

FRONT MATTER

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ENVIRONMENTAL ENTERIC DYSFUNCTION: ADVANCING CURRENT KNOWLEDGE

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Abbreviations

ΔHAZ	delta height-for-age Z-(score)
ΔWAZ	delta weight-for-age Z-(score)
ΔWHZ	delta weight-for-height Z-(score)
AGP	alpha-1-acid glycoprotein
ANOVA	analysis of variance
CF	cystic fibrosis
CI	confidence interval
CMPA	cow's milk protein allergy
CONSORT	Consolidated Standards of Reporting Trials
CRP	C-reactive protein
ED	enteric dysfunction
EE	environmental enteropathy
EED	environmental enteric dysfunction
ESR	erythrocyte sedimentation rate
ETEC	enterotoxigenic <i>E. coli</i>
FA	fatty acid
GAG	glycosaminoglycan
GCA	glycocholate
HAZ	height-for-age Z-(score)
HBT	hydrogen breath test
HCT	hematocrit
HGB	hemoglobin
HLA-DR	human leukocyte antigen DR-1
HPLC	high-performance liquid chromatography
HSPG	heparan sulfate proteoglycan
IEL	intraepithelial lymphocytes
IFN-γ	interferon gamma
IL	interleukin
IBD	inflammatory bowel disease
L:Cr	lactose:creatinine ratio
L:M	lactulose:mannitol ratio
L:R	lactulose:rhamnose ratio

LBW	low birth weight
MCV	mean corpuscular volume
MGA	maltase-glucoamylase
MN	micronutrient
mRNA	messenger RNA
NCD	non-communicable disease
OR	odds ratio
ORT	oral rehydration therapy
PD	persistent diarrhea
PDF	portable document format files
PEM	protein energy malnutrition
PICO	population intervention comparison outcome
RA	research analyst
RBC	red blood cell
RR	relative risk
SBBO	small bowel bacterial overgrowth
SBT	sucrose breath test
SCL:L	sucralose:lactulose ratio
SEM	scanning electron microscopy
SES	socioeconomic status
SGA	small for gestational age
STARD	Standards for Reporting of Diagnostic Accuracy
SUC:L	sucrose:lactulose ratio
TE	tropical enteropathy
TG	triglyceride
TGF- β	tumor growth factor- β
TMS	tropical malabsorption syndrome
TNF	tumor necrosis factor
TNF- α RI	tumor necrosis factor- α receptor I
TS	tropical sprue
UK	United Kingdom
WaSH	water, sanitation and hygiene
WAZ	weight-for-age Z-score
WBC	white blood cell
WHO	World Health Organization
WHZ	weight-for-height Z-score

Synopsis

Purpose of Project: Gut dysfunction in children in resource-poor environments is well documented. The precipitant of this dysfunction is unknown. However, infections, nonspecific inflammation, malabsorption, and leakiness of mucosa are frequently incriminated as processes that underlie this dysfunction. Major consequences of this dysfunction have been postulated, the most critical of which is poor growth, especially stunting. The study of gut dysfunction in children would have as its ultimate goal the prevention of growth consequences. In this project, we have collated literature published between 2000 and 2010, with the purpose of guiding near-term research into the causes and pathophysiology of enteric dysfunction. In particular, we have attempted to identify biomarkers with which to detect this dysfunction.

Rationale for seeking biomarkers: Theoretically, tissue from the small bowel, the organ of greatest interest, could shed light on the underlying pathophysiology. However, analyzing this tissue poses challenges. These challenges include the practicalities of gaining access to this organ, incomplete confidence regarding sampling strategies to pursue, risk of sampling error, and the yet-to-be-determined value of the information that would be obtained. Thus, the more readily obtained and potentially more informative biomarkers found in stool or blood could feasibly advance the field.

Methods: A systematic literature review was performed by trained research analysts, two physicians, and two epidemiologists. Materials were collated in a master, highly inclusive database of publications relevant to environmental enteric dysfunction (EED) in children in resource-poor settings. This process was undertaken for two reasons. First, because search terms sensitive and specific for “enteropathy” and “enteric dysfunction” are not well indexed in literature databases (including PubMed), we had to create a resource with which to find data related to biomarkers. Second, the project was built to address multiple and different inquiries

related to the topic. Development of an internal library was the most efficient preparation for multiple interrogations, including those seeking to identify publications relevant to the following systematic review question, which is a main focus of this book:

What biomarkers or diagnostic tests have been used to identify, or have been shown to be associated with, mucosal dysfunction of the small intestine or host inflammation in children less than five years of age from developing-country settings?

Findings: 67,903 unique references were obtained from PubMed, Embase, Global Health and World Health Organization (WHO) Regional Libraries (1980-2010). 9,675 of these publications met EED Library inclusion criteria and 374 between 2000 and 2010 were potentially relevant to the systematic review question. Of these, 77 met the review inclusion criteria.

Each relevant publication was thoroughly and systematically reviewed and summarized in evidence table format. Biomarkers were categorized as being relevant to one of eight processes that could underlie, be associated with, or reflect enteric function/dysfunction in children: (1) absorption; (2) porosity/permeability; (3) digestion; (4) intestinal inflammation and/or intestinal immune activation; (5) systemic inflammation and/or systemic immune activation; (6) microbial drivers; (7) nonspecific intestinal injury, and (8) non-small intestinal organ function. A meta-analysis of pooled data from these publications was not possible because of the heterogeneity of study populations and methods, non-standardized information portrayal, scant attempts to correlate biomarkers to intestinal pathology (and where this was attempted, correlation was lacking), small population sizes, and limited relation of biomarkers with outcomes of interest, i.e., stunting. However, the data do strongly suggest the presence of broad categories of intestinal dysfunction, and imply a high prevalence of poorly functioning guts, in children in resource-poor environments. It is quite likely that a panel of biomarkers reflecting multiple physiologic derangements might predict intestinal injury.

Conclusions: Our novel search and EED construction methodology effectively identified a diffusely defined and poorly indexed (in the literature)—but nevertheless important—public health problem. Our EED Library format permits efficient information retrieval for multiple EED-related inquiries and the methodology can be applied to other health issues that face similar definition and search/retrieval issues.

Using this comprehensive data collation and extraction system, we found no evidence of a globally applicable, simple, single-purpose biomarker that reliably correlates with intestinal dysfunction in children or to growth faltering mediated by such a lesion. The studies that are available were often not performed with this goal in mind. However, there is a large body of evidence that enteric dysfunction in children is highly prevalent in resource-poor settings, and that this dysfunction could be an important, and potentially remediable, cause of stunting.

Therefore, we urge that future research on biomarkers in human populations be pursued. We also urge that future work adheres to the following principles:

1. Assess function-related candidate biomarkers.
2. Relate the biomarker data to consequential outcomes.
3. Rigorously describe the study design and methodology underlying the data produced.
4. Provide robust data repositories. Employ best practices publication guidelines, such as those endorsed by the Consolidated Standards of Reporting Trials (CONSORT) system including the Standards for Reporting of Diagnostic Accuracy (STARD) Initiative.
5. Consider indices of enteric dysfunction, incorporating “stacking” multiple biomarkers representing diverse pathophysiologic processes, potentially also including non-laboratory test derived clinical characteristics.
6. Explore invasive, field-adaptable, host assessments (e.g., saliva, transcutaneous), even if technology needs to be developed or adapted.