in the inpatient management of patients with type 2 diabetes undergoing general surgery (RABBIT 2 surgery). Diabetes Care 2011;34:256–261
8. Finfer S, Chittock DR, Su SY, et al.; NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360:1283–1297
9. Baldwin D, Villanueva G, McNutt R, Bhatnagar S. Eliminating inpatient sliding-scale insulin: a reeducation project with medical house staff. Diabetes Care 2005;28:1008–1011
10. Kyi M, Wraight PR, Rowan LM, Marley KA, Colman PG, Fourlanos S. Glucose alert system improves health professional responses to adverse glycaemia and reduces the number of hyperglycaemic episodes in non-critical care inpatients. Diabet Med 2018;35:816–823
11. Umpierrez GE, Hellman R, Korytkowski MT, et al.; Endocrine Society. Management of hyperglycemia in hospitalized patients in non-critical care setting: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2012;97:16–38
12. Dhatariya K, Levy N, Kilvert A, et al.; Joint British Diabetes Societies. NHS Diabetes guideline for the perioperative management of the adult patient with diabetes. Diabet Med 2012;29:420–433
13. Australian Diabetes Society. Australian Diabetes Society guidelines for routine glucose control in hospitals [Internet], 2012. Available from https://diabetessociety.com.au/documents/adsguidelinesforroutineglucosecontrolinhospitalfinal2012_000.pdf. Accessed 1 December 2017
14. Draznin B, Gilden J, Golden SH, et al.; PRIDE Investigators. Pathways to quality inpatient management of hyperglycemia and diabetes: a call to action. Diabetes Care 2013;36:1807–1814
15. Rajendran R, Round RM, Kerry C, Barker S, Rayman G. Diabetes patient at risk score—a novel system for triaging appropriate referrals of inpatients with diabetes to the diabetes team. Clin Med (Lond) 2015;15:229–233
16. Rajendran R, Kerry C, Round RM, Barker S, Scott A, Rayman G; DICE Team. Impact of the Diabetes Inpatient Care and Education (DICE) project and the DICE Care Pathway on patient outcomes and trainee doctor's knowledge and confidence. Diabet Med 2015;32:920–924
17. Sampson MJ, Crowle T, Dhatariya K, et al. Trends in bed occupancy for inpatients with diabetes before and after the introduction of a diabetes inpatient specialist nurse service. Diabet Med 2006;23:1008–1015
18. Pietras SM, Hanrahan P, Arnold LM, Sternthal E, McDonnell ME. State-of-the-art inpatient diabetes care: the evolution of an academic hospital. Endocr Pract 2010;16:512–521
19. Cook CB, Castro JC, Schmidt RE, et al. Diabetes care in hospitalized noncritically ill patients: more evidence for clinical inertia and negative therapeutic momentum. J Hosp Med 2007;2:203–211
20. Newton CA, Young S. Financial implications of glycemic control: results of an inpatient diabetes management program. Endocr Pract 2006;12(Suppl. 3):43–48
21. Rushakoff RJ, Sullivan MM, MacMaster HW, et al. Association between a virtual glucose management service and glycemic control in hospitalized adult patients: an observational study. Ann Intern Med 2017;166:621–627
22. Seheult JN, Pazderska A, Gaffney P, et al. Addressing inpatient glycaemic control with an inpatient glucometry alert system. Int J Endocrinol 2015;2015:807310
23. Swee DS, Ang LC, Heng WM, et al. Inpatient glucose management programme in the Asian healthcare setting. Int J Clin Pract 2017;71:e12985
24. Umpierrez GE, Reyes D, Smiley D, et al. Hospital discharge algorithm based on admission HbA_{1c} for the management of patients with type 2 diabetes. Diabetes Care 2014;37:2934–2939
25. Weinberg ME, Bacchetti P, Rushakoff RJ. Frequently repeated glucose measurements overestimate the incidence of inpatient hypoglycemia and severe hyperglycemia. J Diabetes Sci Technol 2010;4:577–582
26. Wagstaff AE, Cheung NW. Diabetes and hyperglycemia in the critical care setting: has the evidence for glycemic control vanished? (Or . . . is going away?). Curr Diab Rep 2014;14:444
27. Umpierrez GE, Smiley D, Hermayer K, et al. Randomized study comparing a basal-bolus with a basal plus correction insulin regimen for the hospital management of medical and surgical patients with type 2 diabetes: basal plus trial. Diabetes Care 2013;36:2169–2174
28. NHS Digital. National Diabetes Inpatient Audit (NaDIA) [Internet], 2016. Available from http://www.digital.nhs.uk/pubs/nadia2016. Accessed 1 December 2017
29. Bersoux S, Cook CB, Kongable GL, Shu J, Zito DR. Benchmarking glycemic control in U.S. hospitals. Endocr Pract 2014;20:876–883
30. Critchley JA, Carey IM, Harris T, DeWilde S, Hosking FJ, Cook DG. Glycemic control and risk of infections among people with type 1 or type 2 diabetes in a large primary care cohort study. Diabetes Care 2018;41:2127–2135
31. Martin ET, Kaye KS, Knott C, et al. Diabetes and risk of surgical site infection: a systematic review and meta-analysis. Infect Control Hosp Epidemiol 2016;37:88–99
32. Kotagal M, Symons RG, Hirsch IB, et al.; SCOAP-CERTAIN Collaborative. Perioperative hyperglycemia and risk of adverse events among patients with and without diabetes. Ann Surg 2015;261:97–103
33. Furnary AP, Zerr KJ, Grunkemeier GL, Starr A. Continuous intravenous insulin infusion reduces the incidence of deep sternal wound infection in diabetic patients after cardiac surgical procedures. Ann Thorac Surg 1999;67:352–360; discussion 360–362
34. Ehrenfeld JM, Wanderer JP, Terekhov M, Rothman BS, Sandberg WS. A perioperative systems design to improve intraoperative glucose monitoring is associated with a reduction in surgical site infections in a diabetic patient population. Anesthesiology 2017;126:431–440
35. Kansagara D, Fu R, Freeman M, Wolf F, Helfand M. Intensive insulin therapy in hospitalized patients: a systematic review. Ann Intern Med 2011;154:268–282
36. Wang YJ, Seggelke S, Hawkins RM, et al. Impact of glucose management team on outcomes of hospitalizaron in patients with type 2 diabetes admitted to the medical service. Endocr Pract 2016;22:1401–1405
37. Murad MH, Coburn JA, Coto-Yglesias F, et al. Glycemic control in non-critically ill hospitalized patients: a systematic review and meta-analysis. J Clin Endocrinol Metab 2012;97:49–58
38. Davies M, Dixon S, Currie CJ, Davis RE, Peters JR. Evaluation of a hospital diabetes specialist nursing service: a randomized controlled trial. Diabet Med 2001;18:301–307
39. Flanagan D, Moore E, Baker S, Wright D, Lynch P. Diabetes care in hospital–the impact of a dedicated inpatient care team. Diabet Med 2008;25:147–151
40. Bally L, Thabit H, Hartnell S, et al. Closed-loop insulin delivery for glycemic control in noncritical care. N Engl J Med 2018;379:547–556