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Beyond Antibiotics: A Practical Guide to Host-Directed Therapy in Severe Infections

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Abstract

Background: While antimicrobial therapy and source control are the pillars of infectious disease management, host factors significantly influence outcomes. Metabolic derangements, malnutrition, and immune dysregulation contribute to treatment failure and prolonged recovery in patients with severe infections such as sepsis, necrotizing soft tissue infections, and diabetic foot infections. **Objective:** To provide a practical, evidence-based review of non-antimicrobial interventions—specifically glycemic control, nutritional support, immunomodulation, and early rehabilitation—that optimize host resilience. **Methods:** We reviewed current guidelines and key randomized controlled trials published between 2010 and 2026 regarding adjunctive care in severe infections. **Results:** Moderate glycemic control (140 - 180 mg/dL) with attention to glycemic variability is superior to intensive control, reducing hypoglycemia without compromising immune function. Early enteral nutrition is preferred over parenteral routes, with a focus on phase-appropriate protein supplementation. Adjunctive corticosteroids benefit specific subsets, such as patients with refractory septic shock or severe community-acquired pneumonia. Early mobilization and delirium prevention strategies significantly reduce long-term disability. **Conclusion:** Integrating these "host-directed" interventions into a standardized care bundle can improve clinical outcomes. Clinicians should adopt a multidisciplinary approach that treats the patient's metabolic and functional status with the same urgency as the infection itself.

Keywords

Sepsis, Glycemic Control, Clinical Nutrition, Host-Directed Therapy, Critical Care, Rehabilitation

1. Introduction

The management of severe infectious diseases has traditionally been pathogen-centric. The primary goals are rapid identification of the causative organism, initiation of appropriate antimicrobial therapy, and source control (e.g., drainage, debridement) [1]. Despite advances in these areas, mortality from sepsis remains high, and survivors often suffer from significant long-term physical and cognitive impairments [2].

This discrepancy highlights a critical gap: the host's physiological response to infection. Hyperglycaemia, catabolism, immune paralysis, and muscle wasting create an internal environment that hinders recovery and increases susceptibility to secondary complications [3]. This concept, known as **Host-Directed Therapy (HDT)**, focuses on modulating the host's response to enhance resilience and repair [4].

While HDT is well-established in chronic infections like tuberculosis, its application in acute bacterial infections is often fragmented. This narrative review synthesizes current evidence into a practical framework for clinicians, focusing on four manageable pillars: glycemic control, nutrition, immunomodulation, and functional recovery.

2. Glycemic Control: Avoiding the Extremes

Stress hyperglycemia is a common feature of severe infection, driven by the release of cortisol, catecholamines, and pro-inflammatory cytokines. While mild hyperglycemia may be an adaptive energy source, persistent elevations impair neutrophil function, increase oxidative stress, and promote biofilm formation [5].

2.1. Evidence Summary

The landmark **NICE-SUGAR trial** demonstrated that intensive insulin therapy (targeting 81 - 108 mg/dL) increased mortality and severe hypoglycemia compared to conventional control (<180 mg/dL) in critically ill adults [6]. Subsequent analyses have confirmed that hypoglycemia is an independent predictor of death and neurological injury [7].

Recent data emphasizes **glycemic variability** (GV) as a key metric. High GV, measured by coefficient of variation, is associated with endothelial dysfunction and worse outcomes, even if mean glucose levels are acceptable [8] [9]. A contemporary systematic review confirmed that glycemic variability is an independent predictor of ICU mortality across diverse patient populations [10].

2.2. Practical Recommendations

- **Target Range:** Maintain blood glucose between **140 - 180 mg/dL (7.8 - 10.0 mmol/L)** for most hospitalized patients with severe infection [1].
- **Monitoring Variability:** Use point-of-care testing every 1 - 2 hours during insulin titration. Continuous Glucose Monitoring (CGM) is emerging as a useful tool to detect variability and minimize glycemic excursions [11].

- **Avoid Hypoglycemia:** Treat glucose <70 mg/dL immediately. Hypoglycemia is more dangerous than moderate hyperglycemia.
- **Diabetic Foot Infections:** In non-critical settings, aim for tighter control (HbA1c <7%) post-discharge to prevent recurrence, but avoid aggressive lowering during the acute inflammatory phase [12].

3. Nutritional Support: Timing and Composition in Severe Infection

Severe infection triggers a profound metabolic response to stress (MRS) characterized by three distinct phases: acute (hypermetabolic catabolism), subacute (transition), and chronic (recovery or persistent catabolism) [13]. Understanding these phases is crucial for phase-appropriate nutritional therapy, as inappropriate timing or dosing can exacerbate metabolic dysfunction and impair recovery [13].

3.1. The Phased Approach to Nutrition

Acute Phase (Days 1 - 3): During the initial 72 hours, patients experience intense catabolism with anabolic resistance and endogenous energy production estimated at 500 - 1400 kcal/day [13] [14]. Early full feeding during this phase adds to endogenous production, potentially causing overfeeding, suppressing protective autophagy, and increasing complications [13] [14]. **Stabilization & Recovery Phase (Day 4+):** As hemodynamic stability improves and vasopressor requirements decrease, endogenous production declines and exogenous nutrition becomes essential [13] [14].

3.2. Energy Targets: Avoiding Early Overfeeding

Current **ESPEN** guidelines strongly recommend hypocaloric nutrition not exceeding 70% of energy expenditure (EE) during the first week of critical illness [14]. This is supported by the **NUTRIREA-3 trial**, which demonstrated that low calorie/protein feeding during the first 7 days in ventilated adults with shock resulted in faster readiness for discharge compared to standard feeding [15]. After day 3 - 4, energy delivery can be progressively increased to 80% - 100% of measured EE as the patient transitions to an anabolic metabolism [13] [14]. Indirect calorimetry remains the gold standard for determining EE; predictive equations should be avoided when possible due to significant inaccuracy [14]. If indirect calorimetry is unavailable, oxygen consumption (VO_2) from a pulmonary arterial catheter or carbon dioxide production (VCO_2) from the ventilator can be utilized to calculate EE. In instances where neither indirect calorimetry, VO_2, nor VCO_2 can be secured, a weight-based equation (20 - 25 kcal/kg/day) may be used as a last resort to determine energy targets [14].

3.3. Protein Provision: Challenging the High-Protein Paradigm

Recent evidence challenges the routine use of high-dose protein supplementation in critical illness. **ESPEN 2023** recommends 1.3 g/kg/day of protein equivalents

delivered progressively [14]. The **EFFORT Protein** and **PRECISe** trials demonstrated that higher protein dosing (targeting >2.0 g/kg/day) showed no overall mortality benefit and suggested potential harm, particularly in patients with acute kidney injury, alongside higher gastrointestinal intolerance and reduced health-related quality of life [16] [17]. Mechanisms of potential harm include anabolic resistance, mitochondrial toxicity from high ammonia levels, and increased glucagon promoting amino acid catabolism [13] [14].

3.4. Route of Administration: Enteral Nutrition Preferred

ESPEN 2023 strongly recommends early enteral nutrition (EN) within 48 hours for patients whose gastrointestinal (GI) tract is functioning but oral intake is not possible, rather than delaying EN or initiating early parenteral nutrition (PN) [14]. EN preserves gut barrier function and reduces infectious complications. Continuous EN is preferred over bolus administration to reduce diarrhea [14].

However, in patients who are hemodynamically compromised, ASPEN guidelines advise withholding EN until full resuscitation is achieved, and the initiation of EN should be observed closely in those undergoing withdrawal of vasopressor support [18]. Furthermore, PN should be withheld for the first 7 days if EN is feasible, even if caloric targets are not met; PN may be initiated during the first week only when oral and EN are strictly contraindicated [13] [14].

3.5. Immunonutrition and Micronutrients

- **Immunonutrition and Metabolic Modulation:** The type of nutrient utilized can significantly influence the metabolic response to stress (MRS). Specific substrates, such as omega-3 fatty acids, arginine, and glutamine, play distinct roles in modulating inflammation, promoting the production of specialized pro-resolving mediators (SPMs), and supporting immune function [13]. However, routine use of these supplements in medical sepsis or general ICU patients is not recommended due to inconsistent mortality benefits and potential harm in hemodynamically unstable subgroups [18].
- **Micronutrients:** High-dose antioxidant monotherapy (selenium, vitamin C, vitamin E) should not be administered without proven deficiency [14]. Vitamin D status can be determined in at-risk patients, but routine high-dose supplementation shows no mortality benefit [19].

3.6. Microbiome Preservation and Gut-Directed Strategies

Severe infection and critical illness induce profound gut dysfunction, characterized by stress-induced splanchnic vasoconstriction, epithelial hypoxia, and dysbiosis. This leads to a collapse of short-chain fatty acid (SCFA)-producing taxa, impairing epithelial nutrition and immunomodulation, and increasing the risk of bacterial translocation [13]. While routine probiotic or prebiotic supplementation is not currently recommended due to a lack of specific indications, preserving the gut microbiome is a critical component of host-directed therapy [13] [14]. Early

enteral nutrition is the primary strategy to maintain gut barrier integrity and prevent bacterial translocation [14]. Emerging gut-directed strategies under investigation include elemental or peptide-based formulas to reduce digestive workload, SCFAs such as butyrate for their anti-inflammatory effects, and targeted modulation of enterohormones like glucagon-like peptide-1 (GLP-1) to support enterocyte recovery [13].

4. Immunomodulation and Adjunctive Therapies

Antibiotics kill bacteria but do not neutralize toxins or dampen the excessive inflammatory response that causes organ damage. Adjunctive therapies aim to modulate this response. Current recommendations vary significantly by intervention and clinical context.

4.1. Corticosteroids: Conditional Recommendation

Adjunctive corticosteroids are conditionally recommended for specific populations based on robust RCT evidence:

Septic Shock: The **ADRENAL trial** demonstrated that hydrocortisone speeds up the resolution of shock but has a modest or neutral effect on mortality [20]. Similarly, the **APROCCHSS trial** showed that hydrocortisone plus fludrocortisone reduced 90-day mortality in patients with septic shock requiring vasopressors [21]. Current guidelines recommend considering hydrocortisone (200 mg/day) for patients with refractory septic shock despite adequate fluid resuscitation and vasopressors [1].

Severe Community-Acquired Pneumonia (CAP): For adults with severe CAP requiring ICU admission and mechanical ventilation, adjunctive corticosteroids are recommended based on the **CAPE COD** randomized clinical trial, which demonstrated reduced mortality and respiratory failure [22]. This recommendation is further supported by systematic reviews and meta-analyses confirming benefit in this specific population [23] [24]. Typical regimens involve hydrocortisone 200 mg/day for 5 - 7 days, tapered based on clinical response.

4.2. IVIG, Albumin, and Statins: Recommendation Status

Intravenous Immunoglobulin (IVIG): Remains investigational for general sepsis. While retrospective database studies suggest potential impact on mortality and inflammatory status [25], and expert opinion acknowledges possible benefit in modulating immune response [26], no large-scale RCT has demonstrated definitive outcome improvement. IVIG is not routinely recommended outside of specific indications like toxic shock syndrome.

Human Albumin: Should be considered primarily as a resuscitation fluid in patients requiring substantial volume expansion, particularly those with hypoalbuminemia or septic shock [27]. Its role as an immunomodulatory or nutritional adjunct remains unproven, and it should not be used solely for these purposes.

Statins: There is no support for de novo statin initiation in general sepsis. While

previous large randomized trials failed to show benefit from initiating them de novo in sepsis-associated acute respiratory distress syndrome [28], and recent systematic reviews indicate that statin use may be associated with reduced mortality in sepsis [29], these findings are largely observational. Continue statins if the patient was already taking them, but do not initiate specifically for infection treatment.

5. Functional Rehabilitation and Delirium Prevention

Surviving the infection is only half the battle. Post-Intensive Care Syndrome (PICS) affects a substantial proportion of survivors, causing muscle weakness, cognitive decline, and psychological distress [2].

5.1. The ABCDEF Bundle and Early Mobility

The Society of Critical Care Medicine recommends the **ABCDEF Bundle** (Assess pain, Breathing trials, Choice of sedation, Delirium monitoring, Early mobility, Family engagement) to minimize iatrogenic harm. Bed rest leads to rapid muscle loss. Systematic reviews confirm that physical therapy in the ICU improves functional outcomes and may reduce delirium duration [30]. A landmark randomized trial demonstrated that early exercise in critically ill patients enhances short-term functional recovery [31]. Expert consensus guidelines have established clear safety criteria for active mobilization of mechanically ventilated patients [32].

However, clinicians should temper expectations regarding universal benefits. The recent **TEAM** randomized trial demonstrated heterogeneous effects of early mobilization on patient-cantered outcomes, with no significant improvement in physical function at hospital discharge compared to usual care in some cohorts [33]. Therefore, early mobilization should be individualized based on patient stability, baseline function, and ongoing clinical trajectory rather than applied uniformly.

5.2. Practical Recommendations

- **Daily Sedation Vacations:** Perform Spontaneous Awakening Trials (SATs) daily.

- **Delirium Screening:** Use CAM-ICU or ICDSC tools daily. Treat underlying causes before using antipsychotics.

-**Get Them Moving:** Consult physical therapy early. Even passive range-of-motion exercises help prevent contractures in sedated patients, but intensity and timing should be tailored to individual patient response.

Figure 1 **The Host Optimization Bundle.** Schematic representation of the multidisciplinary approach to managing severe infections. Beyond antimicrobial therapy and source control (central patient), optimal outcomes rely on four supporting pillars: **Glycemic Control** (maintaining 140 - 180 mg/dL with attention to glycemic variability), **Nutritional Support** (phased enteral feeding with protein prioritization), **Immunomodulation** (judicious use of adjunctive corticosteroids,

IVIG, albumin, and statins), and **Functional Rehabilitation** (early mobility and delirium prevention). Implementation of this bundle requires coordinated care among infectious disease specialists, intensivists, endocrinologists, dietitians, and rehabilitation therapists.

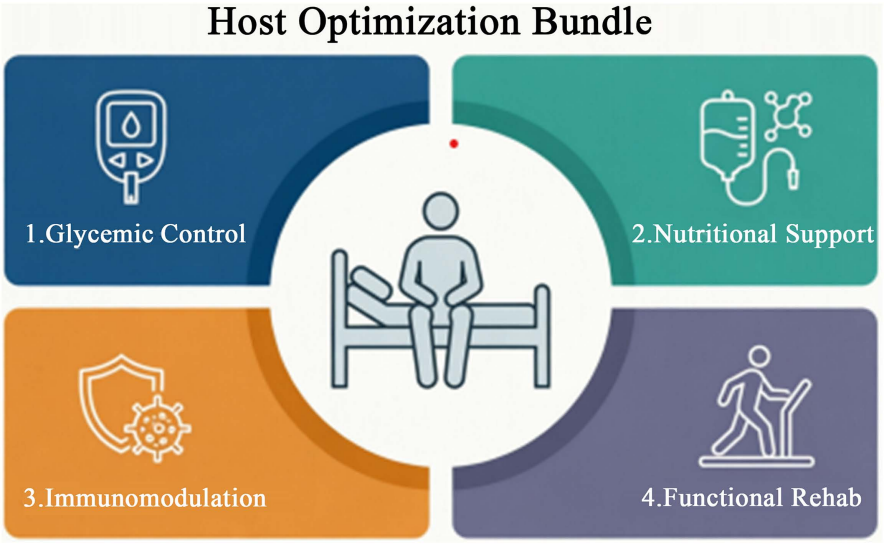

Figure 1. The host optimization bundle.

6. Proposed Clinical Algorithm: The Host Optimization Bundle

To facilitate implementation, we propose the following checklist for patients with severe infections (Table 1).

Table 1. Host optimization bundle checklist.

Domain	Action Item	Target/Goal
Glycemic	Monitor glucose q1 - 2 h if on insulin; assess variability	Target 140 - 180 mg/dL; CV < 36%
Nutrition	Start enteral feeds within 24 - 48 h	Trophic feeds initially; advance to protein goal (1.3 g/kg) by Day 4
Immunology	Assess need for steroids	Consider if refractory shock despite fluids/vasopressors or severe CAP
Prophylaxis	VTE Prophylaxis	LMWH unless contraindicated
Mobility	PT/OT Consult	Out of bed within 72 h if stable
Delirium	Daily CAM-ICU Screen	Minimize benzodiazepines; reorient patient

7. Discussion

Implementing Host-Directed Therapy requires a shift in mindset from "treating the bug" to "treating the patient." The evidence supports a bundled approach

where metabolic stability, nutrition, and mobility are prioritized alongside antibiotics.

Recent updates, including the ESPEN 2023 practical guideline and the 2025 review on the metabolic response to stress, reinforce a paradigm shift away from early full feeding and high-protein targets toward phase-appropriate, hypocaloric, and moderate-protein strategies [14] [15]. Furthermore, the integration of metabolomics and biomarkers holds promise for identifying the exact transition from catabolic to anabolic phases, enabling truly personalized nutritional and pharmacologic support [14].

Limitations: Most trials in this field are heterogeneous, and patient responses vary. For example, while early mobility is beneficial, it must be balanced against hemodynamic stability, and recent RCTs like TEAM highlight heterogeneous effects on patient-centered outcomes [32]. Similarly, nutritional needs differ between a young trauma patient and an elderly diabetic. The Host Optimization Bundle proposed herein is a conceptual framework requiring prospective validation.

8. Conclusion

Optimal management of severe infectious diseases extends beyond antimicrobials. By integrating moderate glycemic control with attention to variability, phased nutritional support, judicious immunomodulation, and early rehabilitation, clinicians can address the host factors that drive morbidity and mortality. We encourage institutions to adopt a multidisciplinary "Host Optimization" protocol to standardize this care, while recognizing the need for further validation of this bundled approach.

Announcement

Qwen 3.7-plus was used for language polishing and grammar correction of this manuscript.

Author Contributions

Waleed Amasaib Mohamed Ahmed (WA Ahmed): Conceptualization, Supervision, Project administration, Writing—Review & Editing, Final approval of the version to be submitted.

Dalia Qutub (Q.D.M): Writing—Original Draft (Nutritional Support section), Methodology (Nutrition guidelines synthesis), Validation.

Osama Jamaan AlZahrani (Alzahrani O.J.M): Investigation, Literature Search and Screening, Data Curation, Resources.

Hanin Hussain Alsharif (AlSharif H.H): Writing—Original Draft (Manuscript preparation), Visualization, Formatting, Writing—Review & Editing.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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