Management of Glycemia in Acute Febrile Illness

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Abstract

With increasing the prevalence of diabetes and prediabetes across the globe, a large number of patients with acute febrile illness (AFI) are likely to have concomitant diabetes or stress hyperglycemia. Management of associated hyperglycemia in patients with AFI is of utmost importance for early recovery and to prevent complications. There is no published literature, detailing the strategies and targets for glycemic control in AFI specifically; however, guidelines do exist for the management of hyperglycemia in hospitalized or outpatients in general. This review attempts to provide pragmatic and practical suggestions to facilitate effective and safe management of hyperglycemia in patients with AFI.

Keywords: Acute febrile illness, chikungunya, dengue, diabetes, fever, insulin, malaria, stress hyperglycemia

INTRODUCTION

Acute febrile illness (AFI) refers to a syndrome of suddenly occurring fever, which may not be associated with localizing symptoms, signs or unique laboratory anomalies. A wide variety of etiologic factors may cause AFI. These include infections such as bacterial, viral, protozoan and chlamydial organisms, and noninfectious causes including inflammations, malignancies, and trauma.

The ubiquitous occurrence of AFI and the rapidly increasing prevalence of diabetes, suggests that both may co-occur at some time or the other, in most individuals with diabetes. AFI may unmask preexisting, but undiagnosed diabetes; may be associated with stress hyperglycemia; may be treated by drugs which can cause hyperglycemia (steroids, dopamine) or hypoglycemia (quinine) and may have atypical presentations (e.g., lack of fever, lack of neutrophilia, relative bradycardia) in persons with diabetes. Infections such as chikungunya and dengue fever have a significant negative impact on glycemic control and result in greater morbidity in diabetics as compared to nondiabetics.

Good glycemic control is known to influence clinical outcomes in both surgical and medical illness. Various studies have shown the beneficial effects of tight glycemic control, achieved through intensive insulin therapy, in critically ill persons with hyperglycemia. Evidence is also available to support the use of insulin in infections such as tuberculosis.

NEED FOR GUIDANCE

There is no published literature; however, detailing the strategies and targets for glycemic control in AFI, as AFI is a heterogeneous group of diseases. It is more plausible, however, that AFI place a disproportionate burden on the developing world, which has relatively less resources and trained workforce to generate and publish evidence-based data and recommendations. It is also noteworthy that the management of AFI cannot be straitjacketed into compartments of “critically” and “noncritically” ill; there will be many patients of AFI with compromised oral intake, due to either gastrointestinal and/or cognitive dysfunction, not willing to, or unable to, receive critical care because of lack of availability, accessibility, affordability, or acceptability. This is especially true in third world countries, which bear the brunt of AFI.

These factors create a need for guidance regarding management of glycemia in AFI in developing countries. Such guidance should be pragmatic and practical, accurate and appropriate.

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Hypoglycemia must be avoided at all costs,[11] and glycemic variability should be minimized. Stress hyperglycemia and acute decompensation of hitherto well-controlled diabetes are frequently encountered in meningitis, dengue fever and chikungunya fever, and should be brought down to euglycemic levels.

Glycemic targets may be modified by the availability and frequency of blood glucose monitoring (BGM) facilities. The target levels of glycemia should be inversely proportional to the frequency of BGM. In malaria, which is associated with a high glucose turnover, and a high risk of hypoglycemia, glycemic targets may be relaxed.

**Noninsulin Glucose Lowering Medication**

Most oral glucose lowering drugs can be used without dose modification in patients with AFI. Conventional/traditional sulfonylureas should be stopped and substituted by safer drugs, while modern sulfonylureas (gliclazide modified release, glimepiride) can be used in reduced dose.[13] Scored tablets allow the flexibility of self-titration by the patient, depending on the oral intake. Drugs such as metformin and glucagon-like peptide 1 receptor agonists (GLP1RA) may need dose adjustment if they are perceived to contribute to gastrointestinal symptoms. Patients on long-acting GLP1RA may wish to reduce the frequency of injections during intercurrent AFI complicated by nausea and vomiting: however, regular BGM is important.

**Insulin**

Insulin is the best way to control hyperglycemia in the inpatient setting especially in the critically ill patients. Intravenous insulin with continuous infusion is recommended in critically ill patients with AFI. The majority of noncritical ill hospitalized patients can be managed with multiple subcutaneous insulin injections. Patients already on insulin may need to reduce their dose according to oral intake/carbohydrate counting and BGM. Insulin analogs with a lower risk of hypoglycemia are preferred in such situations.[14] Rapid acting analogs offer the flexibility[13] of being injected after meals, thus allowing dose titration based on oral intake. Patients on basal bolus regimens may have to de-escalate to basal plus regimens if meals become infrequent.

**Adequate Oral Intake**

Patients treated by diet alone usually need no specific hypoglycemic therapy. However, frequent BGM is advised to check for hyperglycemic episodes. Patients treated with oral antihyperglycemic drugs can continue their usual drug regimen in some circumstances (patient eating well, glucose well-controlled, and no contraindication to oral agents). If blood glucose are poorly controlled with the usual oral agents or if the patient is not eating, drug therapy should be discontinued, and insulin should be initiated. Insulin therapy should be continued in all patients already taking it to maintain basal level of circulating insulin.

### Table 1: Causes of dysglycemia in acute febrile illness

| Causes of hyperglycemia | Disease related |
|-------------------------|----------------|
| Stress hyperglycemia    | Acute pancreatitis |
| Iatrogenic/treatment related |
| Drugs-steroids, dopamine, quinolones (gatifloxacin, levofloxacin) |
| Use of dextrose containing fluids in inpatients |

| Causes of hypoglycemia | Disease related |
|------------------------|----------------|
| Certain infections with high glucose turnover like malaria |
| Sepsis |
| Poor oral intake |
| Deranged liver or kidney function related to acute febrile illness |
| Secondary adrenal insufficiency associated with certain infections (tuberculosis, histoplasmosis) and malignancies (lymphomas, carcinoma breast) |
| Iatrogenic/treatment related |
| Drugs-quinine, fluoroquinolones (ciprofloxacin, levofloxacin), metronidazole, sulfamethoxazole-trimethoprim, clarithromycin, tramadol |
| Inadvertent higher dose of insulin or oral drugs like sulfonylureas |

Flexible, and physiology based. For lack of published data, such guidance should be based on collective experience. It should provide a framework which is applicable to a wide spectrum of AFI (from infections to noninfections), health-care levels (from primary to tertiary), health-care resources (from extremely challenged to optimal), and geographies (from the first world to the third world).

### Existing Recommendations

Comprehensive recommendations are available for the management of hyperglycemia in inpatient settings.[10] The same guidelines apply to the management of AFI in critical as well as noncritical hospitalized patients. Patient-centered guidance is also available regarding the management of diabetes in outdoor settings.[12] This brief communication adds experience to already published evidence-based guidelines on glycemic management. It focuses on the specific needs of persons with AFI and hyperglycemia.

Persons with AFI may have compromised gastrointestinal, renal, hepatic and cognitive dysfunctions or may experience significant asthenia and/or cachexia. In a setting with limited health-care resources, such patients may or may not have access to screening, diagnostic, and monitoring of glucose. Glycemic management strategies have to take these factors into account. Patients may have to opt for domiciliary treatment or day care treatment, because of the limited availability of indoor beds and/or medical staff. This may also impact strategies and goals of glycemic management.

### Glycemic Targets

Patients with AFI should aim to achieve glycemic targets similar to those of patients with other medical illnesses.
Compromised Oral Intake
Oral intake may be compromised, to varying degrees, and for varying durations during AFI episodes. This may be due to multiple factors, including altered taste, nausea, vomiting, oral ulcers, and drug-induced gastritis.

Patients of AFI who are unable to take regular and sufficient oral calories may need modification of dietary advice and pharmacotherapy. Patients should be encouraged to consume adequate calories, including fruits, fresh fruit juices, and easily digestible vegetables, cereals, eggs, and yoghurt. Protein and complex carbohydrates, which are relatively difficult to digest, may be taken as per gastrointestinal tolerability. A simple adage which may be used to encourage consumption of healthy, home cooked food is to suggest preparation and serving of foodstuffs similar to a weaning diet, in small portion sizes, at frequent intervals.

Concomitant Corticosteroid Therapy
Subcutaneous insulin using a basal or multiple daily injections regimen will be the most appropriate choice to achieve glycemic control in the majority of patients with steroid-induced or worsened hyperglycemia. Morning administration of basal human insulin may closely fit the glucose excursion induced by a single morning dose of oral steroid. Basal analog insulin may be appropriate if hyperglycemia is present for more prolonged periods. However, care should be taken to identify and protect against hypoglycemia overnight and in the early morning if long-acting insulin analogs are used in this context.

Compromised Hepatorenal Function
AFI may be associated with transient derangement in hepatic and/or renal function. Glycemic management strategies should be re-evaluated in such cases, and appropriate regimen or dose modifications made. In patients with clinically or biochemically significant hepatic/renal dysfunction, rapid acting insulin in small, frequent doses is the safest means of managing hyperglycemia. Insulin acts immediately, has no contraindications, requires no biochemical monitoring apart from BGM, and can be titrated rapidly.

Compromised Sensorium
Altered sensorium is a part of many AFI syndromes, including meningitis and cerebral malaria. Sensorium may be altered due to bacteremia/viremia/parasitemia or may be due to dyselectrolytemia. Altered sensorium is an absolute indication to discontinue noninsulin antidiabetic therapy and to initiate insulin, if not done so already.

Intravenous insulin is the drug and route of administration of choice in such patients. If facilities for delivery and monitoring of intravenous insulin are not available, intramuscular or subcutaneous rapid-acting insulin may be used. Intramuscular insulin absorption is highly variable and should be used only under expert oversight.

Elderly
In AFI and elderly, the symptoms associated with hyper- or hypoglycemia may be atypical. Therefore, elderly patients need to take extra precautions on sick days to avoid diabetic crises. The elderly are vulnerable to hyperglycemia and dehydration, hyperosmolar hyperglycemic syndrome because insulin sensitivity and thirst mechanisms decrease with increasing age. Frequent BGM is recommended and sick-day plan management is important in elderly and AFI because of heterogeneity of presentation.

Cachexia/Asthenia
Many patients with AFI, during the febrile or convalescence phase, complain of generalized weakness, or lack of energy (asthenia), with or without wasting, loss of weight, muscle atrophy, fatigue, and loss of appetite (cachexia). Such cases may not require admission to indoor care facilities but must be provided intensive medical support.

As per existing guidelines, insulin is the drug of choice in such situations. This fact should be highlighted to all health-care professionals associated with AFI management. Insulin has anabolic and anti-inflammatory properties which may support resolution of AFI. Therefore, insulin should be initiated, if not done so already, in patients with AFI-related asthenia and cachexia. An insulin regimen which provides both prandial and basal coverage, such as premixed/dual action or basal plus/basal-bolus insulin, is preferable. Patients may revert to preexisting therapy once normal health is restored. We have noticed decompensated hyperglycemia lasting for weeks in patients recovering from chikungunya fever. This hyperglycemia is associated with severe arthralgia and arthritis. Such patients respond better to short-term insulin therapy, which can be discontinued once symptoms abate.

Resolution
AFI, by definition, are acute and should respond to appropriate curative and supportive therapy. Once AFI is resolved, oral intake and systemic functions are normal, and convalescence is over, patients can revert to their earlier therapeutic regimens and doses.

Summary
This brief communication provides pragmatic and practical suggestions to facilitate effective and safe management of hyperglycemia in patients with AFI. It offers a simple, clinical framework, based on presence or absence of symptoms, signs and laboratory anomalies, to guide glycemic management. This flexible framework will help health care professionals manage AFI, complicated by diabetes, in a more efficient manner. This should achieve best possible outcomes, within available means and resources.

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Conflicts of interest
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