BRIEF COMMUNICATION

Insulin Stewardship in Times of Change

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A century has passed by since insulin was discovered, and times are now changing. The last few decades have seen an unprecedented evolution in the preparations and delivery devices of this life-saving hormone. Newer analog insulins have replaced earlier formulations such as lente, semilente, and ultralente insulin, as well as bovine and porcine insulins. Modern delivery devices, including next-generation insulin pen and pumps, coexist with traditional needles and syringes and vials[1]. Many insulin manufacturers, located in countries as diverse as Poland and India, have also been taken over by large competitors.

All these changes have been taken in stride by the diabetes care ecosystem. Each time a disruption in insulin source, preparation or delivery device has occurred, it has been said to be "for the better". The justification given has been that purity has improved, insulin "security" has been stepped up, or efficacy, safety and tolerability have been enhanced[2]. This has allowed advocates of change to browbeat custodians of conservatism into accepting newer insulins, even if they are more expensive or less equitable. Persons living with diabetes, and those who care for them, have therefore had to manage with the alternatives on offer.

Today, however we face a different challenge. Certain types of insulins, and some insulin delivery devices, are being withdrawn from the global as well as South Asian market. These include disposable pens and reusable cartridges of some human insulin brands, and originator formulations of biphasic aspart (BIAsp), detemir and insulin degludec liraglutide (IDegLira)[3]. No "newer" or ultramodern insulin has been developed to replace them. However, existing preparations, such as lispro, LisproMix, aspart, insulin degludec aspart, degludec, glargine U100, glargine U300, and glulisine will continue to be available in most South Asian countries. The withdrawal of popular insulins from the market has led to multiple complaints, concerns, and challenges. Complaints from consumers, who are unable to source their life-saver, and do not know what to do; concerns from policymakers, who wonder how to ensure procurement of sufficient supplies; and challenges for diabetes care professionals, who are unsure how to substitute or interchange various insulins, abound.

In this expert opinion, we share suggestions on insulin stewardship at a macro-, as well as micro- level. We draw upon debate about insulin security and insulin equity[4], to call for a global movement to ensure adequate availability and accessibility of affordable insulin supplies, in an enduring (sustainable) and equitable manner, with strong safeguards for quality control. Cessation of production of insulins has led to concerns regarding insulin security. While Bangladesh, China, and India have a wide choice of reliable insulin manufacturers to choose from, the same is not true for most other countries in the world. It may be prudent, therefore, to call for stockpiling of insulin by global health organizations. This would be similar to maintenance of back up stocks for petrochemicals, food grains, and vaccines.

Table 1 lists pertinent aspects of insulin security and stewardship, which must be addressed by policymakers, planners, and professionals. It enumerates features that need focus at a national or regional level, and also those that must be addressed at institutional, departmental, and individual platforms.

Keeping recent as well as anticipated disruptions in mind, Table 2 suggests a pragmatic way of interchanging insulin if availability is hampered. Preparations should be substituted by available alternatives with similar pharmacokinetic and dynamic characteristics, in a similar price range. Similarly, insulin delivery devices that are similar to the ones in current use should be preferred. Intensive glucovigilance and pharmacovigilance must be instituted whenever an insulin brand is substituted. Professional leaders should use relevant educational platforms to spread awareness about rational shift and substitution of insulin, keeping local reality in mind[5]. Table 3 summarizes our responsibilities in today's world, which is characterized by constant change.

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Table 1. Insulin Stewardship at Macro Level

Production
- Diversity in production facilities
- Minimizing vulnerability to disruption
- Stockpiling insulin as an essential commodity

Procurement and Processing
- Supply chain management
- Cold chain maintenance
- Equity in distribution and delivery

Resource husbandry
- Price stability
- Affordability
- Free insulin for the needy

Resilience
- Adaptability to change in supply and demand
- Disaster management (both natural and manmade)
- Rational label substitution/ interchange if needed

Person-centered pharmacovigilance
- An empathic ear for the end-user
- Good clinical practices, including glucovigilance
- Pharmacovigilance

Innovation
- Protect intellectual rights
- Foster innovation and improvement
- Value added services to enhance convenience and comfort

Quality control
- Green manufacturing practice
- Ensure consistency in quality
- Focus on efficacy, safety, and tolerability

Table 2. Insulin Interchange Policy

Pre-existing insulin preparation	Preferred insulin preparation/device
Human insulin	• Same originator brand in vial: Keep same dose, focus on injection technique • Biosimilar human insulin in similar device: Keep same dose
Basal insulin: Detemir	• Glargine/degludec: Reduce starting dose by 20% • Inj NPH insulin: Keep same dose
Premixed analog insulin: Biphasic aspart (BiAsp)	• Biosimilar BIAsp in same dose, if available • LisproMix or IDegAsp in same dose
Insulin degludec liraglutide (IDegLira)	• Inj glargine lixisenatide (iGlarLixi): Keep same units of glargine as those of degludec • Degludec + oral semaglutide: Keep same dose of degludec; convert 0.6 mg liraglutide to 3 mg oral semaglutide • Degludec + injectable semaglutide/ tirzepatide: Keep same dose of degludec; convert 0.6 mg liraglutide to 0.25 mg semaglutide or 2.5 mg tirzepatide/week
Inj liraglutide	• Biosimilar liraglutide in same dose, if available • Oral semaglutide: Convert 0.6 mg liraglutide to 3 mg oral semaglutide • Injectable semaglutide/tirzepatide: Convert 0.6 mg liraglutide to 0.25 mg semaglutide or 2.5 mg tirzepatide/week

Table 3: Responsibilities Toward Insulin Stewardship: The AEIOU Framework

- **Awareness and Advocacy:** Be aware of current status of insulin availability; advocate for enhanced accessibility and affordability.
- **Education:** Educate all stakeholders about rational interchange of insulin preparations, brands and delivery devices, while being realistic.
- **Intensification of care**: Intensify glucovigilance, i.e., glucose monitoring during any change of insulin
- **Optimization:** Optimize availability of insulin in your health care system, through proactive measures.
- **Upgradation:** Upgrade pharmacovigilance and glucovigilance strategies and styles, especially during times of change

We advocate for insulin security, as well for insulin equity, at a global level. We advocate for health.

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