Interactions between Nutrition and Infection in the Developing World

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- Has worked in international health for three decades, concentrating on the epidemiology and prevention of malnutrition in the developing world
- Presently directing a large research project on maternal and child micronutrient deficiency prevention in northern Bangladesh
Overview

- Section A
  - Defining and Quantifying Undernutrition
- Section B
  - The Effects of Undernutrition on Infection
- Section C
  - Micronutrient Deficiencies
Section A

Defining and Quantifying Undernutrition
Definitions Related to Undernutrition

- **Undernutrition**
  - Result of undernourishment, poor absorption and/or poor biological use of nutrients consumed

- **Vulnerability**
  - Presence of factors that place people at risk of becoming food insecure or malnourished, including factors that affect their health and ability to cope

- **Vulnerable group**
  - Group of people with common characteristics, a high proportion of whom are food-insecure or at risk of becoming food insecure

Food and Agriculture Organization (FAO) of the United Nations, 2001
Undernutrition Leads to Deficiencies in . . .

1. Protein
   - Deficit in amino acids needed for cell structure, metabolic function

2. Energy
   - Calories (joules) derived mostly from macronutrients
     a. Protein
     b. Carbohydrate
     c. Fat

3. Micronutrients
   - For example, vitamins A, D, E and K; B-complex (thiamin [B1], riboflavin [B2], niacin, folate, pyridoxine [B6], cyanocobalamin [B12]), vitamin C; iron, zinc, iodine, calcium, others
Undernutrition can be milder, “hidden,” affecting:
- Survival
- Development
- Behavior
- quality of life
- economic potential.
Undernutrition

Conceptual Model of the Effects of Undernutrition throughout the Life Cycle

- Baby
  - Low Birth Weight
  - Impaired mental development
  - Increased risk of adult chronic disease
  - Inadequate catch-up growth
  - Reduced capacity to care for baby

- Older Adults
  - Malnourished
  - Higher mortality rate
  - Inadequate food, health, and care
  - Reduced mental capacity

- Child
  - Stunted
  - Untimely/inadequate weaning
  - Frequent infections
  - Inadequate food, health, and care

- Women
  - Malnourished
  - Inadequate fetal nutrition
  - Inadequate food, health, and care
  - Reduced mental capacity

- Pregnancy
  - Low Weight Gain
  - Higher maternal mortality
  - Inadequate food, health, and care

Adapted by CTLT from ACC/SCN, 4th Report on the World Nutrition Situation, 2000
Population Distribution of Nutritional Status:

- Weight for Age, Height for Age, Weight for Height
- Serum concentration of micronutrients
- Functional test distributions
Population Distribution of Nutritional Status:
This is what exists, theoretically

- Weight for Age, Height for Age, Weight for Height
- Serum concentration of micronutrients
- Functional test distributions (e.g., dark adaptometry)
Population Distributions of Micronutrient Status

Population Distribution of Micronutrient Status in Undernourished Societies:
This is what actually exists

- Undernourished, Deficient, <-2 Z-scores or SNDs
- Normally Nourished
- Overnourished, Toxic

- Low weight or height for age……Normal weight or height for age
- Low weight for height……Normal weight for height
- Deficient plasma retinol……Normal circulating retinol levels
- Abnormal dark adaptation……Normal dark adaptation
Malnutrition Anthropometric Definitions

- **Underweight**
  - Weight for age < -2 SD of the median value of the NCHS/WHO reference; BMI < 18.5 (wt in kg/Ht² in m) in adults

- **Stunting**
  - Height for age < -2 SD of the median value of the NCHS/WHO reference

- **Wasting**
  - Weight for height < -2 SD of the median value of the NCHS/WHO reference

- **Overweight**
  - Weight > 2 SD above median value of NCHS/WHO reference; BMI > 25 in adults

- **Obesity**
  - BMI > 30 kg/Ht² in adults
Classification of Child Undernutrition by Anthropometry

- General classification of child undernutrition by anthropometry (Waterlow classification)

<table>
<thead>
<tr>
<th>Weight for height</th>
<th>Height for age</th>
<th>Normal (&gt; -2 SD HAZ)</th>
<th>Stunted (&lt; -2 SD HAZ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (&gt; -2 SD WHZ)</td>
<td>Normal</td>
<td>Normal</td>
<td>Stunted</td>
</tr>
<tr>
<td>Wasted (&lt; -2 SD WHZ)</td>
<td>Wasted</td>
<td>Wasted</td>
<td>Stunted and wasted</td>
</tr>
</tbody>
</table>

Proximal Causes of Childhood Undernutrition

- Maternal undernutrition leading to intrauterine growth retardation (IUGR; small size at birth)
- Chronic low energy and protein intake
  - Unclean/non-nutritious, complementary foods of low energy and micronutrient density
  - Too early displacement of breast
  - Dilution of formula
  - Exclusive breast feeding for too long
- Infection (e.g., measles, diarrhea, others)
- Xenobiotics (aflatoxins)
Complementary Feeding in Developing Countries

Breast Feeding . . .

- Breast milk supplies ideal mix, density, and physiologic form of nutrients to promote adequate infant growth and development
- Reduces exposure of infant to enteropathogens
- Antibacterial and antiviral
- Reduces infant infections
- Provides biologic and emotional bond between mother and infant
- Healthy for mother—reduces risk of ovarian and breast cancer, post-partum hemorrhage and anemia; increases birth spacing
- Low cost

Photo source: K. West, Jr.
Nutritional Concerns about Complementary Feeding

- Density and total intake of energy
- Quality vs. quantity
- Hygienic delivery
- Appropriate age at introduction
- Impact of complementary feeding (CF) intake on breast milk intake

Source: Piwoz et al. (2003). FNB.
Section B

The Effects of Undernutrition
Malnutrition–Infection Interactions

Undernutrition
- Decreased Immune Function
  - Innate
  - Acquired

Infection
- Impaired Absorption
  - Altered gut lumen
  - Mucosal injury
General Effects of Undernutrition on Immune System

- Diminished T-cell help in immune responses dependent on mature CD4 cells
- Delayed Ab responses to certain Ag
- Depressed mucosal SIgA and associated Ab in response to mucosal infections
- Impaired complement activation
- Impaired opsonic activity
- Thymic atrophy

Effects of Infection on Nutritional Status

- Protein catabolism and negative nitrogen balance
- Altered priorities for protein anabolism
- Depletion of CHO stores
- Increased resting energy metabolism
- Increased gluconeogenesis
- Peripheral insulin resistance
- Altered lipid metabolism
- Trace element (Fe, Cu, Zn) redistribution
- Increased vitamin utilization and excretion

The “Vicious Cycle” of Undernutrition and Infection

Infection

- Complement system impaired and decreased lysozyme levels in leukocytes
- Secretory IgA levels are low and antibody responses reduced
- Reduced cell-mediated immune response
- Phagocytic & bactericidal activities reduced

Undernutrition

- Loss of appetite
- Reduced food intake
- Malabsorption of nutrients
- Metabolic losses
Diarrhea in South Asian children (e.g., children under 24 months in Bangladesh)

<table>
<thead>
<tr>
<th>Weight for length</th>
<th>Duration (mean days)</th>
<th>Incidence (episodes per 1,000 child days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent median</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥90%</td>
<td>6.8</td>
<td>16.9</td>
</tr>
<tr>
<td>80–89%</td>
<td>8.5</td>
<td>16.2</td>
</tr>
<tr>
<td>&lt;80%</td>
<td>10.6*</td>
<td>16.4</td>
</tr>
</tbody>
</table>

Black et al. (1984). *p < 0.05

*Am J Clin Nutr.*
## Undernutrition and Incidence and Duration of Diarrhea

Undernutrition and incidence and duration of diarrhea in African children

<table>
<thead>
<tr>
<th>Nutritional status (% median)</th>
<th>n</th>
<th>Attack rate per child in 3 months</th>
<th>% time with diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight/age &gt;75%</td>
<td>220</td>
<td>1.2</td>
<td>8.5</td>
</tr>
<tr>
<td></td>
<td>123</td>
<td>1.5</td>
<td>11.3*</td>
</tr>
<tr>
<td>Weight/age &lt;75%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height/age &gt;90%</td>
<td>245</td>
<td>1.4</td>
<td>7.9</td>
</tr>
<tr>
<td></td>
<td>98</td>
<td>1.4</td>
<td>10.8*</td>
</tr>
<tr>
<td>Height/age &lt;90%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight/height &gt;80%</td>
<td>302</td>
<td>1.3</td>
<td>7.6</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>1.9*</td>
<td>13.6*</td>
</tr>
<tr>
<td>Weight/height &lt;80%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Infection/Morbidity Impairs Weight Gain

Weight gain per day of illness (g)

<table>
<thead>
<tr>
<th>Country</th>
<th>Age</th>
<th>Diarrhea</th>
<th>Fever</th>
<th>Apathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uganda</td>
<td>6–36</td>
<td>-5.4</td>
<td>-4.0</td>
<td>–</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>6–48</td>
<td>-5.0</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>6–32</td>
<td>-4.4</td>
<td>-10.3</td>
<td>–</td>
</tr>
<tr>
<td>Jamaica</td>
<td>9–48</td>
<td>-8.4</td>
<td>-16.8</td>
<td>-15.0</td>
</tr>
<tr>
<td>Guatemala</td>
<td>12–36</td>
<td>-3.5</td>
<td>–</td>
<td>-2.3</td>
</tr>
<tr>
<td>Gambia</td>
<td>Rural</td>
<td>6–36</td>
<td>-25.8</td>
<td>-20.0</td>
</tr>
<tr>
<td></td>
<td>Urban</td>
<td>0–24</td>
<td>-3.7</td>
<td>–</td>
</tr>
<tr>
<td>Sudan</td>
<td>3–12</td>
<td>-32.1</td>
<td>-29.5</td>
<td>–</td>
</tr>
</tbody>
</table>

Effects of Severe Undernutrition Persist after Recovery

- One year after discharge, Bangladesh
  - Diarrhea 67%
  - Pneumonia 58%
  - Mortality 2.3%
  - Mean WHZ adequate
  - Mean HAZ very low

- Returning to same high-risk home setting

Relative Risk of Death by Cause Attributed to Underweight

![Graph showing RR by Cause of Death](image)

- Diarrhea
- Malaria
- Overall
- Pneumonia
- Measles

Adapted by CTLT from Caulfield et al, WHO Burden of Disease Series, 2003
As the percent of children who are malnourished increases in a population, so too does the proportion of child deaths attributable to undernutrition.

\[
\text{Total population attributable rise (PAR)} = 0.87 + 1.42X - 0.0075X^2
\]

Each year due to child and maternal undernutrition…
- 3.75 million deaths
- 137 million DALYs
- Ezzati et al. (2002). *Lancet*, 360, 1347

Adapted by CTLT from BASICS Project USAID, D. Pelletier et al, BWHO 1995
Population Attributable Risk (PAR) of Preschool Child Death Due to the Potentiating Effects of Mild to Moderate Malnutrition (MMM) and Severe Malnutrition on Infectious Disease in 53 Countries
Major Causes of Death among Children

- Pneumonia: 20%
- Diarrhea: 12%
- Malaria: 8%
- Measles: 5%
- HIV/AIDS: 4%
- Other: 29%
- Perinatal: 22%

Adapted by CTLT from EIP/WHO. Caulfield LE, Black RE, 2000
Major Causes of Death among Children

Deaths Associated with Undernutrition 60%

Adapted by CTLT from EIP/WHO.
Caulfield LE, Black RE, 2000
Section C

Micronutrient Deficiencies
Micronutrient Deficiencies: Hidden Hunger

- About 2 billion people affected
- Major deficiencies
  - Iodine, vitamin A, iron, and zinc
- Effects
  - Poor growth, increased morbidity, impaired intellect, increased mortality
- Preventable
  - Supplements, fortification, diet change
Micronutrient Deficiencies and Infection

- Vitamin A deficiency
  - Increases risk of severe diarrhea, fp malaria, measles severity; child mortality

- Zinc deficiency
  - Increases risk of diarrhea, ALRI, fp malaria; (likely child mortality)

- Iron deficiency
  - Unclear effects on infectious disease risk

- Other micronutrient deficiencies
  - Adverse effects on host defenses are likely but remain to be elucidated
Vitamin A Deficiency Disorders

- Gradient of health consequences

- Corneal blindness
- Xerophthalmia
- Metaplasia, impaired immunity, morbidity, anemia, poor growth

- Tissue and plasma depletion

- Chronic dietary deficit

- Systemic effects

- Mortality risk
Dietary Diversification

Photo source: K. West, Jr.
Xerophthalmia

Source: CDC
Child Mortality and Mild Eye Signs

~4000 Indonesian Preschool Children, Quarterly

Adapted by CTLT from Sommer et al, Lancet 1983
Fever-Related Mortality—Sarlahi, Nepal

Fever-Related Mortality, > 6 Months of Age, Sarlahi, Nepal

Days of Morbidity Past Week

Four-Month MR per 1000 Child Visits

- Control
- Vitamin A

RR = 0.49

RR = 0.66 (p < 0.05)

RR = 0.82

0 1-6 > 7
Vitamin A Deficiency and Preschool Child Mortality

A Decade of Research Confirmed an Average 25-30\% Reduction in Preschool Child Mortality

<table>
<thead>
<tr>
<th>Location</th>
<th>Percent Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aceh, 1988</td>
<td>-34</td>
</tr>
<tr>
<td>Java, 1988</td>
<td>-45</td>
</tr>
<tr>
<td>T. Nadu, 1990</td>
<td>-54</td>
</tr>
<tr>
<td>A. Prad, 1990</td>
<td>-6</td>
</tr>
<tr>
<td>Sarlahi, 1991</td>
<td>-30</td>
</tr>
<tr>
<td>Jumla, 1991</td>
<td>-29</td>
</tr>
<tr>
<td>Sudan, 1992</td>
<td>6</td>
</tr>
<tr>
<td>Ghana, 1992</td>
<td>-19</td>
</tr>
</tbody>
</table>

In 1991: VAD led to 1.1 to 2.4 million deaths/yr (Humphrey et al BWHO 1992)
Today: VAD causes ~800,000 deaths, 27 m DALYs (Ezzati et al Lancet 2002)

Adapted by CTLT from Sommer & West, 1996
Vitamin A Reduces Measles Case Fatality Rate (CFR)

Vitamin A Deficiency Increases Measles Fatality; Vitamin A Reduced CFR by 50% to 80%

- London 1932: OR=0.40
- Tanzania 1988: OR=0.49
- Capetown 1990: OR=0.19
- Durban 1991: OR=0.34

### Vitamin A and Severity of Morbidity: Ghana VAST Trials

<table>
<thead>
<tr>
<th></th>
<th>RR (VA/control)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic attendances</td>
<td>0.88</td>
<td>(0.81-0.95)</td>
</tr>
<tr>
<td>Hospital admissions</td>
<td>0.62</td>
<td>(0.42-0.93)</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.81</td>
<td>(0.68-0.98)</td>
</tr>
</tbody>
</table>

Report of a Joint WHO/USAID/NEI Consultation of Principal Investigators

International Vitamin A Consultative Group

Vitamin A Policy Statements

Vitamin A Policy Statement

In 1989, the Steering Committee of the International Vitamin A Consultative Group (IVACG) released an 'interim' statement recognizing the importance of adequate vitamin A status for preventing childhood blindness and reducing childhood morbidity and mortality. That statement was based on results of a small number of completed studies. Since that time, numerous definitive trials have been completed and published. These additional data confirm IVACG's interim statement. As a result, the IVACG Steering Committee re-affirms its original conclusions:

- Adequate vitamin A status prevents nutritional blindness and contributes significantly to child health and survival
- Vitamin A plays an important role in preventing nutritional blindness and in reducing childhood morbidity and mortality
- The impact of improved vitamin A nutrition varies with the severity of existing vitamin A deficiency and the contributions of other ecological factors.
- It is therefore imperative to improve the diet and employ other approaches as appropriate for improving vitamin A nutritional status where it is deficient.

The IVACG Steering Committee hopes that this statement will be useful in the process of formulating country and regional policies and programs to control and combat vitamin A deficiency.
Zinc Deficiency

- Vast problem!
- Highly prevalent in cultures with
  - Low meat and fish (low zinc) intakes
  - High grain (high phytate) intakes
Effects of Zinc Deficiency on Immune Function

- Reduces nonspecific immunity, including PMN and NK function and complement activity
- Reduces T and B lymphocytes
- Multiple effects on function, including suppressed delayed hypersensitivity, cytotoxic activity and antibody production
Effects of Daily Zinc Supplement Use on Diarrhea and Pneumonia in Preschoolers

Odds Ratio and 95% CI

Diarrhea Incidence (9 countries)
Diarrheal Prevalence (9 countries)
Pneumonia Incidence (4 countries)

~25% reduction for diarrhea
~40% reduction for pneumonia

Adapted by CTLT from Zinc Investigators' Collaborative Group
J Pediatrics 1999;135:689
Zinc for Treating and Preventing Acute Diarrhea

- Treatment (based on 12 RCTs): Zinc ~2x RDA…
  - Reduced duration by ~15%
  - Reduced severity by ~20% (for episodes of >7 d)
  - Reduced stool output and frequency
  - Reduced antibiotic use
- Prevention (based on 3 RCTs, 2–3 mo surveillance): Zinc for 14 d after end of episode of acute diarrhea at 2–4x RDA…
  - Reduced incidence of diarrhea by 11%
  - Reduced prevalence of diarrhea by 34%
WHO/UNICEF Joint Statement

June 2004

- More than 1.5 million children die of acute diarrhea each year
- Case fatality can be reduced with ORS, fluids in the home, breast feeding, continued feeding, selective use of antibiotics and zinc supplementation for 10–14 days
- Provide 20 mg per day of zinc (half-dose < 6 mo)
- Available in 20 mg dispersible tablets as zinc sulfate
Efficacy of Zinc in Therapy of Measles and Malaria

- Indian study found no effect of 20 mg zinc per day in therapy of measles\(^1\)
- Multicenter study (Ecuador, Ghana, Tanzania, Uganda, Zambia) found no effect of 20/40 mg zinc per day in therapy of malaria\(^2\)

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\(^1\)Mahalanabis et al. (2002). *Am J Clin Nutr.*

Zinc and Malaria Attacks in Papua New Guinea

Zinc Supplementation Reduced Malaria Attacks in PNG Children

Efficacy Trials of Zinc Supplementation on Child Mortality

- Children 1–35 months old (30,000–70,000)
- Randomized, controlled trials
- All children receiving vitamin A
- Zanzibar
  - Zinc and/or iron and folate factorial
- Nepal
  - Zinc and/or iron and folate factorial
- India
  - Zinc (all receive iron and folate)
Conclusions: Zinc Supplementation

- Reduces diarrhea, pneumonia, and possibly malaria incidence
- Reduces diarrhea duration and severity
- Preliminary—may reduce child death
- Supplements and fortification along with iron (and other MN) need more study
Iron: Double-Edged Sword?

- Iron supplementation increases hemoglobin production and reduces risk of anemia

- But potential hazardous effect of iron on infection—based on reviews,* generally where malaria is endemic, iron...
  - Increased episodes of clinical malaria (5/9 trials)
  - Increased episodes of other infections in 4/8 trials

- Mechanisms related to malaria
  - Iron supplementation may inhibit zinc absorption
  - Iron is essential for pathogen (plasmodium, bacteria) growth

Iron + Folic Acid Trial in Pemba, Zanzibar

- Randomized, double-masked, 2 x 2 factorial trial of daily iron (12.5 mg) + folic acid (50 ug), zinc, or both vs. placebo
- N = 24,076 children 1–35 months of age
- Half-doses to infants 1–11 months of age
**Effect of Iron + Folic Acid (± Zinc)**

- Effect of iron + folic acid (± zinc) on mortality and hospital admissions

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (n = 295)</td>
<td>1.15 (0.93–1.41)</td>
<td>0.19</td>
</tr>
<tr>
<td>Hospitalization (n = 1840)</td>
<td>1.11 (1.01–1.23)</td>
<td>0.03</td>
</tr>
<tr>
<td>Adverse event (n = 2135)</td>
<td>1.12 (1.02–1.23)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Micronutrient Deficiency Prevention
Dietary Diversification

Photo source: K. West, Jr.
Micronutrient Supplementation

Photo source: K. West, Jr.
E.g., The UN World Food Programme is establishing regional mill capabilities in Bangladesh to fortify wheat flour with iron, zinc, vitamin A, and multiple water-soluble vitamins.