Virtual testing of decision support for tight glycemic control in the ICU

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Abstract: The Glucosafe decision support system for glycemic control in intensive care has previously been tested clinically. Evaluating modifications to advice generation requires clinical trials. This study evaluates the use of virtual patients, derived from real patients, and which modifications to Glucosafe advice generation are necessary to lower blood glucose under 6.1 mmol/L. Based on data from 5 real patients, 5 virtual patients were constructed and the groups were compared. Results show that virtual patients are applicable in evaluating modifications to advice generation, with reasonable deviations and that decreasing nutritional intake is necessary to lower mean blood glucose below 6.1 mmol/L.

Keywords: Medical decision support, tight glycemic control, physiological modeling, penalty functions, virtual patients.

1. INTRODUCTION

Hyperglycemia is common in patients hospitalized for critical illness, trauma or in post-surgery, and has been associated with increased morbidity and mortality (Falciglia et al. 2009) (Corathers, Falciglia 2011).

The Glucosafe system was developed to provide decision support for control of stress hyperglycemia in the intensive care unit (ICU). The Glucosafe system consists of two parts. The first part is a mathematical model of glucose metabolism (Pielmeier et al. 2010b), which can be used to predict future blood glucose concentrations. The second part of Glucosafe is an advice generator.

The advice generator provides advice in the form of suggestions for the next doses of insulin and nutrition to be administered to the patient. The advice generator uses the metabolic model to predict future blood glucose, dependent on the advice. The optimal advice is the advice that gives the “most desirable” predicted blood glucose over the next four hours, balanced with insulin and nutritional input. To decide what amount of nutrition and insulin, as well as the predicted four-hour blood glucose profile results in the “most desirable” outcome, the advice generator uses a set of penalty functions (Pielmeier, Boudreau & Andreassen 2010).

The Glucosafe metabolic model can be evaluated by determining its predictive accuracy, i.e. its ability to minimize the distance between predicted and measured blood glucose concentrations. This can be done from retrospectively collected data and the effects of modifications to the model can conveniently be tested by evaluating the modified model on the same retrospective data. Evaluation of the advice generator is more complicated. This is done by conducting a clinical trial, where the Glucosafe system is allowed to recommend insulin and nutrition to a patient cohort and then determining the performance of the system on this cohort in terms of the clinical goals for blood glucose, nutrition and insulin.

For example, the Glucosafe system has twice previously been tested clinically for its ability to lower blood glucose without inducing hypoglycemic incidents. Glucosafe achieved a mean blood glucose of 7.0 mmol/L (± 1.1 mmol/L), significantly lower than in the 24 hour pre- and post-intervention periods (Pielmeier et al. 2010a), and a mean blood glucose of 7.0 mmol/L (± 1.19 mmol/L), significantly lower than the control group (Pielmeier et al. 2012). Neither trial successfully achieved a mean blood glucose in the 4.4 to 6.1 mmol/L band aimed for and the authors suggested the penalty functions for advice generation be adjusted to achieve more aggressive insulin recommendations (Pielmeier et al. 2010a).

This does not provide a constructive answer to how the penalty functions should be modified to achieve the desired outcome and while intensive insulin therapy has been tested as a means to achieve glycemic control, evidence supports that managing blood glucose by permissive underfeeding (Arabi et al. 2011) may be an alternative.

In this study we will investigate if virtual patients, derived from real patient data, can be used to test modifications to the Glucosafe advice generator. This will be done by constructing virtual patients using data from real patients and comparing the results of the real patients and the virtual patients. We will also show the use of virtual patients in evaluating the effect of modifying different parameters in the Glucosafe penalty functions used for advice generation.

2. METHODS

2.1 The Glucosafe model

A simplified diagram of the Glucosafe model is shown in Fig. 1. Glucosafe models plasma insulin and peripheral insulin concentrations from the endogenous production and exogenous infusions of insulin and the removal of insulin by
Fig. 1. A simplified diagram of the Glucosafe model for blood glucose prediction
the kidneys and by insulin degradation in the liver and peripheral tissue. The insulin sensitivity scales the effect of insulin on hepatic removal and peripheral absorption of glucose. Blood glucose is modelled from insulin-dependent and insulin-independent removal and glucose from nutrition and intravenous infusions (Pielmeier et al. 2010b).

2.2 Penalty Functions

For advice generation, Glucosafe uses four penalty functions. Penalties are based on total amount of nutrition, amount of enteral nutrition, insulin dosage, and the resulting predicted blood glucose. A grid search minimizes the sum of these penalties to present the optimal advice on nutrition and insulin use. The following provides a short description of the penalty functions. The rationale for the shapes of the functions has previously been described (Pielmeier, Boudreau & Andreassen 2010). Penalty functions are constructed to be identical to the penalty functions used during the data collection (Pielmeier et al. 2010a).

Glycemic Penalty – The penalty is for the predicted blood glucose, resulting from the recommended insulin and nutrition use. The penalty (Fig. 4A) is defined as:

\[ f_G(G) = \left( \ln \left( \frac{G}{G_0} \right) \right)^2 \times P_G \]  

where \( G \) is the predicted blood glucose, \( G_0 = 5.5 \text{ mmol/L} \) is the specific blood glucose concentration where the penalty is zero, and \( P_G = 22.56 \) is a dimensionless scaling factor. The blood glucose penalty is used to limit the magnitude of penalties calculated from the predicted blood glucose concentrations at 1, 2, 3, and 4 hour predictions.

Insulin Dose Penalty – To decrease the use of excessive insulin doses the use is penalized with the following function (Fig 4B):

\[ f_I(P) = \left( \frac{(P \times C + K_m)^2}{K_m^2} - 1 \right) \times P_I \]  

where \( P \) is the insulin infusion rate (mU/(kg×min)), \( C = 98.1 \text{ kg/min×xL} \) is a factor for converting insulin infusion to plasma concentrations, \( K_m = 28 \text{ mU/L} \) is a Michaelis-Menten saturation constant, and \( P_I = 1/109.2 \) is a dimensionless scaling factor.

Mucosal Damage Penalty – To maintain a healthy intestinal mucosa, the amount of nutrition administered enterally is maximized using the following function (Fig. 4C):

\[ f_D = (N_{enteral} - 1)^2 \times P_D \]  

where \( N_{enteral} \) is the percentage of the goal feed that is administered enterally and \( P_D = 1 \) is a dimensionless scaling factor. Goal feed is a term indicating a patient specific caloric intake needed to cover 100% of the patient’s estimated Resting Energy Expenditure (REE). In Glucosafe the REE is calculated using the Mifflin St. Jeor equations.

Nourishment Penalty – To administer an amount of nutrition that covers the patient’s REE, the following function (Fig. 4D) is used to penalize under- or over-feeding:

\[ f_N(N_{total}) = (N_{total} - 1)^2 \times P_N \]  

where \( N_{total} \) is the total nutrition administered, as a percentage of goal feed, and \( P_N = 1 \) is a dimensionless scaling factor.

2.3 Insulin Sensitivity

Glucosafe estimates patient-specific insulin sensitivities from data on nutrition, insulin consumption, and blood glucose concentrations. This insulin sensitivity is a dimensionless parameter where values close to one indicate a normal response to insulin and lower values indicate insulin resistance. In the model the estimated insulin sensitivity is assumed to be a time-varying, patient-specific parameter, which is independent of the treatment the patient is receiving. The insulin sensitivity is estimated for every blood glucose measurement. An example of an insulin sensitivity profile is given in Fig. 2.

2.4 Virtual Patients

The virtual patients are based on insulin sensitivity profiles from real patients, using the profile to describe patient behaviour over time.

Fig. 3 shows diagrams of Glucosafe when used in real-time with patients and when using virtual patients. In real-time, an amount of insulin and nutrition is given to the patient with a resulting measured blood glucose (BG) concentration. The measured BG and administered insulin and nutrition amounts are used by the Glucosafe model to estimate an insulin sensitivity at that specific time. To generate an advice for new insulin and nutrition amounts, several temporary combinations of insulin and nutrition are input to the Glucosafe model, which estimates predicted BG concentrations at 1, 2, 3, and 4 hours from the current time.
Using the penalty functions, a penalty score is calculated for every set of temporary nutrition and insulin amounts. D: Penalty for total ingested calories in percentage of goal feed, original and divided by a factor of 2.

Using the penalty functions, a penalty score is calculated for every set of temporary nutrition and insulin amounts, and the resulting predicted BG. The amount of nutrition, insulin, and the predicted BG producing the lowest total penalty is given as an advice.

In the virtual patient the insulin sensitivity profile previously estimated from the real patient is used by the Glucosafe model to simulate blood glucose during subsequent testing. With the insulin sensitivities read from the insulin sensitivity profile, a single original blood glucose measurement is used as a starting point and Glucosafe is asked for an advice on insulin and nutrition. The advice is followed and at the time-point for the next original blood glucose measurement the blood glucose predicted by the model is used instead of the measured blood glucose and together with the insulin sensitivity, a new advice is requested. This continues for the full length of time for which patient data is available.

Using this method it is possible to observe the behaviour of Glucosafe and evaluate the influence of modifications to the advice generation.

The virtual patients are derived from, and compared to, real patient data. The data used were obtained during a clinical study of Glucosafe (Pielmeier et al. 2012).

2.5 Modifications to Evaluate

Several different modifications are made and tested for their influence on glycemic control. The different modifications are tested separately and compared to the initial set of virtual patients.

Glycemic Penalty – The blood glucose concentration where the penalty is zero (\(G_0\)), is lowered from 5.5 mmol/L to 5.0 mmol/L, resulting in a higher penalty for blood glucose concentrations above the target, than before the change (Fig. 4A).

Insulin Dose Penalty – Two different changes are made to the insulin dose penalty function, reducing the penalties for any given insulin infusion by a factor of 2 and 10 (Fig. 4B).

Mucosal Damage Penalty – The function is modified to be raised to the fourth power instead of the second power:

\[
f_d = (N_{enteral} - 1)^4 \times P_d
\]  (5)

This changes the shape and lowers the penalty for use of less enteral feeding (Fig. 4C).

Combined Penalty Modifications – Several modifications are combined to achieve a mean blood glucose in the 4.4 - 6.1 mmol/L band. The modifications are: lowering the blood glucose target (\(G_0\)) to 5.0 mmol/L, halving the insulin penalty scaling factor (\(P_i\)), lowering of the mucosal damage penalty as given in equation (5), and reducing the nourishment penalty compared to the initial set of virtual patients.

\[
\text{Glycemic Penalty} \quad \	ext{Insulin Consumption Penalty} \quad 
\text{Mucosal Damage Penalty} \quad 
\text{Nourishment Penalty}
\]
penalty (Fig. 4D) by reducing the scaling factor \( (P_N) \) by a factor of 2.

### 2.6 Evaluation of Results

To evaluate the use of virtual patients, ten virtual patients are constructed from the original patient data. One set of virtual patients is constructed with a similar model and penalty function setup as used during the original study. These results are compared to the original result from the use of Glucosafe. The changes to the penalty functions are evaluated by comparing the virtual patients before and after the modifications.

The evaluation of the results is done by comparing the individual real and virtual patients and the patient groups. Evaluations are performed using median and mean blood glucose concentrations, the number of blood glucose measurements in the 4.4-6.1 mmol/L band, insulin use in U/h, percentage of goal feed (by calculating the percentage of goal feed covered by administered nutrition), and the variability of blood glucose as calculated in equation (6).

\[
\sum \frac{|X_n - X_{n+1}|}{|t_n - t_{n+1}|} \times N^{-1}
\]

where \( X_n \) and \( X_{n+1} \) are two consecutive blood glucose concentrations, \( t_n \) and \( t_{n+1} \) are the times (in hours) for the respective blood glucose measurements, and \( N \) is the total number of measurements (Ali, Krinsley & Preiser 2009).

### 3. RESULTS

Comparative values of the real and virtual patients are shown in Table 1. Results show that the virtual patients do not replicate the real patient exactly, evident from the lower median BG, higher insulin usage, and generally higher goal feed percentage. The smallest and largest difference between real and virtual patients are shown in Fig. 5, which shows plots of BG for the two virtual patients with the largest and smallest mean difference from the measured BG of the real patients they were based on.

Group results of the virtual patients and results of modifying the different parameters in the penalty functions are shown in Table 2, along with the results from the real patient group. Results show that, as a group, the virtual patients exhibit a higher goal feed percentage and an increased insulin use, compared to the real patients, but an almost identical mean BG and comparable percentage measurements in band.

When comparing the virtual patients to evaluate the modifications to penalty functions, the results show that modifying the glycemic penalty has resulted in lowering mean blood glucose by 0.3 mmol/L and an increase of 10 percentage points of measurements in the 4.4-6.1 mmol/L band. However this has also resulted in a 0.6 U/h increase in insulin usage and less nutrition administered.

Halving the insulin dose penalty resulted in a 1.2 U/h increase insulin use, but also a 1.1 percentage point increase

### Table 1. Comparison of real patients (R), virtual patients before modifications (V), and virtual patients with the combined modifications (Vm).

<table>
<thead>
<tr>
<th>BG^a (mmol/L)</th>
<th># in band^b</th>
<th># above band</th>
<th>Total #^c</th>
<th>Mean insulin dosage (U/h)</th>
<th>Percentage of goal feed</th>
<th>BG variability (Δmmol/L/hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (IQR)</td>
<td></td>
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<tr>
<td>Real patients</td>
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<td></td>
</tr>
<tr>
<td>R1</td>
<td>6.8 (5.9-7.2)</td>
<td>39 %</td>
<td>57 %</td>
<td>23</td>
<td>2.5</td>
<td>56.0 %</td>
</tr>
<tr>
<td>R2</td>
<td>6.7 (6.3-7.7)</td>
<td>18 %</td>
<td>82 %</td>
<td>28</td>
<td>2.0</td>
<td>83.6 %</td>
</tr>
<tr>
<td>R3</td>
<td>6.8 (6.3-7.5)</td>
<td>16 %</td>
<td>84 %</td>
<td>38</td>
<td>7.7</td>
<td>84.1 %</td>
</tr>
<tr>
<td>R4</td>
<td>8.1 (7.5-8.4)</td>
<td>5 %</td>
<td>95 %</td>
<td>20</td>
<td>5.4</td>
<td>56.7 %</td>
</tr>
<tr>
<td>R5</td>
<td>6.2 (5.6-6.8)</td>
<td>47 %</td>
<td>53 %</td>
<td>43</td>
<td>3.8</td>
<td>78.0 %</td>
</tr>
<tr>
<td>Virtual patients</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>V1</td>
<td>6.5 (5.9-7.6)</td>
<td>30 %</td>
<td>70 %</td>
<td>23</td>
<td>4.5</td>
<td>82.8 %</td>
</tr>
<tr>
<td>V2</td>
<td>6.5 (6.0-7.9)</td>
<td>36 %</td>
<td>64 %</td>
<td>28</td>
<td>3.9</td>
<td>87.1 %</td>
</tr>
<tr>
<td>V3</td>
<td>6.5 (6.3-7.0)</td>
<td>16 %</td>
<td>84 %</td>
<td>38</td>
<td>8.6</td>
<td>81.6 %</td>
</tr>
<tr>
<td>V4</td>
<td>8.0 (8.0-8.4)</td>
<td>5 %</td>
<td>95 %</td>
<td>20</td>
<td>6.3</td>
<td>64.2 %</td>
</tr>
<tr>
<td>V5</td>
<td>6.0 (5.2-6.6)</td>
<td>60 %</td>
<td>40 %</td>
<td>43</td>
<td>3.7</td>
<td>78.2 %</td>
</tr>
<tr>
<td>Virtual patients with the combined modifications</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vm1</td>
<td>5.9 (5.3-6.7)</td>
<td>48 %</td>
<td>43 %</td>
<td>23</td>
<td>5.5</td>
<td>63.6 %</td>
</tr>
<tr>
<td>Vm2</td>
<td>5.8 (5.3-7.1)</td>
<td>57 %</td>
<td>43 %</td>
<td>28</td>
<td>4.6</td>
<td>68.6 %</td>
</tr>
<tr>
<td>Vm3</td>
<td>5.7 (5.4-6.1)</td>
<td>74 %</td>
<td>26 %</td>
<td>38</td>
<td>9.8</td>
<td>62.6 %</td>
</tr>
<tr>
<td>Vm4</td>
<td>6.7 (6.6-7.6)</td>
<td>15 %</td>
<td>85 %</td>
<td>20</td>
<td>7.5</td>
<td>39.7 %</td>
</tr>
<tr>
<td>Vm5</td>
<td>5.2 (4.7-6.0)</td>
<td>67 %</td>
<td>23 %</td>
<td>43</td>
<td>4.4</td>
<td>65.7 %</td>
</tr>
</tbody>
</table>

^a Blood glucose concentration.  
^b Percentage of BG measurements between 4.4 – 6.1 mmol/L.  
^c Total number of BG measurements for this patient.
in goal feed, with a 0.1 mmol/L decrease in mean blood glucose.

Reducing the insulin dose penalty by a factor of ten resulted in a 0.1 mmol/L decrease in mean blood glucose, achieved by decreasing the nutrition. It also resulted in a decrease in insulin usage and percentage of goal feed. The virtual patients show a lower mean BG variability, 25.5% higher insulin doses and 10% more nutrition. Several factors explain these differences. The most important being that for the real patients, the insulin and nutrition pumps were occasionally turned off. During these off periods, BG usually rose sharply due to the discontinued insulin infusions, thus contributing substantially to the variability. The five patients were disconnected from the nutrition pumps seven times for a total of 40.7 hours or 16% of the time and from the insulin pumps 8 times for a total of 42.4 hours or 17% of the time.

To compensate for the increase in blood glucose by the increased nutrition, larger insulin doses are needed. As insulin doses increase insulin saturation occurs, in effect decreasing the effectiveness of insulin (Andreassen, Pielmeier & Chase 2008). This may explain the relatively large increase in insulin use.

Another factor which may have minor contributions to the deviations between real and virtual patients is that during the combined modifications to penalty functions, lowering of the mucosal damage penalty as given in eq. (5), and reducing the nourishment penalty by reducing the scaling factor ($P_I$) by a factor of two, resulted in the lowest mean blood glucose of 5.9 mmol/L, the lowest goal feed (60.0%), and the highest number of measurements in band (57%), with a 1.0 U/h increase in insulin usage. The combined modifications resulted in a group mean BG in the 4.4-6.1 mmol/L band, with 4 of the 5 virtual patients having a median BG in the band.

The lowest blood glucose concentration was 4.1 mmol/L, occurring with the combined modifications. As such there were no hypoglycemic incidents, defined in the original trial as a BG concentration below 3.5 mmol/L.

### 4. DISCUSSION

From the comparison of the original patient measurements and the primary virtual patients the results indicate that virtual patients do not replicate the real patients exactly, evident from the increased insulin use and percentage of goal feed. The virtual patients show a lower mean BG variability, 25.5% higher insulin doses and 10% more nutrition. Several factors explain these differences. The most important being that for the real patients, the insulin and nutrition pumps were occasionally turned off. During these off periods, BG usually rose sharply due to the discontinued insulin infusions, thus contributing substantially to the variability. The five patients were disconnected from the nutrition pumps seven times for a total of 40.7 hours or 16% of the time and from the insulin pumps 8 times for a total of 42.4 hours or 17% of the time.

Table 2. Comparison of glycemic, insulin and nutrition results, from original patient data and virtual patient data.

<table>
<thead>
<tr>
<th></th>
<th>BG&lt;sup&gt;a,b&lt;/sup&gt; (mmol/L)</th>
<th># in band&lt;sup&gt;c,d&lt;/sup&gt; (%)</th>
<th>Insulin&lt;sup&gt;e&lt;/sup&gt; (U/h)</th>
<th>Goal feed&lt;sup&gt;e&lt;/sup&gt; (%)</th>
<th>BG Variability&lt;sup&gt;d&lt;/sup&gt; (Amol/L per hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Real patients</td>
<td>6.8 ± 1.2</td>
<td>27 (25 ± 17)</td>
<td>4.3 ± 2.3</td>
<td>71.7 ± 14.2</td>
<td>0.68 (0.74 ± 0.34)</td>
</tr>
<tr>
<td>Virtual patients (before modifications)</td>
<td>6.7 ± 1.2</td>
<td>33 (29 ± 21)</td>
<td>5.4 ± 2.0</td>
<td>78.8 ± 8.8</td>
<td>0.34 (0.34 ± 0.05)</td>
</tr>
<tr>
<td>Glycemic penalty: $G_0 = 5$ mmol/L</td>
<td>6.4 ± 1.2</td>
<td>43 (39 ± 22)</td>
<td>6.0 ± 2.2</td>
<td>73.4 ± 10.0</td>
<td>0.33 (0.33 ± 0.04)</td>
</tr>
<tr>
<td>Insulin dose penalty: $P_I / 2$</td>
<td>6.6 ± 1.2</td>
<td>34 (30 ± 23)</td>
<td>6.6 ± 2.5</td>
<td>79.9 ± 9.4</td>
<td>0.34 (0.34 ± 0.05)</td>
</tr>
<tr>
<td>Insulin dose penalty: $P_I / 10$</td>
<td>6.6 ± 1.2</td>
<td>35 (32 ± 22)</td>
<td>7.4 ± 2.4</td>
<td>80.7 ± 10.1</td>
<td>0.35 (0.35 ± 0.05)</td>
</tr>
<tr>
<td>Mucosal damage penalty: $4^b$ power</td>
<td>6.5 ± 1.2</td>
<td>41 (37 ± 22)</td>
<td>4.9 ± 2.0</td>
<td>70.7 ± 10.5</td>
<td>0.34 (0.34 ± 0.04)</td>
</tr>
<tr>
<td>Combined modifications to penalty functions</td>
<td>5.9 ± 1.2</td>
<td>57 (52 ± 23)</td>
<td>6.4 ± 2.3</td>
<td>60.0 ± 11.6</td>
<td>0.34 (0.34 ± 0.04)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Blood glucose concentration  
<sup>b</sup> Mean (log-normal) ± Standard deviation (SD)  
<sup>c</sup> Percentage of BG measurements between 4.4 - 6.1 mmol/L  
<sup>d</sup> Total mean (per patient mean ± SD)  
<sup>e</sup> Per patient data, mean ± SD
original trial, the nurses using Glucosafe were allowed to modify the nutritional advice by forcing the system to give more or less nutrition when patients had digestive problems. Such modifications of the nutritional advice may also affect the insulin advice. The advice was modified a total of 44 times for the patient group.

Furthermore, two of the patients received propofol (an anaesthetic with a minor nutritional value) during part of the Glucosafe trial. The virtual patients do not take into account the commencement or halting of propofol, but continues whatever treatment was occurring at the beginning of the trial period. Finally, using the original trial the Glucosafe advice was always accepted (and thereby registered by the Glucosafe system) immediately, which happens in the virtual patients. This may cause minor differences in treatment.

Evaluating the modifications to the penalty functions reveals that no single modification alone was enough to lower the mean blood glucose into the 4.4-6.1 mmol/L band. Reductions to the insulin dose penalty resulted in a substantial increase in insulin doses, but with only a small effect on mean BG. This in turn allowed a small increase in nutrition. It appears that even large insulin doses will not be sufficient to control BG in all patients, and that such large increases in insulin use may be hazardous: large doses of insulin may increase the risk of hypoglycemic incidents, should the patient’s insulin sensitivity increase.

The results so far indicate that decreasing the nutrition, is necessary in some patients to lower the blood glucose. This is evident in the virtual patients with the combined modifications which resulted in a mean blood glucose inside the 4.4 - 6.1 mmol/L band.

While these combined modifications resulted in a decrease in the nutrition rate this may not be a problem, but an advantage. The percentage goal feed achieved in this study matches the 60-70% goal feed (calculated with the Harris-Benedict equations) used by (Arabi et al. 2011) which showed reduced mortality with permissive underfeeding.

6. CONCLUSIONS

While there are deviations between real patient behaviour and virtual patient behaviour, these can be explained mainly by the periods where the real patients were disconnected from their insulin and nutrition pumps. As such the use of virtual patients can be applied to the evaluation of modifications to decision support systems that cannot otherwise be evaluated retrospectively.

In order to achieve a mean blood glucose in the 4.4 - 6.1 mmol/L band, it is necessary to reduce the amount of administered nutrition, as increasing the insulin usage alone is not sufficient.

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