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ORIGINAL ARTICLE

Nasogastric Aspiration as an Indicator for Feed Absorption in Model-Based Glycemic Control in Neonatal Intensive Care

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Abstract

Background:

STAR (stochastic targeted) is a glycemic control model-based framework for critically ill neonates that has shown benefits in reducing hypoglycemia and hyperglycemia. STAR uses a stochastic matrix method to forecast future changes in a patient's insulin sensitivity and then applies this result to a physiological model to select an optimal insulin treatment. Nasogastric aspiration may be used as an indicator to suggest periods of care when enteral feed absorption is compromised, improving the performance of glycemic control. An analysis has been carried out to investigate the effect of poorly absorbed feeds on glycemic control.

Method:

Clinical data were collected from eight patients on insulin therapy and enteral feed, which included large or significantly milky aspirates. Patients had a median gestational age of 25 weeks and postnatal age of 5.5 days. Virtual patients were created using the NICING model, and insulin sensitivity (S_I) profiles were fit. Alternative feed profiles were generated whereby enteral feed absorption was redistributed with time to account for poor feed absorption. The effect of poor feed absorption, as indicated by aspirates, is investigated.

Results:

The average percentage change of S_I 4 h before a significant aspirate was 1.16%, and 1.49% in the 4 h following the aspirate. No distinct relationship was found between the fractional change in S_I and the volume of the aspirate. Accounting for aspirates had a clinically negligible impact on glycemic control in virtual trials.

Conclusion:

Accounting for aspirates by manipulating enteral feed profiles had a minimal influence on both modeling and controlling glycemia in neonates. The impact of this method is clinically insignificant, suggesting that a population constant for the rate of glucose absorption in the gut adequately models feed absorption within the STAR framework.

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Abbreviations: (BG) blood glucose, (NICU) neonatal intensive care unit

Keywords: computer methods, glycemic control, nasogastric aspiration, neonate, physiological modeling

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Introduction

Stress-induced hyperglycemia is a common complication for preterm infants in the neonatal intensive care unit (NICU) due to underdeveloped glycemic regulation mechanisms in the neonatal body and hormone-based stress response.[1] Prevalence of hyperglycemia is linked to increased mortality,[2] risk of complications such as intraventricular hemorrhage,[3] ventilator dependence,[4] and length of stay.[3,4] There is neither a widely accepted method or approach for glycemic control in this cohort nor specified best blood glucose (BG) targets.[5]

Glycemic control protocols often use fixed methods that do not account for interpatient and intrapatient variability[6] or are *ad hoc* and rely extensively on clinical experience.[7] Some protocols rely on varied nutritional inputs that may adversely affect growth.[8] Using insulin to treat hyperglycemia has been linked to positive outcomes[8–12] but has proven difficult and risky.[9]

Model-based glycemic control has shown positive outcomes in both the NICU and the adult intensive care unit.[13,14] These methods capture interpatient variability and evolving patient condition to best describe a patient's sensitivity to insulin[14,15] in contrast to fixed protocols that typically assume a constant insulin sensitivity across all patients and weight-based methods, both of which neglect changes in a patient's metabolic condition. Both of these frameworks are inaccurate, resulting in poor control and hypoglycemia.[7,15]

The STAR (stochastic targeted) framework uses model-based control methods to identify patient-specific insulin sensitivity and forecast how this will change between clinical interventions using a stochastic model.[13,15] Using this forecasted insulin sensitivity and the clinically validated NICING model,[15] an optimal treatment is selected that overlaps a forecast BG range with a clinically defined target band. It thus ensures a specific risk of hypoglycemic or hyperglycemic outcomes for each intervention.

Knowledge of nutritional inputs is critical for accurate metabolic modeling and control. As it is impractical to measure feed absorption directly, models typically make the assumption that given feed is absorbed by some regular transfer mechanism. However, actual feed absorption is uncertain and may vary over time and between patients. This adds uncertainty to the forecast changes in patient glycemia and condition, potentially leading to poorer control. This research investigates the use of nasogastric aspirates to indicate poor feed absorption and its potential to improve glycemic control.

Methods

Aspirates

Nasogastric aspiration is the process of feeding a nasogastric tube into the stomach of a patient and draining the stomach contents by suction. This action is normally performed for neonates as they are introduced to enteral feed, typically expressed breast milk, to ensure digestion is functioning correctly and to remove bile or gastric secretions. Occasionally, the contents of these aspirates are large in volume and milky in texture, indicating that a significant fraction of given feed remains in the stomach and thus has not been absorbed. Such variations may significantly alter modeled response.

NICING Model

The clinically validated NICING model,[15] with the variables and parameters given in **Table 1**, is defined as follows:

$$\dot{G} = -p_G G(t) - S_I G(t) \frac{Q(t)}{1 + \alpha_G Q(t)} + \frac{P(t) + EGP * m_{body} - CNS * m_{brain}}{V_{g,frac}(t) * m_{body}} \quad (1)$$

$$\dot{I} = -\frac{n_L I(t)}{1 + \alpha_I I(t)} - n_K I(t) - n_I (I(t) - Q(t)) + \frac{u_{ex}(t)}{V_{I,frac} * m_{body}} + (1 - x_L)\, u_{en} \quad (2)$$

$$\dot{Q} = n_I(I(t) - Q(t)) - n_c \frac{Q(t)}{1 + \alpha_G Q(t)} \quad (3)$$

$$\dot{P}_1 = -d_1 P_1 + P(t) \quad (4)$$

$$\dot{P}_2 = -\min(d_2 P_2, P_{\max}) + d_1 P_1 \quad (5)$$

$$P(t) = \min(d_2 P_2, P_{\max}) + PN(t) \quad (6)$$

$$u_{\text{en}} = \mathrm{I_B} e^{\frac{-k_I u_{ex}}{V_I m_{body}}} \quad (7)$$

Table 1.
Variables and Parameters in the NICING Model

Variable	Description	Values
G	BG level	mg/dl
I	Plasma insulin concentration	mU/liter
Q	Interstitial insulin concentration	mU/liter
p_G	Endogenous glucose clearance	0.0030 min^{-1}
α_G	Saturation parameter for insulin mediated glucose removal	0 liter/mU
α_I	Saturation parameter for plasma insulin clearance	0.0017 liter/mU
S_I	Insulin sensitivity	liter/mU/min
EGP	Endogenous glucose production	5.112 mg/min
CNS	Central nervous system glucose uptake	15.84 mg/min
$P(t)$	Glucose appearance in plasma from dextrose intake	mg/min
PN	Parenteral nutrition	mg/min
P_{max}	Maximal glucose flux from gut to plasma	1100 mg/min
$P1$	Glucose level in stomach	mg
$P2$	Glucose level in gut	mg
V_G	Plasma glucose distribution volume	0.5961 liter
k_I	Interstitial insulin transport rate	0.1 min^{-1}
I_B	Endogenous insulin production	15 mU/liter/min
n_I	Rate of transport between plasma and interstitial insulin compartments	0.003 min^{-1}
n_K	Renal insulin clearance	0.150 min^{-1}
n_L	Hepatic insulin clearance	1 min^{-1}
n_C	Interstitial insulin degradation	0.003 min^{-1}
x_L	First-pass hepatic insulin clearance	0.67
$u_{ex}(t)$	Exogenous insulin	mU/min
$u_{en}(t)$	Endogenous insulin production	mU/liter/min
V_I	Plasma insulin distribution volume	0.0450 liter/kg
d_1	Glucose absorption rate from stomach	0.0347 min^{-1}
d_2	Glucose absorption rate from gut	0.0069 min^{-1}
$D(t)$	Dextrose intake	mg/min
m_{body}	Body mass	kg
m_{brain}	Brain mass (14% m_{body})	kg

Clinical Data

Nasogastric aspirate data were collected from patients who underwent insulin therapy at Christchurch Women's Hospital NICU between 2008 and 2012. Insulin was administered as an infusion under the STAR protocol, as the standard of care. Starting criteria for STAR are two consecutive BG measurements in excess of 180 mg/dl, and stopping criteria are eight successive hours without requiring insulin.

Aspirate data were analyzed retrospectively. Aspirates of interest met the following criteria:

- The patient was receiving insulin,
- The patient was currently on an enteral feed of 1 ml/h or more, and
- One of either
  - The size of the aspirate taken was at least half the volume of the feed given in the last 4 h or
  - The aspirate exceeded 2 ml in volume.

Data collected included time, aspirate volume, a qualitative description of the consistency (milky, bile), and whether the contents were returned to the stomach. The enteral feeds given for the last 4 h were already recorded by STAR.

Aspirate consistency recorded by clinicians was a qualitative measure, primarily used to indicate unusual aspirates. As such, this measure was likely subjective and not particularly useful for analysis. Instead, aspirate consistency is discriminated in analysis between aspirates that were returned and those that were not returned.

From a cohort of 35 patients, 8 had aspirates that fit these criteria, with a total of 108 aspirates of interest over 959 h of data. The median gestational age of the included group was 25 weeks, and median postnatal age was 5.5 days. All patients were younger than 28 weeks. These 8 patients are summarized in **Table 2**.

Table 2.
Patient Summary Statistics

Patient ID	Gender	Birth weight (kg)	Gestational age (weeks)	Postnatal age (days) at the start of STAR	Insulin therapy period (h)	Number of BG measurements	Average expressed breast milk per day (ml/day)	Number of aspirates	Median aspirate volume (IQR [ml])	Median aspirate volume per last 4 h feed (IQR [ml/ml])	Number of aspirates without feed in past 4 h
1	Female	0.46	25	7	92	30	11.0	3	1.0 (1.0–1.1)	0.6 (0.5–1.6)	0
2	Female	0.87	27	6	34	14	1.5	8	1.0 (1.0–1.6)	1.0 (0.6–2.7)	1
3	Female	0.53	25	22	141	41	34.2	17	1.8 (1.0–2.1)	0.2 (0.2–0.4)	0
4	Female	0.64	25	5	142	48	42.1	5	2.0 (2.0–2.8)	0.3 (0.2–0.6)	3
5	Female	0.69	25	8	67	19	4.7	39	2.0 (1.2–2.8)	0.3 (0.1–0.6)	0
6	Male	0.61	25	<1	278	101	21.8	4	0.8 (0.5–1.0)	0.4 (0.2–0.8)	1
7	Male	0.88	26	<1	109	31	4.9	22	2.0 (1.5–2.9)	0.6 (0.4–1.2)	1
8	Female	0.77	26	5	143	38	30.0	10	1.0 (1.0–2.8)	0.8 (0.5–1.6)	0

IQR, interquartile range.

No patients in the cohort were on trophic feeds. However, enteral feed volumes were not necessarily great enough to be considered full nutrition. The volumes of medications were small compared with enteral feed rates and so have been neglected. A summary of the cohort's additional medicinal requirements is given in **Table 3**.

Modeling Poor Feed Absorption

Aspirates are accounted for using a simple feed redistribution model. When significant aspirates are taken, they are removed from the patient's enteral feed profile over recent hours; if they are returned, they are added to the feed profile at the time that they are returned. A simple diagram of this process is shown in **Figure 1**.

Aspirates that have been recorded are assumed to be equivalent in volume to enteral feed that has failed to absorb. The balance of the aspirate is taken from enteral boluses from the patient's feed profile, starting from the most recent feed. Thus a 2.5 ml aspirate given a feed rate of 1 ml every hour for the prior 4 h is removed as 1 ml from each of the immediately prior 2 h and 0.5 ml from the third prior hour. This process was performed for both milky and bile-like aspirates.

When an aspirate is returned, it is assumed to be equivalent to giving the patient an enteral feed bolus of that volume. The concentration of the returned aspirate is modeled as equal to the concentration of the most recent enteral feed.

Table 3.
Summary of Additional Medication Given to the Cohort

Clinical characteristics	n = 8
Ventilated	7
Antibiotics	7
Indomethacin (for patent ductus arteriosus)	4
Inotropes	2
Morphine	6
Dexamethasone	2
Hydrocortisone	1

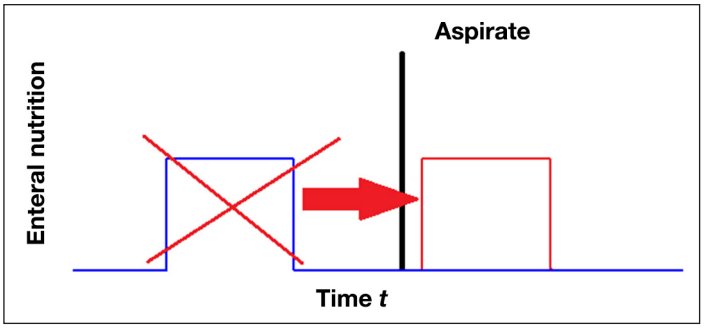

Figure 1. A simple depiction of the feed redistribution model used to account for aspirates.

Virtual patients[15,16] were created using the NICING model of **Equations (1)–(7)** and clinical data. A virtual patient is defined by a time-varying, patient-specific insulin sensitivity (S_I) found by fitting **Equations (1)–(7)** to clinical data. Two cases are compared: (1) the model fit to clinical data, when aspirates are not accounted for, and (2) the model fit when aspirates are modeled via the modified enteral feed profile described. Thus there are two sets of virtual patients created, where one accounts for changes in enteral absorption and the other does not.

Analysis and Impact on Control

Insulin sensitivity (S_I) describes insulin-mediated removal and changes in patient metabolic state, in particular, capturing changes in endogenous glucose and insulin secretion and peripheral insulin sensitivity. In the case of poorly absorbed feeds, there is reduced appearance of glucose in the blood plasma. If this reduction is not accounted for in the model, it is seen as an increase in insulin sensitivity. It is hypothesized that, by explicitly modeling poor feed absorption, variation in S_I will be reduced, thus improving the tightness of glycemic control.

Changes in S_I between these cases are measured both as absolute values and as fractional changes, with respect to the volume of the aspirate. They are examined for 4 h either side of an aspirate event.

The impact of modeling feed uptake using aspirates on tight glycemic control is evaluated *in silico* using clinically validated virtual trials.[16] The STAR framework[15,17] uses insulin sensitivity and the NICING model to describe the current metabolic state of a neonate. Stochastic forecasting is used to quantify variation in S_I over the coming intervention interval, allowing treatments to be selected that find corresponding BG levels that overlap with a clinical target band.

In virtual trial simulation, four cases were investigated, as shown in **Table 4**, by selecting which S_I profiles are seen in the simulation of the patient response and the control protocol. The S_I profile selected for simulation describes the response of the virtual patient based on clinical data. In contrast, the S_I profile selected for control describes the current patient condition from which stochastic forecasting and treatment selection is based. The four cases compare the

impact of assuming aspirates are (or are not) important in control for cases where aspirates and changes in enteral feed profile have (aspirates virtual cohort) or have not (original cohort) a physiological impact. Three-hour windows are used in this case, as this is the typical length of the insulin intervention interval.

Four performance metrics are used to assess virtual trials. For performance, a maximal fraction of BG measurements within 72–144 mg/dl (time in band) and a minimal fraction of measurements that are in excess of 180 mg/dl (hyperglycemia) is desirable. For safety, minimizing the fraction of BG measurements <54 mg/dl (hypoglycemia) and the number below 47 mg/dl (severe hypoglycemia) is desired. Finally, interventions are compared between the four cases to indicate how accounting for aspirates modified insulin treatment interventions.

Table 4.
S_I Profiles Used in Virtual Trials

		S_I profile in simulation	
		Original virtual cohort	Aspirates virtual cohort
S_I profile in control	Original control	Simulation—original Control—original **Assume** aspirates are not important and control without them.	Simulation—aspirates Control—original **Assume** aspirates are important but control without them.
	Aspirates control	Simulation—original Control—aspirates **Assume** aspirates are not important but control with them.	Simulation—aspirates Control—aspirates **Assume** aspirates are important and control with them.

Results

Figure 2 shows that S_I is lower in the hours before an aspirate is taken when it has been accounted for, as expected. Similarly, S_I is greater following an aspirate when the contents have been returned to the stomach, because insulin-mediated glucose removal appears higher.

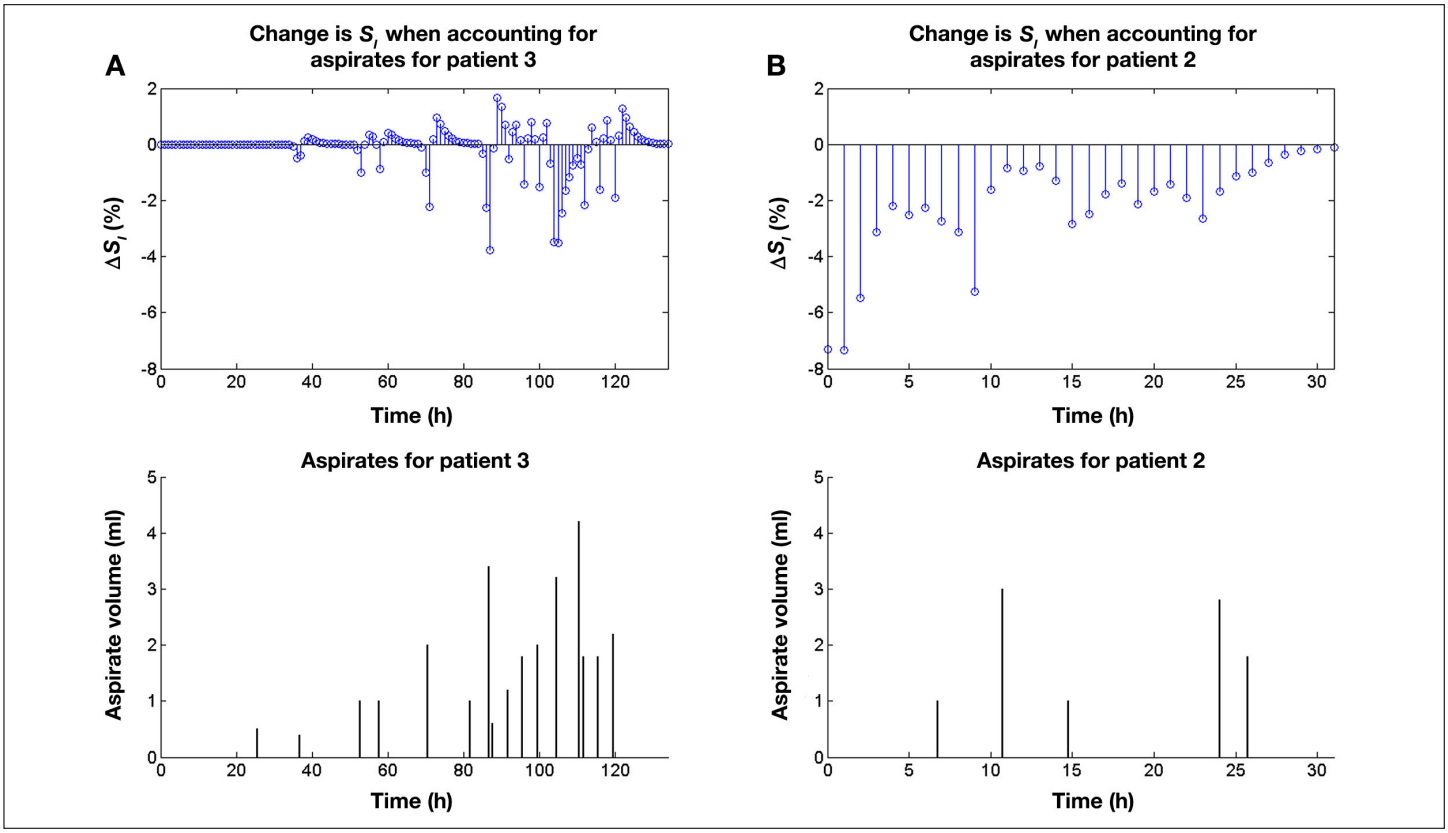

Figure 2. Change in S_I when accounting for aspirates. Patient 3 **(A)** is a typical patient, while patient 2 **(B)** had persistent bile-like aspirates that were not returned.

Aspirate events appear to generate first-order impulse responses in the change ΔS_I, where the magnitude of the change in S_I decays for times farther away from the event. Although the enteral feed profile has been manipulated for a maximum of 4 h before the event, changes to S_I appear to last longer. Where aspirates are not returned, as shown for patient 2 in **Figure 2**, changes to S_I are always negative. These results match hypothesized expectations.

The absolute difference in S_I between both methods is analyzed over the 4 h either side of each aspirate. Changes are also given where they are weighted by the volume of the aspirate. The median magnitude of the change in S_I is shown in **Table 5** as an absolute value, weighted by aspirate size, and as a percentage.

Table 5.
Median and Interquartile Range Change in S_I over a 4 h Period When Accounting for Aspirates

Period	Absolute ΔS_I (ml/mU/min)	Weighted absolute ΔS_I (ml/mU/min/ml_{asp})	Fractional ΔS_I (%)	Weighted fractional ΔS_I (%/ml_{asp})
4 h before aspirate	0.026 (0.007–0.067)	0.016 (0.004–0.031)	1.16 (0.31–2.68)	0.73 (0.16–1.36)
4 h after aspirate	0.036(0.010–0.077)	0.020 (0.008–0.038)	1.49 (0.45–3.03)	0.86 (0.33–1.67)

The fractional change in S_I as a function of the aspirate volume is shown in **Figure 3** for all events 4 h before and after the time of the aspirate. There is no distinct relationship between the fractional change in S_I and the aspirate volume.

The effect of aspirates on glycemic control is shown in **Table 6**. Changes in the percentage of time in band across the eight patients are minimal. Contrasting patients where aspirates were or were not included in simulation shows a difference of less than 0.3% of BG measurements in the target band 72–144 mg/dl.

The change in insulin interventions in **Table 6** between accounting and not accounting for aspirates is also small. For the virtual cohort with an original feed profile, accounting for aspirates reduces insulin inputs in the 3 h following an aspirate by a median and interquartile range of 0.0044 (0.0017–0.0064) U/kg/h. By contrast, the

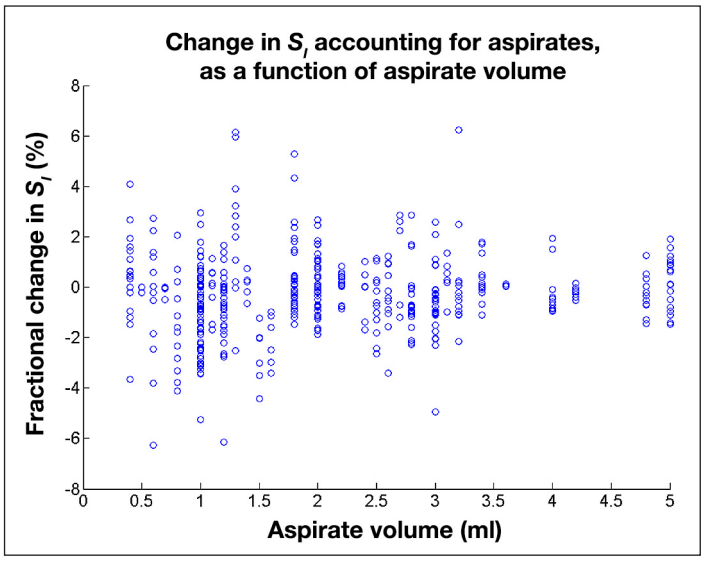

Figure 3. Changes in S_I for all patients 4 h before and 4 h after a marked aspirate event, weighted by aspirate volume.

Table 6.
Virtual Trial Results for All Eight Patients When Accounting for Aspirates

Cohort statistics	Simulation: original Control: original	Simulation: original Control: aspirates	Simulation: aspirates Control: original	Simulation: aspirates Control: aspirates
Median insulin rate (U/kg/h) [interquartile range]	0.036 (0.031–0.053)	0.037 (0.032–0.057)	0.036 (0.031–0.054)	0.038 (0.032–0.058)
Time in band: % of BG in band (72–144 mg/dl)	84.80	84.12	84.90	83.87
Hyperglycemia: % of BG >180 mg/dl	3.00	3.21	3.10	3.31
Hypoglycemia: % of BG <54 mg/dl	0.10	0.31	0	0.31
Severe hypoglycemia: % of BG <47 mg/dl	0	0	0	0

median change in insulin between interventions is 0.0202 U/kg/h. Changes in insulin rates due to aspirates are only approximately 20% of a typical change and less than twice the minimum pump rate step size available. Hence, changes in control inputs due to aspirates are minimal when compared with the effect of other aspects of patient physiology. These results indicate that poor feed absorption is not a dominant parameter in evaluating patient condition for control, even for patients who are primarily enterally fed.

Control results for two patients with no returned feeds are shown separately in **Table 7**. These patients are independent of the assumption that returned aspirates can be modeled as an enteral bolus at the time that it is returned. These patients make up 300 h of data, 102 BG measurements, and 12 of the total 108 aspirates. As with the results shown in **Table 6**, results for these patients are very similar between tested protocols, indicating that modeling returned feeds as an enteral bolus also does not significantly alter results.

Table 7.
Control Results for Patients with No Returned Feeds

Cohort statistics	Simulation: original Control: original	Simulation: original Control: aspirates	Simulation: aspirates Control: original	Simulation: aspirates Control: aspirates
Median insulin rate (U/kg/h) [interquartile range]	0.053 (0.045–0.062)	0.057 (0.049–0.065)	0.054 (0.046–0.062)	0.058 (0.050–0.066)
% of BG in band (72–144 mg/dl)	80.80	79.80	80.13	78.48
% of BG >180 mg/dl	1.66	1.66	1.99	1.99
% of BG <54 mg/dl	0	0.33	0	0.33
% of BG <47mg/dl	0	0	0	0

Discussion

Simulating virtual trials with aspirates had a negligible impact on control performance, as did attempting to control for them. The lack of a distinct relationship between aspirate volume and changes in S_I suggests that other aspects of patient condition or control have a more significant effect on fitting S_I than enteral feed. The change in control inputs due to aspirates was also minimal, less than twice the minimum resolution of the insulin pump used.

Only 8 long-term patients from a cohort of 35 (22%) from Le Compte and coauthors[14] had significant aspirates. Of these patients, 3 had less than one notable aspirate per day on average, and only 3 patients had more than three mean aspirates per day.

Accounting for aspirates had a small overall effect on the glycemic modeling and control process. This is reflected in changes to identified S_I, insulin recommendations by STAR, and control outcomes in virtual trials. Changes in S_I due to accounting for aspirates were less than 2% in magnitude. This suggests that the NICING model is generally robust against the uncertainty introduced by neglecting to account for significant aspirates.

In virtual trials, insulin doses recommended by STAR do not notably deviate when aspirates are accounted for. Hence, if aspirate details were recorded into STAR and factored into the selection of a treatment in a clinical setting, the insulin recommendation would not be notably different. This fact challenges whether the inclusion of such an element would be relevant. The increased nurse workload from entering this additional information would increase clinical burden and potential for error.[18,19] Furthermore, if nurses are aware of the minimal impact of recording aspirates, they may knowingly omit this data to reduce workload, reducing protocol compliance.

Finally, control outcomes in virtual trials show a negligible change in the number of BG measurements inside identified target bands. It is undesirable to include additional complexity to the model without a noted improvement in the quality of control given.

Because of the negligible changes in parameter fitting, protocol output, and control demonstrated for this group of 35 patients and the relatively small cohort that is affected, aspirates do not appear to be a significant problem in neonatal glycemic control.

The approach taken to analyze returned feeds was, by design, simple, to give a baseline indication of the impact of unaccounted-for aspirates on glycemic control. Treating returned aspirates as a bolus feed of volume equal to that of the aspirate may not be strictly accurate, which is suggested in the result that controlling using aspirates worsens control. If the returned aspirate is added as an enteral feed, the modeled transport of glucose to the gut remains at a constant rate d_1 in **Equation** (**4**), and therefore glucose appearance in the gut is increased. In reality, transport rate d_1 is potentially much lower, so glucose appearance is lower.

Results for the two patients who did not have any aspirates returned, and therefore do not rely on a feed absorption model, do not provide a different result. In these patients, negligible changes in insulin recommendation were apparent that were similar to the remainder of the cohort. This result suggests that the simplicity of the feed absorption model does not adversely affect the outcomes of the study. Hence, the approach taken was sufficient to evaluate the magnitude of the impact of aspirates on glycemic control.

The rate at which aspirate volume decayed was observed in care sheets to vary between and within patients. No trends for the duration of time that gut absorption was compromised were seen, reflecting varying feed absorption dynamics. Quantifying and predicting the duration of poor absorption periods may present opportunity for future research.

Conclusion

The presented method provides an approximation for the order of magnitude of how insulin sensitivity S_I in the NICING model, and glycemic control under the STAR protocol, are affected by variable feed absorption, as reflected by nasogastric aspiration. Absolute fractional changes in S_I are $(1.0 \pm 1.4)\%/\mathrm{ml}_{\mathrm{asp}}$ in the 4 h prior to a marked aspirate and $(1.1 \pm 1.7)\%/\mathrm{ml}_{\mathrm{asp}}$ in the 4 h afterward and are not clinically significant. Validated virtual patients confirmed this result, as there was no clinically significant effect on glycemic control in virtual trials. These results indicate that using nasogastric aspirates as a marker for poor feed absorption has a minimal effect on glycemic control outcomes, and high variability in feed absorption is adequately modeled by a population absorption constant for the transport of glucose from the stomach to the gut, relative to other sources of measurement and modeling error. Furthermore, the introduction of such an element would increase nurse workload without clinical benefit. Hence, enteral feed absorption changes reflected by nasogastric aspiration do not need to be accounted for in the STAR framework. This result informs clinicians that neglecting nasogastric aspirates does not adversely affect the quality of glycemic control during insulin therapy.

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