MYANMAR GUIDELINE FOR INSULIN THERAPY

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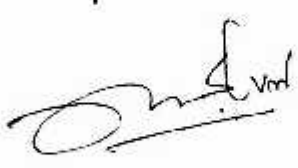
Foreword

Myanmar Society of Endocrinology and Metabolism (MSEM) has been founded since 2008 with the main aim of promoting the practice of clinical endocrinology in the country. Series of continuing medical education for the specialists as well as general practitioners has been conducted during the last five years and national

International Conferences on the endocrinology has been held annually for the same period successfully. Under the leadership and arrangement of the MSEM, Myanmar endocrinologists have been able to attend various international congress and conferences both regionally and globally. The Department of Endocrinology has been successfully established in the North Okkalapa General Hospital which is the one of the main affiliated hospitals of the University of Medicine 2, Yangon. The doctorate course on the endocrinology could also be started in the University of Medicine 2, Yangon.

As for the public and the patients with diabetes, the Myanmar Diabetes Association (MmDA) could also have been founded since early last year. Many health education programs on information, education and communication (IEC) materials could have been developed and distributed throughout the country. All these successful milestones in the history of endocrinology and diabetes in Myanmar has been established with the concerted and untiring effort of Myanmar endocrinologist. It is also made possible to publish series of Clinical Pratice Guidelines on various aspect of Endocrinology in international journals over the last five years. To add to the success story of the MSEM and MmDA, "Myanmar Guideline for Insulin therapy" has been developed by the collaborative effort of Myanmar endocrinologists. Since the prevalence of diabetes has been inexorably rising globally as well as locally, prevention is the prevention of complications of diabetes by achieving optimal glycemic control in patients with diabetes. As insulin is one of the available treatment options it is utmost important to make use of it in the management of diabetes. There has been barriers in the use of insulin therapy in the diabetes management, and I believe that this locally developed Insulin guideline will be of great help in overcoming the hurdles and also in facilitating the appropriate use of insulin for the benefit of diabetes patients.

I would like to thank all those medical professionals taking part in the development of this guideline with their unselfish effort. Without mentioning our heartfelt gratitude to the Novo Nordisk Company for the unlimited educational grant in the development of this insulin guideline, the list of people to be grateful by the MSEM and MmDA will not be complete.



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STATEMENT OF INTENT

This guideline is meant to be a guide for clinical practice, based on the best available scientific evidence at the time of development. Adherence to this guideline may not necessarily guarantee the best outcome in every case. Every healthcare provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally. Please refer to the local prescribing information.

This guideline dose not substitute or replace a medical consultation. Patients are advised to consult a medical professional for further information.

DISCLAIMER

The publication of this clinical practice guideline is made possible through an un restricted educational grant from Novo Nordisk and Value Healthcare.

The taskforce members resumes full authorship and the content is reviewed independently from the funder.

While every attempt is made by the authors to ensure that the medical information is current and accurate, differences of opinion exist and MSEM and MmDA take no responsibility for the views expressed herein, nor do they necessarily reflect the opinions of the publisher or sponsors.

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CHAPTER (1)

BACKGROUND

1.1 Introduction

Type 2 diabetes mellitus (T2DM) has become a major health problem worldwide, especially in Asia region. The prevalence of diabetes in Myanmar has been in a rising trend due to urbanization, life-style changes and new dietary habits. World Health Organization (WHO) STEP survey reported that the prevalence of diabetes in Myanmar were 13.9% for urban, 7.3% for rural areas and 6 % for the nation as a whole.[1] According to International Diabetes Federation, Diabetes Atlas, there was 2.1 million diabetes cases (20-79years) in Myanmar in 2011 and it is estimated to be 3.4 million by the year 2030.[2]

Early and appropriate diabetes care can ensure good glycemic control. However, a recent study done in two private clinics have concluded that only 27% of T2DM patients in Myanmar are able to achieve good glycemic control.[3] As T2DM is often diagnosed late, optimum glycemic control is essential to prevent the development and also further progression of diabetes complications. While there are plenty of therapeutic strategies to achieve glycemic control, insulin remains the most definitive option in the armamentarium. Generally, treatment for Type 2 Diabetic patients start with multiple oral anti-diabetics drugs (OADs) and need to increase the drugs during the course of the disease to overcome the β cell dysfunction. Finally, insulin therapy plays an essential role for glycemic control. Nevertheless, many of primary care physicians remain on these regimens although the target of glycemic control is not achieved. In such cases, insulin is usually administered late and intensified too slowly.[4] This is possibly because many primary care physicians or General Practitioners (GPs) perceive insulin is usually administered late and intensified too slowly.[4] This is possibly because many primary care physicians or General Practitioners (GPs) perceive insulin based regimens as too complicated and are also concerned about adverse effects such as hypoglycemia. Many patients are also highly reluctant to commence insulin therapy because of their prior perceptions about injection pain, inherent risk for hypoglycemia, weight gain and treatment complexity.[5] This problem is exacerbated when one is dealing with financially poor, uneducated, elderly diabetic patients living in small suburbs and towns of the country.[5]

Therefore, it is important to develop guidelines for the use of insulin regimens that are less complicated and enable patients to achieve target glycemic levels with minimal associated adverse effects. The present guideline is targeted not only for general physicians who are the primary care givers to patients with diabetes as well as for physicians in tertiary centers. This guideline is therefore envisaged to equip the primary care physicians with simple and doable algorithms for initating, optimizing and intensifying insulin in their clinical practice.

This guideline is mainly for the management of Type 2 Diabetes mellitus, but also applicable to Type 1 Diabetes.

1.2 Methodology

This guideline was prepared by the guideline development committee that consisted of diabetologists and general physicians (Internists). This guideline was aimed for all primary care physicians in Myanmar. The best available evidences have been incorporated to the guideline as much as possible. When sound and reliable local evidences are not available, the experiences and insights of the guideline development group members are employed. All the evidences were searched systematically and critically appraised by the group members. An appropriate clinical judgment for individual case should be determined with the adaptation according to the specific clinical conditions.

CHAPTER (2)

Raionale for insulin therapy

Type 2 DM is a progressive disease characterized by insulin resistance and impaired insulin secretion from the ß cells. As the disease progresses, ß cell function deteriorates at a rate of approximately 5% per year. The United Kingdom Prospective Diabetes Study (UKPDS) reported that at diagnosis, ß cell function is about 50% of the normal, which is further reduced to about 25% of the normal after 6 years following diagnosis.[6] This deterioration leads to decrease efficacy of OADs, especially the insulin secretagogues. Therefore, at a later stage of the disease, most patients of T2DM require exogenous insulin.

Diabetic complications are mainly or partly dependent on sustained chronic hyperglycemia, which is reflected by HbA 1c level, fasting and/or post prandial blood sugar levels. The UKPDS demonstrated that intensive glycemic control leads to significant reductions in risk of microvascular complications and non-significant reduction of macrovascular complications. However, the results of the UKPDS 10-year post-trial monitoring (UKPDS-PTM) study reported additional macrovascular risk reduction (especially cardiovascular risks) with early intensive glycemic control in newly diagnosed T2 DM patients.[7] Insulin therapy is the most effective treatment option with highest glucose lowering efficacy without maximum limit of dose. It is suitable at all stages of T2DM. Numerous randomized controlled trials and large observational studies have shown that good glycemic control can be achieved in patients with T2DM who are treated with insulin or insulin analogues using treatment algorithms.[8]

As most people with T2DM will ultimately required long-term insulin therapy due to progressive ß cell failure, it seems rational to add insulin therapy earlier rather than later. It can be combined with OAD by using basal or premixed insulin which is more likely to be accepted by the patients. Although sulphonylurea must be discontinued when substitution therapies are used, metformin should be continued with insulin.

CHAPTER (2)

Raionale for insulin therapy

2.1 Barriers to insulin therapy

There are significant barriers exist to the use of insulin therapy in clinical practice. [9] (Table 1)

Table 1

Common patient related barriers	Common physician related barriers
1. Fear of painful injections	1. Concerns risks of hypoglycemia and weight gain.
2. Fear of weight gain, hypoglycemia	2. Concerns putting extra burden on patient with complicated insulin regimen and multiple injections
3. Fear of lifestyle changes and restrictions	3. Concerns patient's adherence to therapy
4. Feeling of becoming more "ill"	4. Lack of familiarity / experience, lack of guidelines and algorithm
5. Social embarrassment and stigma. e.g., discrimination in job availability	5. Time constraints for educating patients, and teaching of injections technique
6. Fear of increased cost of treatment	6. Lack of resources, drug costs, staff, skills

2.2 Indications for insulin therapy in T2 DM

(1) Newly diagnosed patients

Insulin is recommended in newly diagnosed T2DM especially when T1DM & T2DM cannot be differentiated symptomatically (severe osmotic symptoms such as polyuria, polydipsia, polyphagia, dehydration) with RBS>350 mg/dl or FBS> 250 mg/dl and HbA_{1c} of > 10%.

(2) T2 DM patients wiht OAD failure

Poor glycemic control despite maximal tolerable dose of two or three OADs over three months, with FBS> 130mg/dl and PPBS> 180 mg/dl (and/ or HbA_{1c} >7%)

Patients with renal or hepatic diseases (or) allergies that preclude the use of OADs and/or incretin mimetics. Progressive microvascular complications.

(3) Acute clinical conditions

Short term use of insulin therapy in patients with T2 DM, may be considered in the following conditions especially in hospitalized patients.

(a) Acute clinical conditions such as:

- sepsis/severe infection (eg; severe pneumonia, active tuberculosis)
- stroke
- acute myocardial infarction or unstable angina
- acute abdomen
- patient undergoing surgery

(b) Severe metabolic decompensation (eg; DKA or HHS)

(4) Pregnancy

Patient who has pregnancy related diabetes (eg; pre-pregnant or gestational diabetes)

Patient who has poor glycemic control in pre-conceptional state also need insulin.

CHAPTER (3)

INSULIN: BRIEF OVERVIEW

3.1 Physiology of Insulin secretion

The pancreas ß cells secrete a small amount of insulin, termed "basal insulin" even in the fasting stage to suppress catabolism of muscle and fat, and regulate hepatic glucose production. After a meal, the ß cells respond to the glucose challenge of carbohydrate consumption and secrete insulin termed "prandial insulin" in a regulated manner.[10] People with T1 DM depend on exogenous insulin for survival. Although individuals with T2DM are not dependent on exogenous insulin for survival, many of these individuals show decreased insulin production over times. Therefore, they require supplemental insulin for adequate blood glucose control, especially during times of stress or illness.[11]

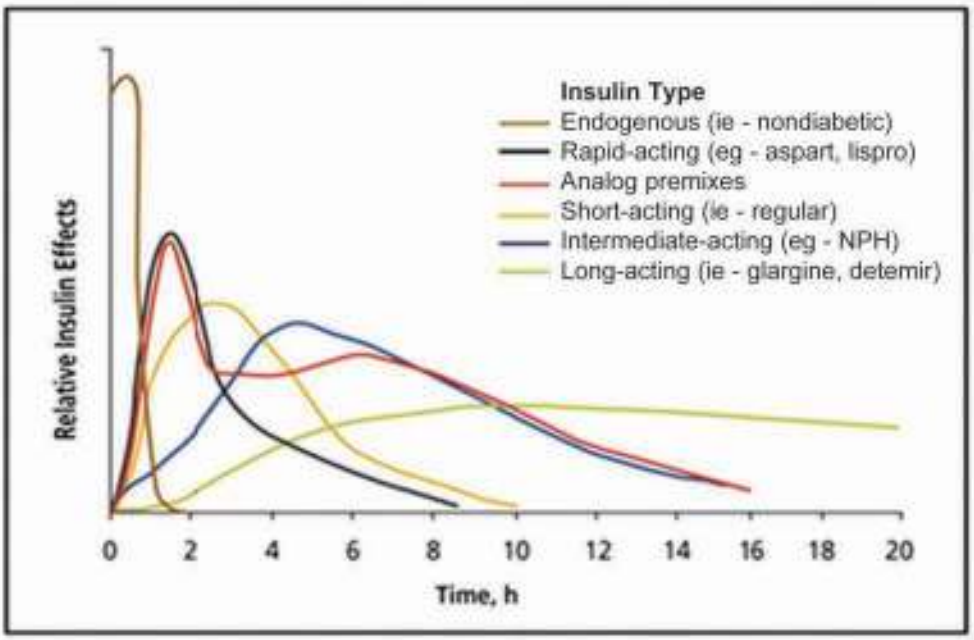
3.2 Types of insulin and insulin preparations

The insulin currently used in medical practice is recombinant human insulin or insulin analogue(Table 2). Insulin analogue is developed by structural modification in the amino acid sequence of the insulin molecule. Human insulin and insulin analogues mostly differ in their pharmacokinetic parameters and propensity for adverse effects(Fig 1). The human insulin does not mimic the normal kinetics and dynamics of endogenous insulin, leading to inadequate control of postprandial glycemic excursions and also has a propensity to cause delayed hypoglycemia.[11]

These problems are significantly reduced with the use of insulin analogues and their combinations. Insulin is available in rapid, short-acting (regular insulin), intermediate acting (NPH), and long acting types that may be injected separately or mixed in the same syringe. Human regular insulin has an onset of action occurs in 30 minutes, requiring dosing 30 minutes before meals for the best effect.[12] The rapid-acting analogues, including aspart, lispro and glulisine, their onset of action starts in 10-15 min so they can be given just before meals.

Intermediate and long acting insulin suppresses hepatic glucose production and maintains near normoglycemia in the fasting stage. Therefore, they are employed as basal insulin.

Insulin Action



J Am Osteopath Assoc January 1, 2009 vol. 109 no. 1 26-36 (Fig 1)

Table 2

Pharmacokinetic profile of various types of Insulin

Brand (Generic) Name	Onset	Peak (Hour)	Duration (Hour)	Timing of insulin
a) Short acting-regular				
• Actrapid ® * (Soluble)	30 min	1-3	8	30 min
• Humulin R ® (Soluble)	30 min	2-4	6-8	Before meal
b) Rapid acting analogue				
• Novorapid ® (Aspart)*	10-20 min	1-3	3-5	5-15 min
• Humalog ® (Lispro)	< 15 min	1	3.5-4.5	Before meal
• Apidra ® (Glulisine)	5.15 nub	1-2	3-5	
c) Intermediate acting NPH				
• Insulatard ® *(Isophane)	1.5 hour	4-12	18-23	Pre-breakfast
• Humulin ® (Isophane)	1 hour	4-10	16-18	Pre-bed
d) Long acting analogue				Same at every
• Lantus ® (Glargine)	2-4 hour	Peakless	Upto 24	day at any time
• Levemir ® (Detemir)*	1 hour	Peakless	Upto 24	of the day
e) Ultra-long acting analogue				Same at every
• Tresiba ® **	1.5 hour	Peakless	beyond	day at any time
(Insulin Degludec)	1 hour		40 hour	of the day
f) Premixed human (30% regular insulin / 70% NPH)				
• Mixtard ® 30*	30 min	Dual	18-23	30-60 min
• Humulin ® 30/70	30 min	Dual	16-18	before meals
g) Premixed analogue				
• NovoMix ® 30*	10-20 min	Dual	Up to 24	
(30% aspart / 70% aspart protamine)				5-15 min before meals
• Humalog mix	< 15 min	Dual	16-18	
(25% lispro / 75% lispro protamine)				
• Ryzodeg ®**	14 min	NA	beyond	once or twice
(30% Insulin aspart / 70% Insulin degludec)			40 hour	with main meals

* **Available in Myanmar** ** **Not available in Myanmar**

CHAPTER (4)

GLYCEMIC TARGETS

Achieving glycemic targets is essential for reducing diabetes - related complications. Guideline Developent Committee recommends adopting ADA Guideline.[12] Therefore, glycemic target for Myanmar people should be < 7% (Table 3). Nevertheless, achievement of HbA 1c below 6.5% should be targeted in individual with low risk for hypoglycemia. The glycemic targets should be individualized. The Committee has decided to keep FBS at 80-130 mg/dl according to local situations.

Less stringent targets (Higher HbA 1c) may be appropriate in the following situation.[13]

* A history of severe hypoglycemia
* Patients with limited life expectancy
* Advanced microvascular or macrovascular complications
* Extensive co-morbidities
* Long-standing diabetics in whom glycemic control remains diffcult despite optimizing patient education, adherence and unsafe.[12]

Table 3

Parameters	Recommendations
HbA1c (%)	< 7.0
Fasting (mg/dl)	80-130
Preprandial (mg/dl)	< 140
Postprandial (mg/dl)	< 180

CHAPTER (5)

INSULIN REGIMENS FOR NON-EMERGENCY CONDITION

The choice of insulin regimens should be individualized based on the patient's glycemic profile, dietary pattern, personal lifestyle as well as desired flexibility.

The two basic insulin regimens are:

- Supplementary therapy
- Substitution therapy

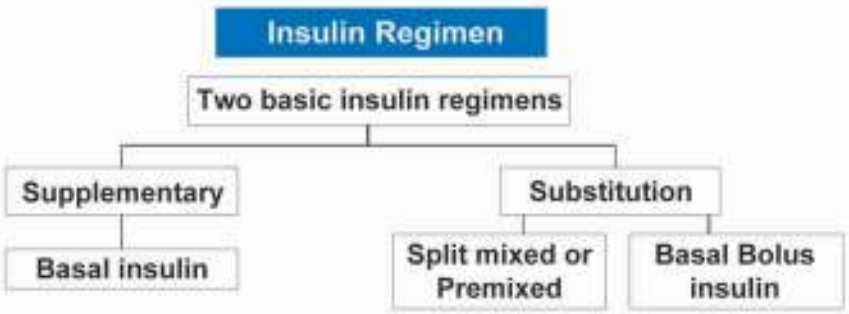
Supplementary therapy is given as basal insulin and Substitution therapy which is given as basal bolus insulin or pre-mixed insulin therapy (Fig 2).

In patients with T2DM, insulin is commonly initiated as supplementary treatment to OAD therapy. Less commonly it is initiated as complete substitution of OAD. Rapid improvement in glycemic control can be associated with adverse outcomes, especially related to frequent hypoglycemia. Therefore, the mantra, "Start low, and go slow" is pertinent while using insulin.[10]

These regimens require individualization which is carried out in phases of initiation, optimization and intensification.

Initiation: entails the selection of the appropriate type of insulin, regimen and starting dose for the patient. This ensures that the patient's individual need based on the glycemic status is appropriately addressed.

Optimization: entails gradual titration/ adjustment of the dose of insulin to obtain an optimal dose which is adequate to achieve the desired level of glycemic control with minimal or no adverse effects for the patient. Dose adjustments are carried out on the basis of blood glucose monitoring (usually self-monitoring of blood glucose, SMBG). SMBG should be carried out three or more times daily for patients using multiple insulin injections.[14]



(Fig 2)

Table 4
Insulin Regimens & Frequency of Injections per day

No. of injections Per day	Insulin regimen	Type of Insulin and Timing
1	Basal	Intermediate acting (NPH) insulin bed time
	Basal	Long-acting analogue once daily
	Premixed OD	Premixed insulin pre-dinner/per-breakfast
2	Premixed BD	Premixed insulin pre-breakfast & per-dinner
3	Premixed analogue	Premixed insulin pre-breakfast, pre-lunch TID & pre-dinner
4	Basal-Bolus	Basal insulin once/ twice daily + prandial insulin pre-breakfast, pre-lunch & pre-dinner

Intensification: entails modification/ switching from one insulin regimen to another in order to achieve better glycemic control. The dose and regimen is individualized based on patient's blood glucose profile, patient's lifestyle and preference.

Table 5
Choice of insulin regimen according the blood sugar profile

Blood Glucose Profile		Preferred insulin regimen
Pre-breakfast	Daytime	
High	Normal/Near Normal	Basal (Bed time) or Premixed OD (Pre dinner)
High	High	1. Basal → Basal Plus → Basal Bolus 2. Premixed Insulin: BID
Normal	High	Prandial insulin and later add on basal insulin

5.1 Basal insulin regimen

The regimen involves addition of basal insulin (i.e. an intermediate acting or long acting insulin analogue) to OAD. This regimen is generally implemented if fasting or per-breakfast blood glucose is high and day time (postprandial) blood glucose is normal or near normal. It is given at bed time (usually 9-10 PM), with starting dose of 10 U or 0.2 U/Kg/Day.[9,10,11] Optimization by adjusting the dose based on pre-breakfast blood glucose levels. Monitoring of pre-breakfast blood glucose level should ideally be done daily. Increments to the daily dose are made once or twice weekly if pre-breakfast blood glucose levels are high. The dose should be increased by 2U if more than one pre-breakfast blood glucose reading is >130 mg/dl (without any associated nocturnal hypoglycemia) and reduced by 2U if more than one pre-breakfast blood glucose reading is < 80 mg/dl. Basal insulin therapy should be stopped if total basal insulin dose reaches 40 U/day.[9,10,11] (Table 6)

Table 6

Treatment	Dose
Initiation	10 units or 0.2 U/kg/day at bed time
Monitoring and targets	Monitor pre-breakfast BS Target pre-breakfast BS 80-130mg/dl
Optimization	Adjust insulin doses after 3 consecutive BG values obtained (every 3-7 days) -<80mg/dl (>1value) → reduce dose by 2 units -between 80-130mg/dl (all values)→ maintain current dose ->130mg/dl (>1value, no hypos) → increase by 2 units
Caution	Watch for nocturnal hypoglycaemia. If hypoglycaemia is the limiting factor to achieve optimum dose, conventional intermediate-acting insulin may be switched to basal insulin analogue

5.2 Premixed insulin regimen

The transition from basal to basal bolus regimen is complex and primary care physicians may find it difficult to use. Premixed insulin has the advantage of a relatively simple and convenient regimen for the primary care physician and the patient. Premixed insulin consists of a rapid/ short- acting component (30% or 50%) that covers mealtime glucose excursions, and intermediate/ long - acting insulin (70% or 50%) that augments background insulin levels.[9,10,12,13,14]

Advantages of premixed insulin are:

- Lower number of injections required daily
- Coverage of both fasting and postprandial sugar (human premixed is less effective than analogue insulin)
- Requirement of patient monitoring is less

Disadvantages of premixed insulin are:

- Difficult to adjust the dose of insulin in patients with irregular eating habits
- May not be effective in some conditions where precise blood glucose control is desired as in patients with unstable medical conditions

Premixed insulin once daily

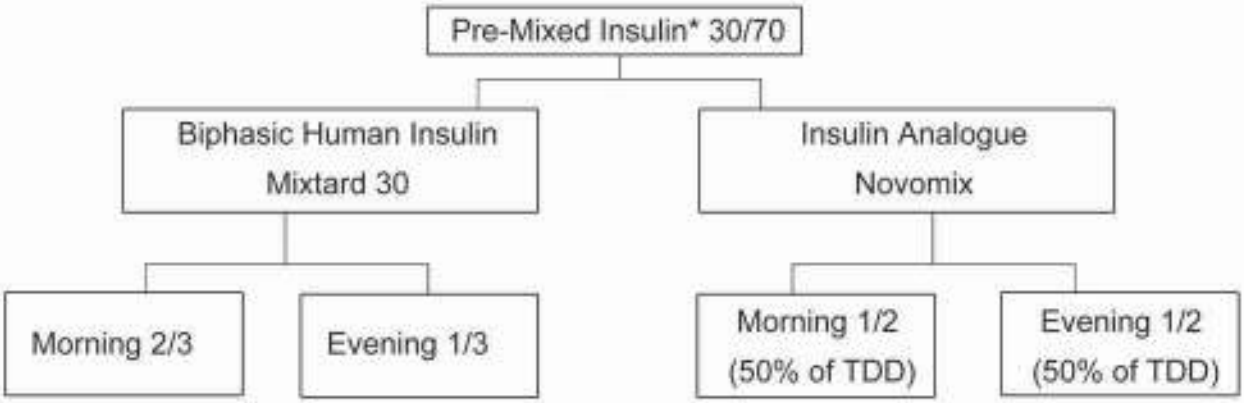
Premixed insulin can be given once daily and usually 10 units or 0.2 Unit/Kg/day administered at pre-dinner when blood sugar is high at bed time or pre-breakfast.

Patients are advised to perform SMBG at pre-breakfast.[14]

Premixed Twice per day Insulin Therapy

Initiation: such a regimen could be an initial starting regimen for T2DM patients who have high fasting and daytime (pre and postprandial) blood glucose level or it could form part of an intensification regimen from an initial basal insulin regimen. Human premixed insulin can be started with dose of 0.5 U/Kg/day, 2/3 of the dose is administered in the morning (pre-breakfast) and 1/3 in the evening (pre-dinner). Premixed insulin analogue can be started with dose of 0.5 U/Kg/day, 50% of the dose is administered in the morning (pre-breakfast) and 50% in the evening (pre - dinner) (Fig 3).

Optimization: Monitoring of pre - breakfast blood glucose level should ideally be done daily and the decision to adjust the insulin dose should be based on at least 3 consecutive blood glucose readings. Adjustment in insulin dose are made once or twice weekly based on pre-breakfast and pre-dinner blood glucose levels. The morning dose of insulin should be increased by 2U if pre-dinner blood glucose reading is more than 130 mg/dl for more than once (without any associated nocturnal hypoglycemia) and reduced by 2U if pre-dinner blood glucose reading is less than 80mg/dl for more than once. The dose is not changed if pre-dinner blood glucose remains in the range of 80-130 mg/dl. Similarly, the evening dose of insulin should be adjusted with the pre- breakfast blood glucose reading as in the morning pre-mixed insulin.



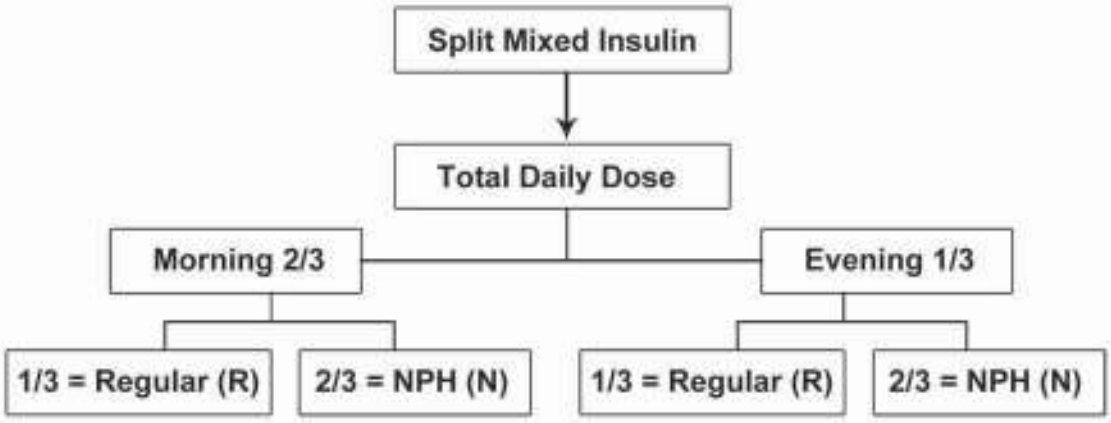
(Fig 3)

Intensification: Further intensification into a basal bolus regimen may be indicated in case of target glycemic control cannot be achieved. Other option would be premixed insulin analogue three times per day.

Split Mixed twice per day Insulin Therapy

This is the twice per day Insulin Therapy where regular insulin and NPH insulin are mixed according to blood glucose respones.

It can be started with 0.3 - 0.5 U/Kg/day, two-third before breakfast and one-third before dinner. Each morning and evening dose will be prepared by self mixture of one-third Regular Insulin and two-third NPH Insulin (Fig 4) .



(Fig 4)

5.3 Basal Bolus insulin regimen

The most precise and flexible prandial coverage is possible with basal-bolus therapy, involving the addition of pre - meal regular short acting or if available, rapid acting insulin analogue to ongoing basal insulin.

Advantages of basal bolus regimen are:

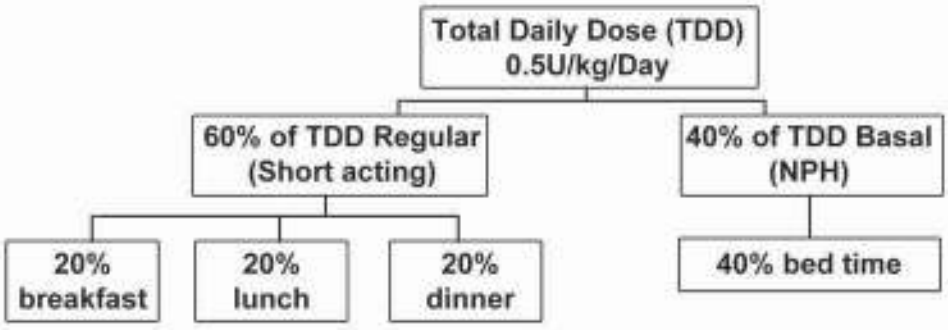
- Mimics physiological insulin secretion
- Greater control over postprandial excursions of blood glucose
- Useful in unstable medical conditions which precise blood glucose control is required
- More effective in achieving HbA 1c target

Disadvantages are:

- Complex regimen requiring multiple (4-5) injections per day
- High degree of motivation required
- More expensive
- More intensive patient monitoring is required

Initiation: This regimen could be an initial starting regimen especially if both fasting and daytime (postprandial) blood glucose levels are high. Conversely, this regimen could be intensification from basal insulin regimen when fasting/pre-breakfast blood glucose level is high (>130mg/dl) and daytime postprandial blood glucose is high (> 180 mg/dl).

Optimization: The usual starting dose is 0.5U/Kg/Day (e.g. 30U for a 60kg individual), 60% (e.g. 18U) of which comprises of rapid acting insulin which has to be administered prior to meals, at 20% dose (6U) before breakfast, 20% dose (6U) before lunch and 20% dose (6U) before dinner. The rest 40% (i.e.12U) comprises of basal insulin which has to be administered at bedtime (Fig 5). Optimization of dose (by titrating 5-10% of the dose) can be based on blood glucose measured pre and post breakfast, pre and post lunch, pre and post dinner and at bedtime.



(Fig 5)

Table 7

Summary of different insulin regimens:

Type of regimens	Indication	Type of insulin used	Timing of insulin Administration	No.of injection/ day
Basal	High Pre-breakfast blood sugar but normal/near normal day time blood sugar	Intermediate acting insulin (NPH) or Long acting insulin analogues	Usually at bed time (9-10 PM) or Any time in evening	One
Premixed	High Pre-breakfast blood glucose and high day time blood BS sugar Tight glycemic control is not very essential Patient prefers simpler regimen	Premixed human insulin 30 / 70 or Premixed insulin Analogue	Pre-Dinner 30 mins before meals (pre-breakfast & pre-dinner) or 5-15 min before/after starting meal (pre-breakfast & pre-dinner)	One-/Two /Three (Premix analogue)
Basal-Bolus	High fasting / pre-breakfast blood sugar and high daytime blood sugar Tight glycemic control is essential (illness or clinically unstable) Patient has irregular food habits Patient is motivated to take multiple injections and monitor blood glucose	Intermediate acting insulin (NPH) or Long acting insulin analogues plus Short acting / rapid acting prandial insulin (pre-break-fast, pre-lunch, pre-dinner	At bed time if intermediate acting insulin or At any time if long acting insulin analogues plus 30 min before meal (if short acting) 5-15 min before / after starting meal (if rapid acting)	One Plus Three

Table 8

Insulin Dose Adjustment according to Blood Glucose

TO CONTROL	ADJUST
Pre Breakfast BG	Pre-bed NPH / long-acting insulin or pre-dinner Premixed or pre-dinner NPH
2-hours Post-breakfast BG	Pre-breakfast short / rapid-acting (Analogues) or premixed insulin analogue
Pre Lunch BG	Pre-breakfast short / rapid-acting or premixed insulin
2 hours Post-lunch BG	Pre-lunch short / rapid-acting (Analogues) or pre-lunch premixed insulin
Pre-dinner BG	Pre-lunch short / rapid-acting or pre-breakfast NPH or pre-breakfast premixed insulin
Post-dinner / Pre-bed BG	Pre-dinner short / rapid-acting human or analogues or pre-dinner premixed insulin

CHAPTER (6)

INSULIN THERAPY FOR ACUTE MEDICAL CONDITIONS (HOSPITALIZED PATIENTS)

Any blood glucose > 140 mg/dl is defined as hyperglycemia in hospitalized patients. Levels that are significantly and persistently above this may require treatment. In undiagnosed patients, HbA_{1c} values > 6.5% suggest that diabetes preceeded hospitalization.

Target of Blood Sugar during acute illness

Recommendation of BG targets according to AACE/ADA consensus at 18th annual meeting.[16]

- For non-critical patients in general medical and surgical wards, keep between 100-180mg/dl for IV infusion. If taking S/C insulin pre meal <140mg/dl and RBS (PPBS) <180mg/dl.

- For critically ill patients in HDU and ICU setting, keep between 140-180mg/dl.

In critically ill patients requiring IV insulin therapy, the target of BG <110mg/dl are not recommended. Higher glucose ranges are acceptable in terminally ill patients and patients with severe co-morbidities.

Methods of insulin therapy in acute illness

There are four methods of insulin administrations:

1. Continuous IV Insulin (CII)
2. Glucose - K^+ - Insulin (GKI)
3. Basal Bolus Insulin or Multiple Daily Insulin (MDI)
4. S/C Sliding Scale Insulin

Continuous Intravenous Insulin (CII)

In this insulin administration, IV insulin infusion with separate IV glucose infusion are used. This is suitable for ill cases with high blood sugar on admission such as DKA, HONK, major surgery, NPO, unstable ill cases e.g, sepsis, MI, steroid, gastroparesis, delivery, etc.

Advantages of intravenous insulin infusion in comparison with subcutaneous insulin injection:

- Rapid time of onset and offset of insulin action.
- Allows smooth and timely achievement of target levels.
- Rapid resolution of hypoglycemia and avoidance of severe hypoglycemia
- Dosing flexibility that can accommodate fluctuating clinical status, illness, stress-related changes in insulin sensitivity

(a) IV Insulin:

- Insulin administration is generally similar to insulin therapy in DKA.
- 50 U Insulin (regular) + 50 cc N/S CII with the rate of 6-8 U/hr (use syringe pump)
- Alternatively, if no syringes pump available, 50U in 500 N/S . i.e. 1U of insulin in 10 ml (5 drops/min is approximately equivalent to 2 U/hour) i.e.for 6-8 U, 15-20 dpm can be given althought it is rather not reliable.

For the choice of insulin infusion rate, IV variable scale chart can be used (Table 9). Initial dose and subsequent adjustment can be done according to variable scale depending on RBS level and response to insulin. Monitor BG hourly. If the response is not satisfactory after 2-3 hours, change to next algorithm (high scale). By this method, glycemic control can be achieved early.

Table 9

Standard IV Insulin Infusion variable scale

BG (mg/dl)	Algorithm 1 (U/hr)	Algorithm 2 (U/hr)	Algorithm 3 (U/hr)
<79	Off	Off	Off
80 - 120	0.5	1	2
121 - 150	1	1.5	3
151 - 180	1.5	2	4
181 - 250	2	4	6
251 - 300	3	6	10
301 - 350	4	8	14
>350	6	12	16
• Algorithm 1 Start here for most patients			
• Algorithm 2 Not controlled with Algorithm 1(corticosteroid therapy , > 80 U/day requirement)			
• Algorithm 3 Not controlled with Algorithm 2			
It is advisable to use your own hospital protocol (which the Dr. used to)			

Note: Where the interavenous access and infusion equipments are not available, intramuscular insulin can be given.
The IM dosages are approximately equivalent to IV dosages.
The needle for intramuscular injection must be changed to longer one. (Better to use 1cc syringe instead of insulin syringe)

(b) Intravenous fluid infusion (Normal saline or Dextrose Water)

IV Normal saline drip in separate line of infusion when BG is high > 250 mg/ dl. This is replaced by IV Dextrose water or Dextrose saline when BG < 250 or 200mg/dl. RBS should be maintained between 100-180 mg/dl by Insulin infusion accompanying with glucose infusion (5 or 10%)

When the patient start oral feeding, it can be changed to S/C insulin either
(a) scheduled Basal Bolus Insulin/Multiple Daily insulin (MDI) or
(b) sliding scale followed by basal bolus regimen.

Transition to SC insulin:

If > 0.5 U/hr IV insulin required with normal BG, start S/C regular insulin ½ to 1 hour before stopping infusion. Establish 24 hr Insulin requirement extrapolating from average insulin requirement over last 6-8 hours, give 40% as Basal. S/C Boluses are based on carbohydrate intake using carbohydrate counting method but it will be difficult for local situation where there are few dietitians available. Therefore alternatively, estimated 20% each for BF, L, D doses as of total daily dose can be given. Monitor BG tid, hs, and 3 am. Additional correction boluses if BS>140 mg/dl or reduction of dose if BS<100 mg/dl can be done.

Formula for Correction bolus:

Correction bolus = (Current BS - 140 mg/dl*)/ Correction Factor (CF)
where CF = 1700/total daily dose or 3000/bodyweight in kg
*BS 140mg/dl is used as upper limit

Glucose - K $^{+}$ Insulin (GKI) regimen

GKI drip is a method of insulin administration commonly used in perioperative period and in patients with nil per oral. GKI drip is more suitable for

those with reasonable blood sugar control in metabolically stable patients where RBS approaching near or below 200 mg/dl.

In this regimen, soluble (regular) insulin and potassium chloride are mixed in a 500 ml of 5-10 % Dextrose water. Generally 500ml of 10% Dextrose plus 10-20 unit of soluble (Regular) Insulin plus 10-20 mmol (0.75 to 1.5 G) of KCL is given in a rate of 100ml/hr. The dose of insulin added is depending on the insulin requirement of the patient, current blood sugar level and insulin sensitivity. Patients who are Insulin resistant (stress, obese, infection, steroid therapy) needs additional 2-6 more units. Check blood glucose every 2-4 hours (i.e. at half bottle of 500 ml). The recommedation for titration of the dose of insulin and potassium according to blood glucose (Tabe 11) and potassium levels are shown in Table (10). Adjust insulin to keep RBS between 120-180 mg/dl. If the blood sugar is too high or too low, start a new 500 ml bag with the corrected insulin dose. In resource limited situation, addition of the 50% of recommended top up insulin can be added at the half bottle.

Table 10

Recommendation for KCL

Serum Potassium (mmol/L)	KCl to be added (mmol/500cc)
<3	**10 - 13mmol (0.75-1G)**
3-5	**7.5 - 10mmol (0.5-0.75G)**
>5	**None**

Table 11

Recommendation for GKI dose titration[17]

Blood	Glucose-Insulin-Potassium Infusion Rate
(mg/dl)	10% Dextrose 500ml
<80	↓ 4 - 6 units
<120	↓ 2 - 4 units
120-180	No change
181-270	↑ 2 - 4 units
>270	↑ 4 - 6 units

Basal Bolus or MDI

Subcutaneous Insulin administration in hospitalized patients are used in certain situations. Moderately hyperglycemic hospitalized patient who are non-critically ill should be treated with s/c insulin if they can take orally or Nasogastric feeding. MDI or multiple daily insulin therapy is now a standard s/c therapy using analogue insulin.

Scheduled subcutaneous insulin with basal, nutritional (bolus dose according to carbonhydrate intake), and correction components is the preferred method for achieving and maintaining glucose control in non-critically ill patients.

- Starting dose = 0.3U to 0.5U x weight in kilograms
- Bolus dose regular insulin or rapid acting analogue (aspart/lispro) = 20% of starting dose at each meal or according to cargohydrate loads
- Basal dose NPH or long acting analogue (Detemir/Glargine) = 40% of starting dose given at bedtime or any time
- Correction bolus = (Current BS - 140 mg/dl*) / Correction Factor
  where CF = 1700/total daily dose or 3000/bodyweight in kg
  *BS 140 mg/dl is used as upper limit

Example of calculation:

TDD = 0.5U/Kg/Day, if patient is 60kg, TDD is 30U/Day
40% as Basal = 30x0.4 = 12U (Insulatard / Detemir)
20% Bolus of TDD for each meal = 6U (B), 6U (L), 6U (D)

- Correction factor = 1700 / TDD
  = 1700 / 30
  = 56.6 (approx: 56)

Assume Current BS is 260mg/dl (lunch)

- Correction dose = (260 - 140) / CF
  = 120 / 56
  = 2 U *(approx:)*

Add 2U for current Insulin dose at lunch (6 + 2U).

Subcutaneous Sliding scale Insulin Therapy

This regimen is indicated for patients with poor control of RBS who are not so ill and taking food orally or with nasogastric tube. American Diabetes Association stated that Intermittent sliding scale insulin regimens should not be used alone to manage hyperglycemia in diabetic patients. Hyperglycemia and Hypoglycemia commonly occurs when sliding scale insulin dosing is used without basal insulin therapy or continuation of oral hypoglycemic agends.[24]

Although a sliding scale can be used to bring down an elevated glucose level, it may not do so for several hours and it may increase the risk of hypoglycemia. Type 2 DM has a component of insulin resistance which differ for each individual at different conditions. Each person is going to have very different insulin requirements especially in newly diagnosed diabetes. Therefore, sliding scale insulin therapy may be still useful in situations with unpredictable glycemic responses & where more frequent monitoring is not feasible because of resource limitation. Usage of the sliding scale should be quickly switching to basal bolus type with early use of intermediate insulin at bed time and use of additional correctional insulin. Initial sliding scale for a few days (1-3 days) should be followed by basal bolus regimen based on the blood sugar trends. It is better to review the trends of blood sugar results twice a day. If the patient's meals are still not regular, and the BS is still >200 mg/dl for 2-3 occasions step up to higher scale (Table 12).

In summary, sliding scale insulin should not be used for long duration and need to evaluate frequently and change the scale early and appropriately, within one day according to the response e.g. lower scale to higher scale. Basal insulin should be used as early as possible. Basal bolus type of dose adjustment should be applied depending on the glycemic trends.

Starting with Sliding Scale

The doses of sliding scale insulin can be prescribed by selecting one of the regimen shown in (Table 12). The selection of the regimen depends on the

body weight and insulin sensitivity apart from degree of hyperglycemia. Patients with sepsis, heart failure and shock will require more insulin.

Table 12

Sliding Scales For Subcutaneous Insulin

Glucose level (mg/dl)	Low Dose Regimen	Medium Dose Regimen	High Dose Regimen	Very High Dose Regimen	Other
100 -150	0	2	4	6	
151-200	2	4	6	8	
201-250	3	6	8	10	
251-300	4	8	10	12	
301-350	6	10	12	14	
351-400	8	12	14	16	
>400	10 Units	14 Units	16 Units	18 Units	

Basal insulin = 0.1 – 0.2 Units /kg

Sliding scale transition to Basal Bolus

After 24 to 48 hours, if patients' condition improve and oral feeding is more regular, it should be changed to basal bolus type with inclusion of intermediate or long acting insulin such as Isophane (NPH at bed time or Insulin Glargine or Levemir at any time). The dosages prescribed are depending on the previous day's RBS trends and patterns. For example, for elevated RBS at lunch, the next day's dose of pre-breakfast regular insulin is increased. For the meantimes, correction dose calculated by formula can be added to pre-lunch insulin dose. Alternative easy way of prescribing correction dose can be done by assuming that 1 unit of insulin will drop the blood glucose 50mg/dl in the low insulin resistant person, 1 unit for 25mg/dl in medium insulin resistant person and 1 unit for 15mg/dl in high insulin resistant person.

At discharge

When the glucose toxicity is over and food intake is more regular, total daily dose can be calculated and then pre-mixed or split mixed regimen can be given if there is long term insulin therapy is indicated. In some patients, insulin therapy can be replaced by OAD.

CHAPTER (7)

COMPLICATIONS OF INSULIN THERAPY

Problems related to insulin therapy includes:

Hypoglycemia
Weight gain
Allergic rection, injection site infection, lipoatrophy and lipohypertrophy

Hypoglycemia

Clinical classification of hypoglycemia includes;

Mild - only autonomic (sympathetic) symptoms

Moderate - autonomic plus neuroglycopenic symptoms but still can be able to self-treat

Severe - plasma glucose < 70 mg/dl, confusion or unconscious, requiring assistance of another person.

Hypoglycemia is an important complication of insulin therapy which can give rise to severe neurological consequenses and the life threatening major cardiovascular and cerebrovascular events. Severe hypoglycemia is more common and higher risks in elderly, advanced long standing poorly controlled diabetes with established micro and macro vascular complications particularly autonomic neuropathy with hypoglycemia unawareness. Such patients can present with asymptomatic hypoglycemia where there is biochemically low blood glucose level without any symptom.

Risk factors for hypoglycemia in patients with T2DM on insulin therapy are:

- Advanced age
- Missed meals/irregular meals
- Intercurrent illness (sick days) e.g. Gastro-enteritis, vomiting due to gastri tis, gastroparesis
- Vigorous exercise or physical activities without dose adjustment or adequate meals
- Alcohol consumption

- Hypoglycemia unawareness
- Long duration of diabetes and long duration of poor diabetes control prior to insulin therapy
- Impaired renal and liver functions
- Stroke and Parkinsonism with swallowing problems
- Concomittent use of insulin secretogogues in intensive insulin regimen
- Lack of adequate care-giver supervision and education on hypoglycemia

Prevention or reduction of hypoglycemic events and its subsequent risks require careful selection of the patients who need insulin therapy by judging the benefit and risk. It is important to provide SMBG and more health educations regarding insulin therapy and its complications, self dose adjustment, sign and symptoms of hypoglycemia, action during the events of hypoglycemia. It is also need to set an individualised HbA_{1c} target and selection of a regimen adapted to each individual's needs and lifestyle. All insulin-requiring individuals should be instructed to carry at least 15g carbohydrate (glucose or sucrose) to be eaten or taken in liquid form in the event of a hypoglycemic reaction. All insulin users should carry medical identification (e.g., a bracelet or wallet card) to alert others that the individual is a user of insulin.[10]

Weight gain

All patients who are treated with insulin will gain weight which can be progressive over time. It can be aggravated by concomittent use of TZDs, SUs and lack of proper diabetes education. Important strategies to counter weight gain are as folow;

- Restriction of calories and portions especially the carbohydrate and fats
- Appropriate dietitian advices (if feasible)
- To avoid defensive eating /snacking for the fear of hypoglycemia
- To keep physically active and regular excersise (difficult for the elderly and disables due to complications e.g. foot problems, stroke, fracture hip e.t.c.)
- Avoid high dose or rapid escalation of insulin dosages by over-enthusiastic patients and care-givers emphasizing mainly on getting the goal of glycemic targets.

CHAPTER (8)

SPECIAL SITUATIONS

Religious fasting practices

(a) Fasting during Buddhist lent

During Buddist lent fasting period is from noon to the next morning. Liquid foods are allowed after noon.

Premixed twice daily can be re-adjusted by:

Morning pre-breakfast premixed insulin reduced by 20% of usual dose and the evening pre-dinner premixed insulin reduced by 50% or skipped if blood sugar is well controlled.

Basal bolus insulin dose can be re-adjusted by:

Pre-breakfast, pre-lunch - bolus insulin in usual dose; skip the pre-dinner dose; reduce basal insulin dose by 20%.

Basal Insulin with OAD can be re-adjusted by:

Reduction of basal insulin dose by 20%; skip OAD (sulphonylurea) for evening meal. More frequent SMBG is required.

(b) Fasting and Ramadan

Those who have very high risk of complications should avoid fasting but those with low risk and satisfactory glycemic control may be allowed to perform fasting. Avoid fasting if HbA $_{1c}$ >10%, or in the presence of frequent hypoglycemia, hypoglycemic unawareness, high fluctuation in blood glucose profile. Also at very high risk are patients with ketoacidosis or hyperosmolar hyperglycemic coma within the last few months of fasting or those with acute illness and pregnant ladies. Patients with cardiovascular, renal or other diabetic complications and elderly with ill health are also at high risk of complications. For T2DM patients on insulin regimen, certain modifications are mandated during the fasting period. They need more frequent SMBG and appropriate insulin dose adjustment.

Reverse the OAD dosing schedule, i.e. the morning dose should be taken in the evening before the meal. The dose of basal insulin should be reduced by 20% . If the patient is on premixed insulin, inject the usual morning dose before the evening meal and reduce the morning dose. One can also consider changing to basal bolus regimen where basal insulin dose is reduced by 20% and bolus dose is given based on meals.

Exercise and insulin therapy

Physical activity/ exercise is an intergral part of the overall management of insulin-treated patients.

There are many factors that need to be considered if a patient undertakes exercise while on insulin regimen:

- How often does the person currently exercise If he or she is not very active the likelihood of hypoglycemia is greater

- The length of time the person is active and the intensity of exercise also affect the blood glucose response.

- Use of other medications, such as sulfonylureas also needs to be considered.

It is recommended to check the blood glucose before, after, and then several hours after exercise because hypoglycemia can occur hours after the exercise. For exercise that continues for 30 minutes or more, carbohydrate intake or the rapid-acting or short-acting insulin may need to be adjusted. If the blood glucose level is less than 100 mg/dl, the person should take 15 g of carbohydrates before starting the activity. If the exercise is planned, the rapid-acting (or shortacting) insulin dose should be reduced 30 to 50%. If the exercise is not planned and it has been more than 2 hours since the last meal it is recommended that the person take an additional 15-20 g of carbohydrates within 15 minutes of initiating the exercise for every 30 minutes of exercise.[18,19]

Sick Days

It is the times when the patient cannot eat solid food or follow their regular meal plan because of concurrent illness, dental or outpatient surgery. Potential problems during sick days are dehydration, Ketoacidosis, hyperglycemia, hypoglycemia.

"Sick Days" Rules:

- Insulin treatment may need adjustment
- Start out with usual insulin doses
- Adjust insulin doses according to SMBG
- Additional rapid-acting insulin if blood glucose more than 15-16 mmol/L (>300 mg/dl)

Any illness should be reported to the physician when it increases blood glucose levels and causes urine ketones. This is especially important if high blood glucose levels (250 mg/dl or greater) last for more than 6 hours and urine ketones last for more than 6 hours. Insulin requirement may increase during illness and supplemental insulin (5-20% increase above the daily required dose based on blood glucose level) may be required to prevent DKA. Conversely, hypoglycemia may also be encountered in case of gastrointestinal illness and dose reduction in insulin may be required. The patient should continue eating foods and drinking fluids even if there is vomiting, and/or diarrhoea.[19]

Common indications for referral to hospital in sick patients:

Certain special clinical conditions also mandate referral for hospital admission/ specialist care include brittle diabetes, features suggestive of DKA or HHS, severe infections, pre-gestational & gestational diabetes where glycemic control is not achieved, advanced diabetic complications like diabetic nephropathy (proteinuria, serum creatinine> 1.5 mg %) myocardial infarction, etc. Howerver, primary care physicians may require to provide initial treatment to such patients before referring them to a higher centre.

Travel

Patients treated with insulin need to plan travel in advance and seek advice whenever necessary and make sure the availability of the insulin. Bring adequate BG monitoring equipment, carbohydrate and diabetes identity card. Long hour flights crossing time zones need insulin dose adjustment due to changes in meal times. Travelling east will shorten the day and therefore need for less insulin. Travelling west will lengthen the day and need for more insulin.

Pregnancy and Lactation

The diagnosis of gestational diabetes mellitus (GDM) is made when any of the following plasma glucose values are exceeded after a 75g OGTT: Fasting> 92 mg/dl; 1 h postprandial >180 mg/dl; 2 h postprandial> 153 mg/dl. GDM carries significant risks for the mother and the neonate. Therefore. all women with GDM should receive intensive treatment by a multi-disciplinary diabetes-obstetric team. In GDM, target pre-prandial<95 mg/ dl and 2 hour post prandial<120 mg/dl. The risk can be greatly reduced by early institution of insulin therapy, optimization of glycemic control prior to conception is utmost importance and it may need insulin therapy. Insulin is considered the standard treatment in managing gestational diabetes mellitus and T2DM during pregnancy. Standard insulin regimen is basal bolus regimen which allows for easier adjustment of insulin doses, improves glycemic control and pregnancy outcomes. The starting dose of insulin in 1st trimester is 0.7 U/Kg/day, in 2nd trimester is 0.8 U/Kg/day and 3rd trimester is 0.9 U/Kg/day. Insulin is discontinued after childbirth in patients of GDM but may require continuation in patients of pre-gestational diabetes. There is adequate evidence and experience that premixed human insulin can be used in pre-gestational and gestational diabetes, and during lactation, the use of pre-mixed analogues is safe.[21,22,23]

* Recommended glycemic targets of diabetes mellitus in pregnancy

Capillary blood glucose Fasting	- 90-99mg/dl (5.0-5.5 mmol/L)
1hr after starting a meal	- <140 mg/dl (<7.8mmol/L) or
2 hr after starting a meal	- < 120 to 127 mg/dl (<6.7-7.1mmol/L)

Patient who develop Diabetic Kidney Disease

Kidney disease is highly prevalent in T2DM, and moderate to severe renal functional impairment (GFR<60 ml/min) occurs in approximately 20-30% of patients. The risk of hypoglycemia is increased in patients with diabetic kidney disease as insulin and OADs are eliminated very slowly. Therefore, careful titration and reduction in dose of insulin is required in patients with severe renal impairment (GFR<30 ml/min).[21,23]

Patient who has Chronic Liver Disease (CLD)

Insulin is probably the safest form of therapy in diabetic patients with CLD. However, there is also a higher risk of developing hypoglycemia in these patients and adequate precautions are required. Insulin therapy can be in the form of basal regimen in patients who are on OADs. In whom OADs are contra indicated, premixed or basal bolus regimen may be initiated. [21,25]

CHAPTER (9)

PRACTICAL ISSUES

Insulin storage, injection technique and insulin pen devices

Storage of insulin

Vials, Penfills & Pens not in use should be stored between 2°C & 8°C in a refrigerator. Storage in or near freezing compartment is to be avoided, this is more important in case of insulin suspensions. Extreme temperatures (<2° or > 25°C) and excess agitation should be avoided to prevent loss of potency, clumping, frosting, or precipitation. In absence of this facility, the vial/pen device may be kept in a cool place (e.g near a pitcher in kitchen) , away from heat and direct sunlight. In use vials can be-stored at room temperature (up to 25°C) up to 6 weeks (vials) & penfills and pens up to 4 weeks. Pens/ Penfills that are in use need not be kept in refrigerator. Insulin in use may be kept at room temperature to limit local irritation at the injection site, which may occur when cold insulin is used. If possible, the prefilled syringes/ pens should be stored with the needle pointing upward, so that suspended insulin particles do not clog the needle.[11]

Preparing for and injecting insulin

The patient administering insulin should inspect the bottle before each use for changes (i.e., clumping, frosting, precipitation, or change in clarity or color) that may signify a loss in potency. Visual examination should reveal rapid-and short-acting insulin to be clear as well as long acting insulin analogues and all other insulin types to be uniformly cloudy. The necessity of re-suspending the premix/NPH insulin preparation immediately before use is to be stressed to the patient. The re-suspended liquid must appear uniformly white and cloudy. Excess agitation should be avoided.

Conventional insulin administration involves subcutaneous injection with syringes marked in insulin units. In addition, different medical devices have been developed to reduce the risk of needle sticks and other sharps injuries

and make the administration of insulin more convenient. The physician should train the patient on the methods of preparing, loading and injecting from the syringe or the medical device.

The patient should be taught about aseptic precautions to be taken prior to and after injection of insulin. The physician should also teach the patient about proper injection sites, selection and preparation. Injections are made into the subcutaneous tissue. Insulin may be injected into the subcutaneous tissue of the upper arm and the anterior and lateral aspects of the thigh, buttocks and abdomen. However, rotation of the injection site is important to prevent lipohypertrophy or lipoatrophy. Most patients will be able to slightly grasp a fold of skin, release the pinch, then inject at a 90° angle. If an injection seems especially painful or if blood or clear fluid is seen after withdrawing the needle, the patient should apply pressure for 5-8s without rubbing.

Managing needle phobia and information about insulin pen devices

Many patients with Type 2 diabetes have some degree of psychological insulin resistance (PIR), which is a term used to identify the avoidance of insulin initiation by patients. PIR typically represents a complex of beliefs including social issues, such as the stigma that using needles carries in society. Patients may be unable to overcome their insulin therapy reluctance until their personal concerns are recognized and addressed.

Self-Monitoring of blood glucose (SMBG)

The methodology and timing of SMBG should be clearly conveyed to the patients. When a patient begins insulin therapy, SMBG should be increased in frequency. For patients starting basal insulin therapy at bedtime, the morning fasting blood glucose levels should be determined daily. This same approach applies for the patient initiating premixed insulin therapy before dinner. For each additional injection of insulin, SMBG should be increased in frequency to ensure successful titration of each dose. Patients should be taught to keep a register/record of their blood glucose levels. The method of injection and patient's SMBG records should be reviewed by the physician on a periodic basis.[22]

CHAPTER (10)

CONCLUSION

Initiation of insulin therapy is an important stage in management of patients with T2DM. The effective use of insulin to obtain the best metabolic control requires an understanding of the duration of action of the various types of insulin and the relationship of blood glucose levels to exercise, food intake, inter-current illness, and stress. Therefore, physicians and patients should carefully understand the principles of initiation, optimization and intensification of insulin treatment and work closely to overcome possible barriers and develop a physiological regimen that effectively controls fasting and postprandial blood glucose levels.

CHAPTER (11)

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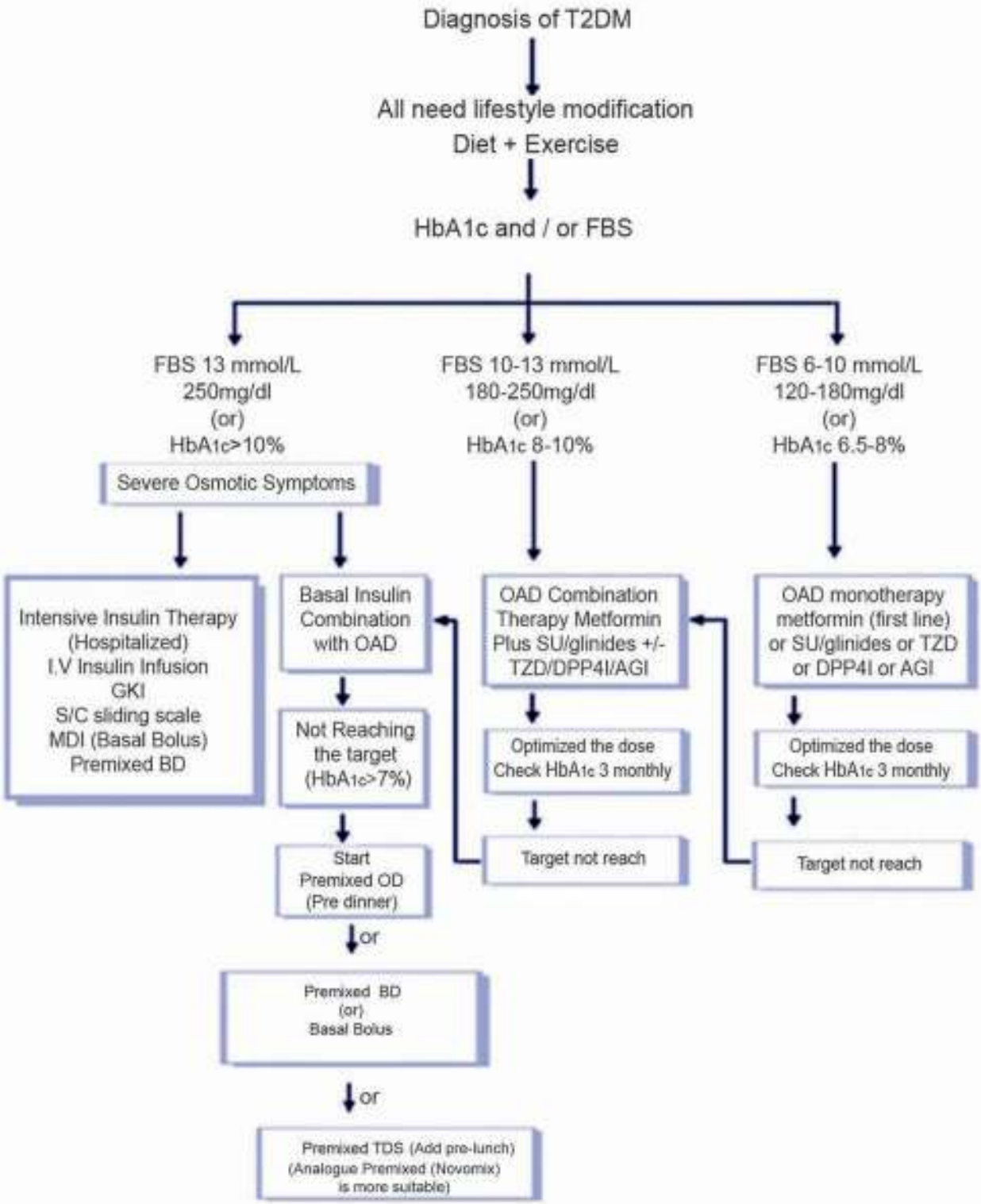
ABBREVIATIONS

T1DM	.....	Type 1 Diabetes Mellitus
T2DM	.....	Type 2 Diabetes Mellitus
GDM	.....	Gestational Diabetes Mellitus
OADs	.....	Oral Anti-Diabetic Drugs
TZDs	.....	Thiazolidine-di-one
SUs	.....	Sulphonylurea
DKA	.....	Diabetic Ketoacidosis
HHS	.....	Hyperglycemic Hyperosmolar state
HONK	.....	Hperglycemic Hyperosmolar Non-Ketoic Coma
NPO	.....	Nil Per Os
MI	.....	Myocardial Infarction
SMBG	.....	Self-Monitoring of Blood Glucose
MDI	.....	Multiple Daily Insulin
CII	.....	Continuous Insulin Infusion
NPH	.....	Neutral Protamine Hagedorn (Isophane Insulin) e.g. Insulatard
OGTT	.....	Oral Glucose Tolerance Test

QUICK REFERENCE GUIDE

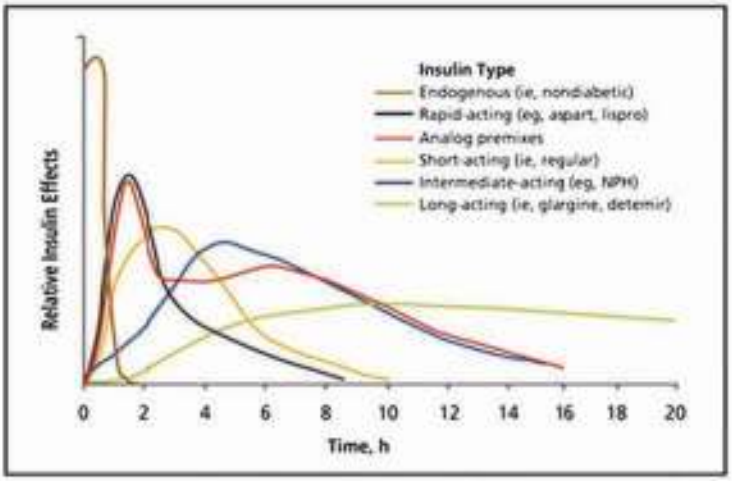
Treatment Algoritham for the menagement of Type 2 Diabetes Mellitus



1. Indication of Insulin

- Type 1 diabetes mellitus
- Newly diagnosed patients with high RBS and severe osmotic symptoms
- Type 2 diabetes with OAD failure
- Acute medical and diabetes emergencies conditions
- Perioperative glycemic control
- Pregnancy (Pre & During Pregnancy)

2. Insulin Action



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3. How to choose insulin regimen ?

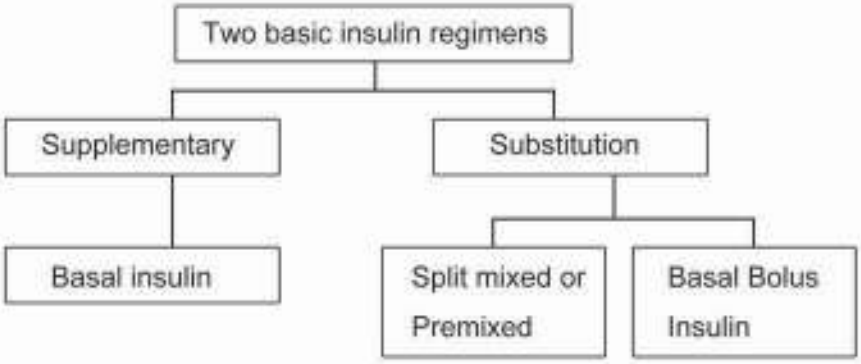
Selecting Initial Insulin Regimen based on blood sugar profile

Blood Glucose Profile		Preferred insulin regimen
Pre-breakfast	Daytime	
High	Normal/Near Normal	Basal (Bed time) or Premixed OD (Pre dinner)
High	High	1. Basal → Basal Plus → Basal Bolus 2. Premixed Insulin: BID
Normal	High	Prandial insulin and later add on basal insulin

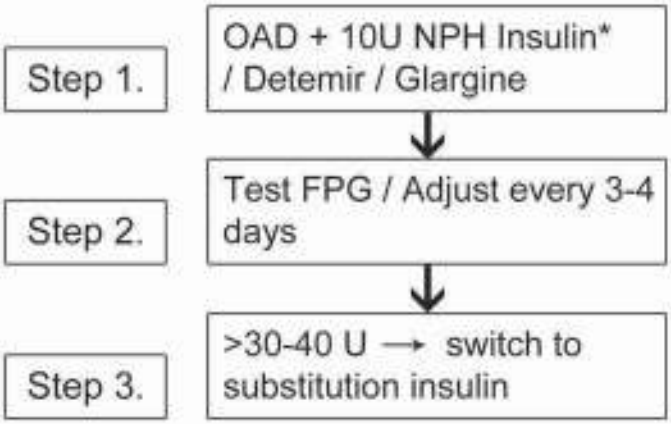
4. Glycemic Target

Parameters	Recommendations
HbA1c (%)	< 7.0
Fasting (mg/dl)	80 - 130
Preprandial (mg/dl)	< 140
Postprandial (mg/dl)	< 180

5. Insulin Regimen



6. Supplementary Insulin Regimen



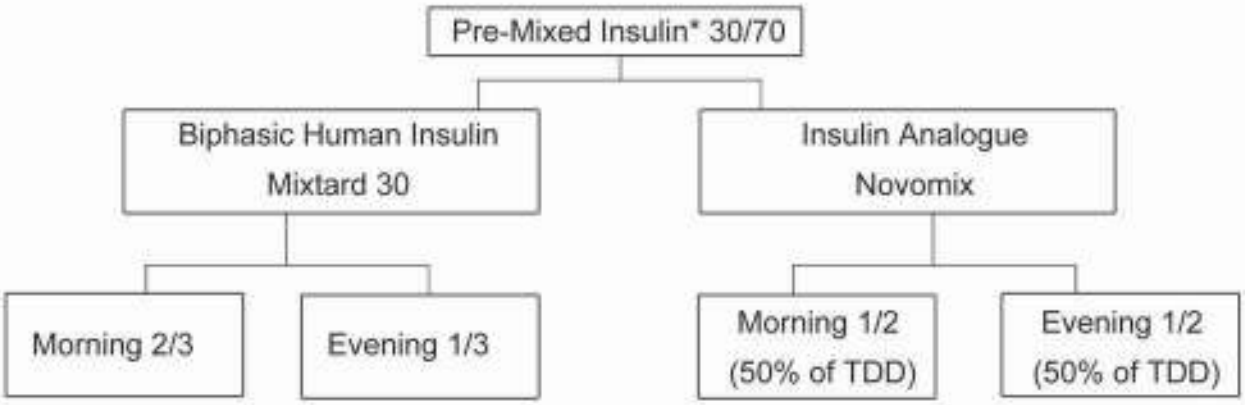
Note: *0.2 units / kg / Day

NPH - at bedtime

Long acting analogue - at anytime

7. Substitution

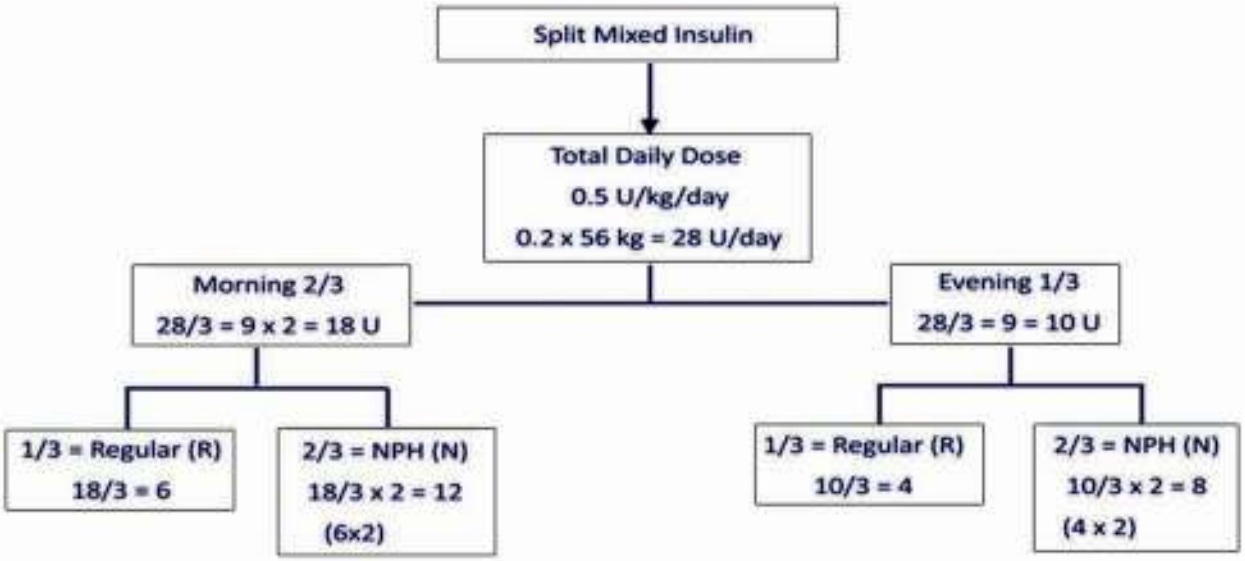
Pre-Mixed Insulin



*0.2-0.5 units/kg/Day

** In case of premix insulin analogues 50% pre-breakfast & 50% pre-dinner

Split-Mixed Insulin (Calculation)

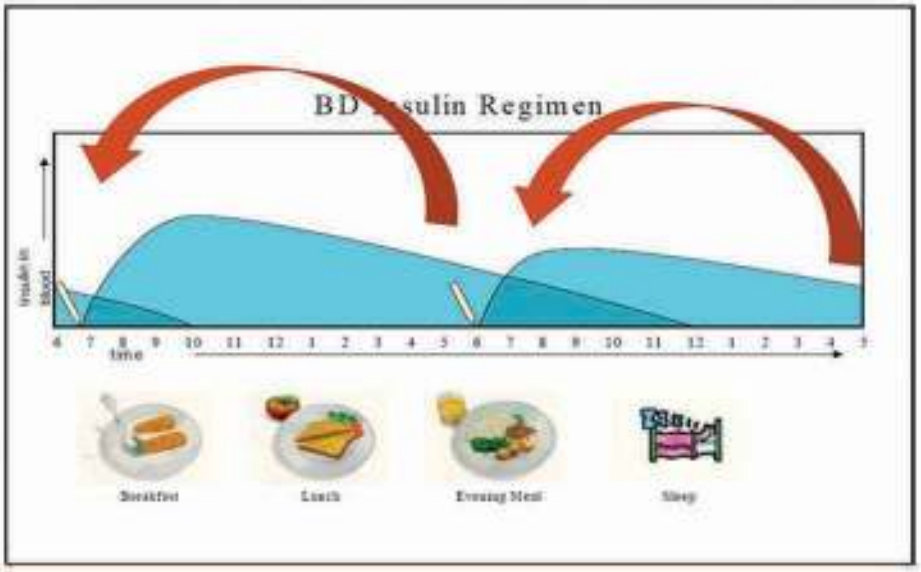


	Regular Rapid acting	Intermediate acting
Morning	6	12
Evening	4	6

Morning ⅔ : Evening ⅓

Regular ⅓ : NPH ⅔

8. Dose adjustment of Pre-Mixed Insulin



Evening RBS ⟷ Morning Insulin
Morning RBS ⟷ Evening Insulin

9. Insulin and blood glucose chart for premixed BD regimen

Day	Pre Breakfast Insulin (Mixtard)	Pre Dinner (BS) (80 - 130)	Pre Lunch (BS) / PPL (120 - 180)	Pre Dinner Insulin (Mixtard)	Pre Breakfast (BS) (80 - 130)	Pre-Bed (BS) (100 – 140)
	2 3 1			2 3 1		

Insulin - Blood Glucose Chart for easy adjustment of Insulin Dose

a. First, record the RBS result at the specific column according to time. Not to adjust the recent dose by using immediate RBS result unless less than 80mg/dl.

b. Then, on the second day, adjust the insulin dose by reviewing the previous day's result.

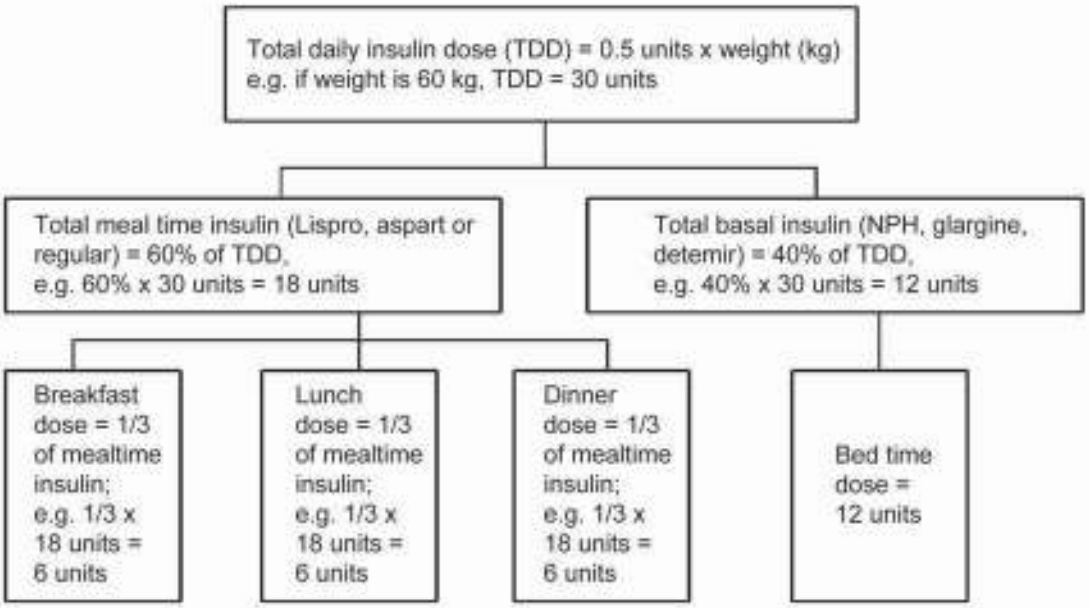
c. Arrow 1 mean: For today's insulin dose, check this (↗) previous day's RBS result whether it is in the range by comparing with target range mentioned at the top of the column.

d. Arrow 2 mean: If not within the range, correct this (←) insulin dose directed by the arrow according to correctional dose as shown in the table

e. Arrow 3: write down the corrected dose at this (↓) place and then inject.

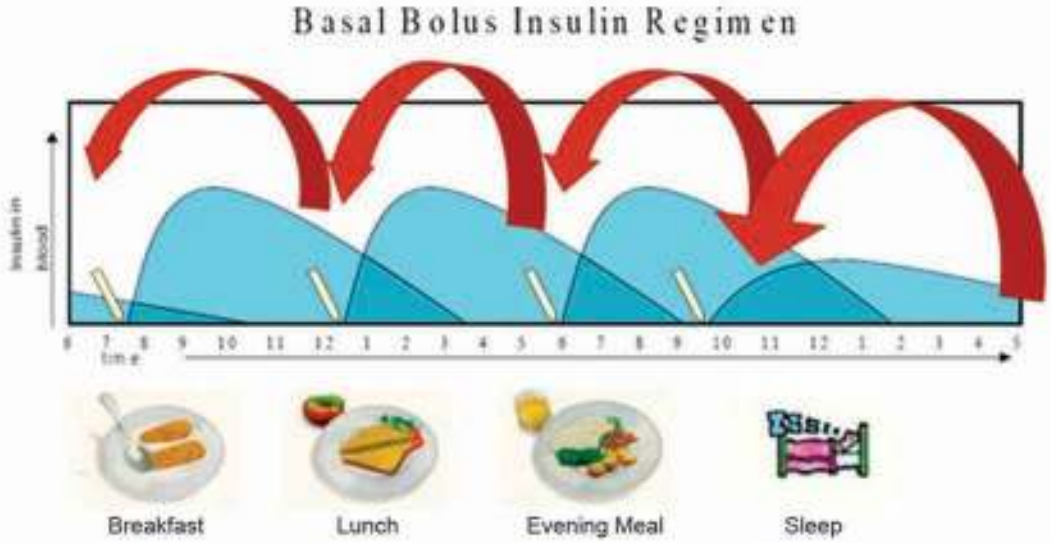
RBS	Correctional Dose	
	Insulin Sensitive	Insulin Resistant
< 80	-2	-4
80 - 130	No change	No change
131 - 200	+1	+2
201 - 250	+2	+3
> 251	+3	+4

10. Basal-Bolus Regimen (Calculation)



Note: For analogue insulin 50% for basal and 50% for total bolus (Pre-meal)

Dose adjustment of Basal Bolus Insulin



Insulin-Blood Glucose Chart for Basal Bolus Regimen

Date	Insulin R bf BF	RBS bf Lunch	Insulin R bf Lunch	RBS bf dinner	Insulin R bf Dinner	RBS bf bedtime	Insulin N bf bedtime	RBS bf BF
								

The meaning of arrow can be referred in Page 53

11. Self Monitoring of Blood Glucose (SMBG)

Recommended timing of SMBG in different insulin regimens

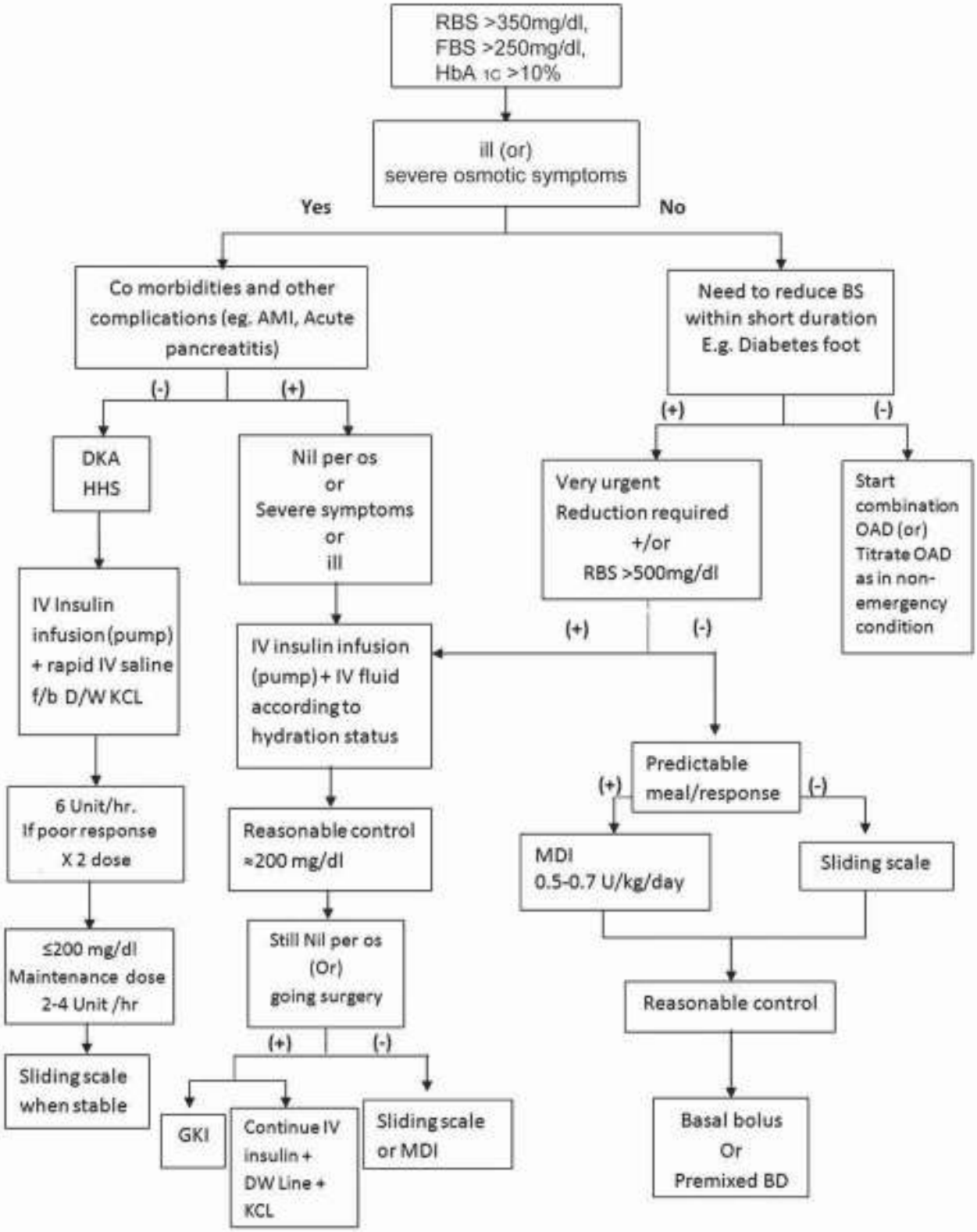
SMBG In Basal / Basal bolus / Premixed Regimen

	Breakfast		Lunch		Dinner		Bedtime
	Pre	Post	Pre	Post	Pre	Post	Pre
Basal only	X						
Basal bolus (short-acting)	X		X		X		X
Basal bolus (rapid-acting)	X	X		X		X	
Pre-mixed	X		X		X		X

Note

* Pre-breakfast glucose readings reflect adequacy of pre-bed basal insulin
* Pre-lunch readings reflect adequacy of pre-breakfast short-acting insulin
* Pre-dinner readings reflect adequacy of pre-lunch short-acting insulin
* Pre-bed readings reflect adequancy of pre-dinner short-acting insulin

12. Algorithm for choice of insulin therapy in patients with high RBS (Hospitalized patients)



13. Glycemic targets for hospitalized patients (AACE - ADA Consensus)

Clinical Conditions	Targets
Non-Critically ill (General Medical and Surgical Patients)	Premeal RBS <140mg/dl (7.8mmol/L) Post-meal RBS<180mg/dl (10mmol/L) Range = 100 to 180
Critically ill (HDU or ICU)	Initate insulin if RBS > 180mg/dl Target of RBS is between 140 and 180mg/dl (7.8 and 10mmol/L)

Note: Higher glycemic targets should be aimed for terminally ill patients with severe comorbidities or patient with inaccessable to glucose monitoring or close supervision.

14. Methods of insulin therapy for hospitalized patients

- Continuous IV Insulin (CII)
- Glucose - K : - Insulin (GKI)
- Multiple Daily Insulin (MDI) / Basal Bolus Insulin
- S/C Sliding Scale Insulin

15. Continuous IV Insulin (CII)

(a) IV Insulin:
Similar to DKA
Initial insulin infusion rate 6-8 U/hr (use syringe pump)
(if no syringes pump, 500U in 500ml N/S .i.e 1U insulin in 10ml or 5 drops/min is approximately equivalent to 2U/hour ie 15~20dpm=6~8 U/hr). When RBS<200mg/dl = maintenance dose of 1-4 U/hr

(b) IV Drip N/S followed by 5% D/W when RBS <200-250 mg/dl

Note: IM insulin injetions is no longer recommended

16. GKI (Glucose - Potassium - Insulin) Regimen

Mix 5% dextrose: 500ml containing 10mEq KCl + 8-10 units regular insulin or 10% dextrose: 500ml containing 10mEq KCl + 14-16 units regular insulin. Dose can be modified according to status of insulin sensitivity. Subsequent insulin dose titration is shown in the table.

Recommendation for insulin dose titration

Blood Glucose	Glucose-Potassium-Insulin Infusion Rate
(mg/dl)	10% Dextrose 500 ml
<80	↓ 4-6 units
<120	↓ 2-4 units
120-180	No change
181-270	↑ 2-4 units
>270	↑ 4-6 units

Serum Potassium(mmol/L)	KCl to be added (mmol/500 CC)
<3	10-13 mmol (0.75- 1 G)
3-5	7.5 -10mmol (0.5 – 0.75 G)
>5	None

17. Basal Bolus Insulin / Multiple Daily Insulin

- Indication - Moderate hyperglycemia, non-critically ill, those who can take oral/Ryle's tube feeding
- Component - Basal + Bolus (nutritional) + Correctional
  Calculation -
  - Starting dose = 0.4 to 0.5 x weight in kilograms
  - Bolus dose (aspart/lispro)=20% of total daily dose at each meal or according to carbohydrate loads

- Basal dose (Detemir / Glargine) = 40% of total daily dose given at bedtime or anytime

18. Subcutaneous insulin sliding scale

Glucose level (mg/dl)	Low Dose Regimen	Medium Dose Regimen	High Dose Regimen	Very High Dose Regimen	Other
100 -150	0	2	4	6	
151-200	2	4	6	8	
201-250	3	6	8	10	
251-300	4	8	10	12	
301-350	6	10	12	14	
351-400	8	12	14	16	
>400	10 Units	14 Units	16 Units	18 Units	

Basal insulin = 0.1 – 0.2 Units /kg

19. Complications of Insulin Therapy

Metabolic	Injection Site	Systemic allergy
Hypoglycemia	Lipohypertrophy	Altered pharmacokinetics
Weight gain	Allergic reactions	Immune Insulin resistance
Insulin oedema	Lipoatrophy	Anaphylaxis
	Local reactions Immediate Delayed	

20. Site of Insulin Injection

Site of injection

- Thighs
- Abdomen
- Arms
- Important to rotate the site
- faster from arm and abdomen than from thigh and buttock

21. Insulin Injection Technique

အင်ဆူလင်ထိုးပုံအဆင့်ဆင့်

Pen-cartridge devices are becoming more popular than the syringe-and-needle system. Replaceable insulin cartridges containing 300 units of regular, NPH, or pre-mixed insulin are used in the pen devices. The dose is dialed into the device, and needles with a very fine gauge are used to minimize the discomfort of injection. This method of insulin administration is convenient, unobtrusive, easy to carry, and very useful for MDI regimens. However, insulins cannot be mixed, so two injections are necessary when both rapid-acting and intermediate-acting insulins are required unless premixed insulins are used

Joslin's diabetes mellitus. --- 13th ed.,2005

ဆေးထားသိုခြင်း။

အေးသောနေရာ၌
ထားရမည်

ပုလွန်းခြင်း
အေးလွန်းခြင်းမှ
ရှောင်ရှားရမည်။

- လက်ကိုဆပ်ပြာနှင့်စင်ကြယ်
အောင်ဆေးပါ။

- အင်ဆူလင်ပုလင်းကို
အကြိမ်များစွာ လက်ထဲ
လှိမ့်ပါ။
- ပြင်းထန်စွာမလှုပ်ခါရပါ။

- အင်ဆူလင်ပုလင်းအဝကိုအရက်ပဲ့စွတ်
ထားသောဝမ်းနှင့်သုတ်ပါ။

- လိုအပ်သောအင်ဆူလင်ကို စုပ်ယူပါ။
- အထစ်သေးတစ်ထစ်သည် နှစ်ယူနစ်ဖြစ်ပါသည်။
- (ဥပမာ-၁၂ယူနစ်အတွက် ၁၀မှတ်အထိ+အသေးတစ်ထစ် စုပ်ရန်)

- ဆေးထိုးပြွန်အတွင်းလေပါမပါ ကြည့်ပါ။
- လေပါနေပါက ဆေးရည်ကိုပုလင်းထဲသို့ ပြန်ထိုးသွင်းပြီး နောက်တစ်ကြိမ် ပြန်စုပ်ပါ။
- လေမပါပါက အပ်ကိုပုလင်းမှ ပြန်ဆွဲထုတ်ပါ။

- ဆေးထိုးမည့်နေရာကို အရက်ပျံငွေ့နှင့်သန့်ရှင်းပါ။
- အရက်ပျံခြောက်အောင် စောင့်ပါ။

- ဆေးထိုးပြွန်ကို ခဲတံကိုင်သကဲ့သို့ကိုင်ပါ။
- အရေပြားကိုလက်ဖြင့်ဖျစ်၍ ဆွဲမလိုက်ပါ။
- ဆေးထိုးအပ်ကိုအရေပြားနှင့် ၉၀ဒီဂရီ ထိုးစိုက်ပြီးဆေးကို ဖြေးညှင်းစွာထိုးပါ။
- ဆေးထိုးအပ်ကို အတည့်အတိုင်း ပြန်ဆွဲထုတ်ပါ။

- ဆေးထိုးအပ်ကို တစ်နေ့တစ်ခါလဲရန် လိုအပ်ပါသည်။
- မသန့်ရှင်းပါက ဆေးထိုးသောနေရာ အနာဖြစ်တတ်သည်။

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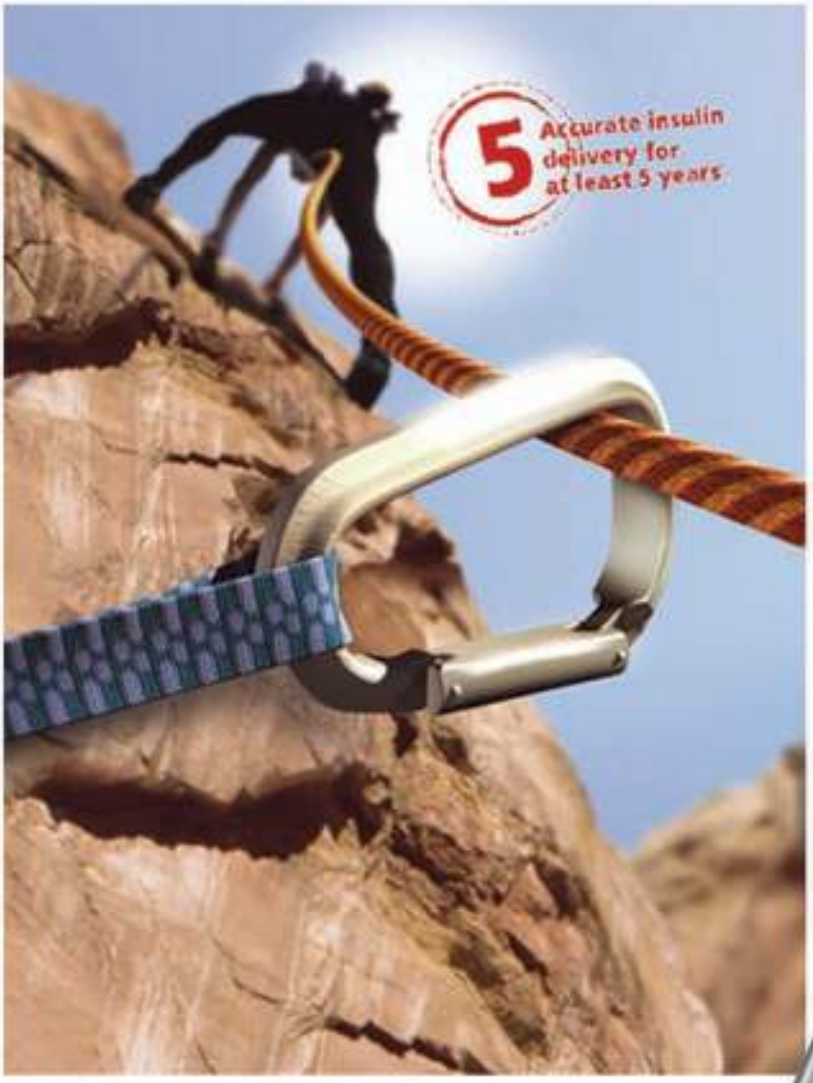

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3 times larger easy-to-read scale
for secure dose setting

Feel
50% less force needed to inject and short push button for controlled dose delivery

Hear
End-of-dose click confirmation for patient convenience

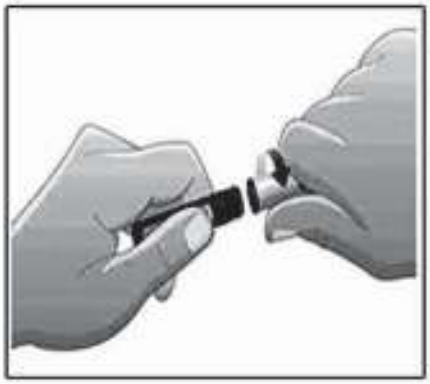
NovoPen®4

The reliable choice

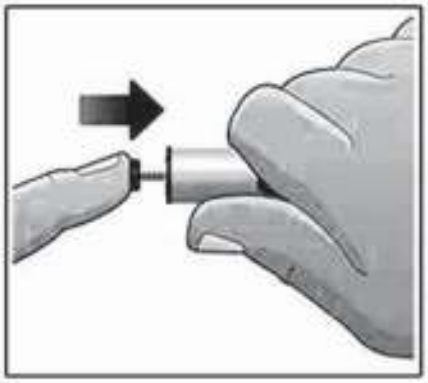
နိုဗိုပန် (ဖိုး)
သုံးစွဲနည်းလမ်းညွှန်

ဆေးထိုးရန် ဆေးထိုးပြွန်အသစ်ထည့်ခြင်း

၁.
အဖုံးချွတ်ပါ။



၂.
ပုံတွင်ပြထားသည့်
အတိုင်းလှည့်လျင်
(၂)ပိုင်း
သီးခြားစီဖြစ်သွားသည်။



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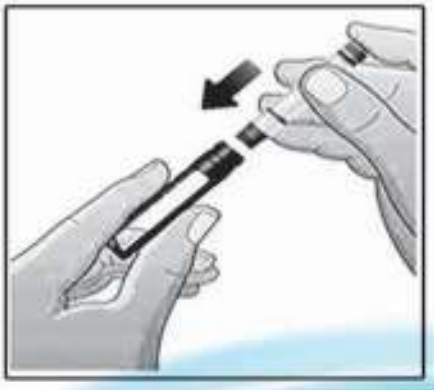
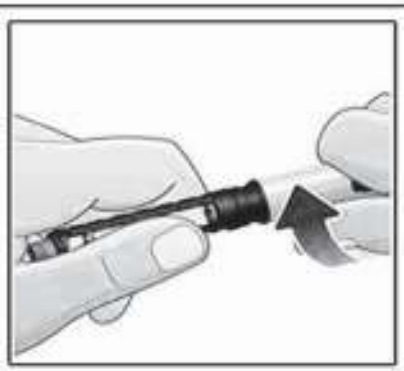
ဖိသွင်းလိုက်ပါ။



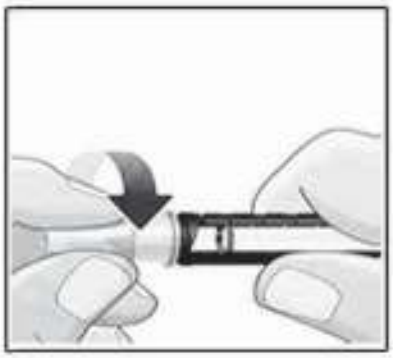
၄.
မိမိသုံးနေကျ
အင်ဆူလင်
မှန်၊ မမှန် အရောင်ကို
စစ်ဆေးပါ။ အင်ဆူလင်
ဆေးရည်ပါပြွန်ကို
အိမ်အတွင်းသို့ထည့်ပါ။

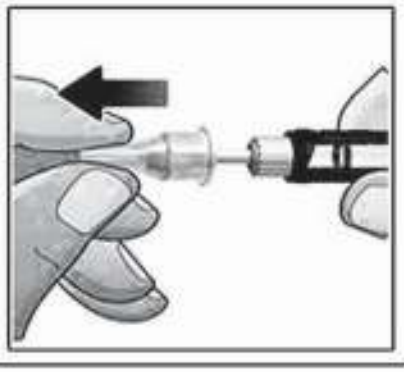
ဆေးထိုးရန် ဆေးထိုးပြွန်အသစ်ထည့်ခြင်း



၅.
လှည့်၍
(၂)ဝိုင်း
ပြန်ဆက်ပါ။

၆.
Novofine
ဆေးထိုးအပ်ကို
ပြထားသည့် အတိုင်း
လှည့်၍ တပ်ဆင်ပါ။





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၈.
ဆေးထိုးအပ်
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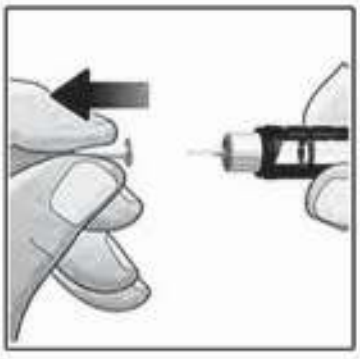


ဆေးထိုးရန် ဆေးထိုးပြွန်အသစ်ထည့်ခြင်း

၉. ခိုနေသော လေကို ထိပ်ဆုံးသို့ ရောက်အောင် ဖြေးညင်းစွာ တောက်ပေးပါ။

၁၀. ယူနစ်ချိန် ခလုတ်ကို ဆွဲထုတ်ပြီး

၁၁. '၁' ယူနစ်သို့ချိန် ပြီး၊ ခလုတ်ကို အပေါ်သို့အသံကြားသည် အထိ တွန်းလျှင် အပ်ဖျားဒဏ် ဆေးရည် တစ်စက် ထွက်လာမည်။

၁၂. မိမိလိုအပ်သော ယူနစ်ရောက်သည် အထိ ခလုတ်ကိုလှည့်ပါ။ 'မ' ယူနစ်များသည် 'စုံ' ယူနစ်များ ကြားတွင် ရှိပါသည်။

ဆေးထိုးရန် ဆေးထိုးပြွန်အသစ်ထည့်ခြင်း

၁၃

မိမိလိုရာ ယူနစ်သို့ ရောက်သည်အထိခလုတ်ကို လှည့်ပြီး ထောင်လိုက် တည့်မတ်စွာ ထိုးသွင်းပါ။ အသံကြားသည် အထိ ခလုတ်ကို လက်မဖြင့် ဖိချပါ။

၁၄

အရေပြားအတွင်း၌ အပ်ကို(၆) စက္ကန့် (၁ မှ ၁၀ အထိ) ကြာအောင် ရေတွက်ခြင်းဖြင့် ထားပါ။

၁၅

အပ်ကို ဆွဲနှုတ်လိုက်ပြီး '၀' ယူနစ် ပြ၊ မပြ စစ်ဆေးပါ။

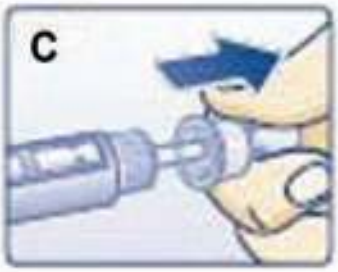
၁၆

အသုံးမလိုသော ဆေးထိုးအပ်ကို အပြင်အဖုံး ပြန်တပ်ပြီးမှ လှည့်ချွတ်ပြီး၊ စနစ်တကျ စွန့်ပစ်ပါ။

Flex Pen အသုံးပြုပုံ

Flex Pen အဖုံးကိုဖွင့်ပါ

Novofine အပ်၏စက္ကူကိုဖွာပြီးအပ်ကို **Flex Pen** တွင်တပ်ဆင်ပါ။ အပ်မှအရစ်ကုန်သွားခြင်းကို ကလစ်ဟူသော အသံ ကြားခြင်းဖြင့် သိရှိနိုင်သည်။



ဆေးထိုးအပ်အပြင်ဖုံးကိုဖွင့်ပါ။

ဆေးထိုးအပ်အတွင်းဖုံးကိုဖွင့်ပါ။

Flex Pen အသုံးပြုပုံ

ယူနစ်ချိန်ခလုတ်ကို (၂)ယူနစ်အထိလှည့်ပါ။

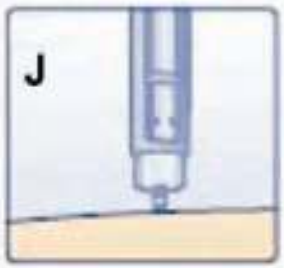
Flex Pen ကိုအပေါ်သို့ထောင်ပြီး အတွင်းလေပိုမှုမရှိစေရန် လက်ညှိုးနှင့် (၂)ကြိမ်ခန့် အသာတောက်ပါ။

၂ယူနစ်အထိ ချိန်ထားသောခလုတ်ကို အပေါ်သို့တွန်းလိုက်ပါ။ အပ်ဖျားတွင် ဆေးရည်သီးလားခြင်းရှိမရှိကြည့်ပါ။

ယူနစ်ချိန်ခလုတ်ကို မိမိထိုးရမည့် အင်ဆူလင်ယူနစ်ရောက်သည်အထိလှည့်ပါ။ ယူနစ်ပိုသွားပါက နောက်ပြန်လှည့်ခြင်းဖြင့် ယူနစ်အတိုး အလျော့ချိန်ညှိနိုင်ပါသည်။ **Flex Pen** အတွင်းကျန်ရှိသော အင်ဆူလင်ပမာဏထက်ပိုပြီး ယူနစ်ချိန်ခလုတ်ကို လှည့်မရနိုင်ပါ။

Flex Pen အသုံးပြုပုံ

Flex Pen ကိုအရေပြားအောက်သို့ ထိုးသွင်းပြီး ခလုတ်ကို လက်မနှင့် ဖိနှိပ်ခြင်းဖြင့် အင်ဆူလင်ကိုထိုးပါ။



ဆေးထိုးရာတွင်ဆေးထိုးသည့်နေရာနှင့် **Flex Pen** သည် **90'** ဖြစ်နေရမည်။ အင်ဆူလင်ယူနစ်အားလုံး အရေပြားအောက်ရောက်ရှိစေရန် ဆေးထိုးပြီး (၆) စက္ကန့်ကြာသည်အထိ (၁ မှ ၁၀ ရေတွက်ပါ) အပ်ကိုကိုင်ထားပါ။

အသုံးပြုပြီးသောအပ်ကို အပြင်အဖုံးပြန်လည်တပ်ဆင်ပြီးမှ လှည့်ချွတ်ပြီး စနစ်တကျစွန့်ပစ်ပါ။

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