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Zelić, Loren Ida

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UNIVERSITY OF ZAGREB

SCHOOL OF MEDICINE

Loren Ida Zelic

Failure to Thrive –

Diagnostic Approach in Pediatric Gastroenterology

GRADUATE THESIS

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ABBREVIATIONS

ANCA	Antineutrophil-cytoplasmic Antibodies
ASCA	Anti-Saccaromyces cerevisiae Antibodies
BMI	Body Mass Index
CBC	Complete blood count
CD	Celiac disease
CDC	Centers for Disease Control and Prevention
CFTR	Cystic Fibrosis Transmembrane Regulator
CrD	Crohn's disease
CF	Cystic Fibrosis
EIM	Extraintestinal manifestation
ESR	Erythrocyte Sedimentation Rate
FPIES	Food Protein Enterocolitis Syndrome
FTT	Failure to Thrive
GER	Gastroesophageal Reflux
GERD	Gastroesophageal Reflux Disease
GFD	Gluten-free Diet
IBD	Inflammatory Bowel Disease
IBS	Irritable Bowel Syndrome
NOFTT	Nonorganic Failure to Thrive
RAST	Radioallergosorbent Test
SGA	Small for gestational age
SPT	Skin Prick Testing
UC	Ulcerative Colitis
WHO	World Health Organization

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Abstract

Failure to thrive (FTT) is seen in children all over the world, and it is a common but challenging problem encountered by primary care doctors and pediatricians. Junior doctors should be aware of the potential causes of faltering growth as the possibilities are vast. Causes may consist of one or a combination of mechanisms, depriving the child of necessary nutrients and energy. With the use of serial anthropometric measurements and standardized growth charts, a child's development is ideally tracked over time. Defining FTT may not be an easy task. A clinician should be well-trained in the recognition of signs and symptoms of a variety of diseases. A thorough patient history and physical examination must be conducted as they are the foundation for the complete evaluation of the child. A differential diagnosis should be established and with the support of laboratory findings, further investigations should be performed. Familiarity with appropriate diagnostic procedures is vital for definite diagnosis and prompt treatment of the child's FTT.

Introduction

Failure to thrive (FTT) is a medical term used to describe a state of undernourishment in a child. Often, deficient growth when compared to other children of the same age is first noted by the primary care-giver and the child's low weight is brought to the attention of the doctor. Junior doctors and pediatric residents in particular may experience many challenges when faced with a child whose development seems to have slowed down or halted as FTT is merely a symptom, not a specific disease. Doctors must monitor the child closely and need to know how and when to intervene. To add to the complexity, the causes of FTT are quite varied, but are grouped as nonorganic or organic. Nonorganic FTT (NOFTT), also referred to as "psychosocial" FTT could be due to neglect, poverty, or incorrect feeding. Organic FTT occurs due to an underlying medical condition. Neurological and gastrointestinal disorders combined are responsible for 60-80% of all organic causes (1). These two groups are not always helpful for clinicians, especially in the case that the child's stunted growth is of mixed etiologies (2). Although some series show as many as 90% of affected children being labeled as having NOFTT, children are principally referred to a doctor for the exclusion of an organic cause (3). It is the doctor's duty to have a systematic and orderly way of approaching these children to discriminate between nonorganic and organic causes. Since the majority of FTT are nonorganic, it is crucial that organic causes are not disregarded. In particular, doctors must consider gastrointestinal disorders in their differential diagnosis, such as celiac disease (CD), inflammatory bowel diseases (IBD) and cystic fibrosis (CF), which are all cause for serious concern. FTT may be the only symptom, or it may be accompanied with many others. Clinicians should focus on a detailed patient history and thorough physical examination, as they are key methods of evaluation. This systematic approach is vital to ensure prompt diagnosis and subsequently proper management to decrease the risk of any possible long-term adverse effects (2). This paper will look at a simplified approach into the necessary investigations and evaluation of a child with FTT and then explain specific diagnostic investigations for organic FTT, particularly due to gastrointestinal causes.

Defining Failure to Thrive

Doctors have a difficult time defining FTT and establishing a consensus for the anthropometric criteria used to describe a child affected by malnutrition (1,4,5). The European Society of Parenteral and Enteral Nutrition describes malnutrition as a nutritional state in which deficiencies of energy, proteins and nutrients have caused bodily and functional adverse effects (6). Classification of nutritional deficiencies can be difficult as they combine anthropometry with clinical signs (7). Malnutrition can be classified as primary or secondary (6). Primary malnutrition is most common in developing countries and is mainly due to the lack of access to food, while secondary malnutrition develops in a child due to an underlying disorder (6). A variety of terminology can be used to describe specific states of malnutrition, including "wasting" and "stunting". It is important for a clinician to differentiate a child with wasting, described as low weight for height, from a stunted child, expressed as low height for age (7). Wasting signifies acute malnutrition while the latter is a slowing of skeletal growth, suggesting a chronic lack of nutrients which has led to FTT.

There are numerous parameters which can be taken into consideration when evaluating a child's size. Ideally, the child's weight, height and head circumference are carefully monitored and measured on numerous occasions. Supine length is best assessed in children up to the age of 2, from which point a stadiometer is used to measure standing height (7). These values are then plotted on a standard growth chart and compared to what is expected for that specific age and sex. Serial measurements create a trend essential to determine the child's velocity and pattern of growth (8). FTT may sometimes be so subtle that the primary care-giver does not notice (9). In 2006, The World Health Organization (WHO) used data from six countries from around the world to create new standardized growth charts using percentiles. They are centered on the basis of breastfed children. Also, measurements can be used to calculate and plot a child's *z*-score (figures 1 and 2). This is a deviation of the patient's measurements from the mean values for a specific age and gender (4). There is a direct relationship between *Z*-scores and percentiles, and they can be used interchangeably (4). *Z*-scores or standard deviation scores allow for easy mathematical manipulation and statistical analysis (7). Body mass index (BMI) can also be used as an indicator of nutritional status in children after infancy (7). It is derived by the square of the child's weight in kilograms,

divided by the square of the height in meters (10). A child is considered to be undernourished with a BMI *z*-score of -2 (7).

Alternatively, doctors have the choice of using The Centers for Disease Control and Prevention (CDC) growth charts (figures 3 and 4). They were released in 2000 and are based on formula-fed infants, which show slightly heavier children on standardized curves (11). Charts are mainly divided into two groups: one used for children until the age of 2 and one for children age 2 up to 20. In the case of premature infants, their age should be corrected for gestation until the age of 2 (12). Olsen *et al*(5) describe the lack of a single gold standard measurement for undernourishment and mention seven main anthropometric criteria used including Gomez and Waterlow criteria and thrive index. Additional parameters that may measure subcutaneous fat, such as skinfold thickness, are not used regularly as they are difficult to reproduce (13). Preferably, it is beneficial to use a combination of anthropometric criteria to distinguish a child affected by FTT (11). Throughout the literature, three main criteria for FTT are repeatedly mentioned. They include:

- Weight below the 3rd percentile or 5th percentile for age
- Weight less than 80% of normal weight for age
- Weight decrease that crosses two major percentile lines on growth chart

Doctors should be aware that switching from the CDC growth chart to those of the WHO causes an increase in the number of children which cross more than two major percentiles in length-for-age and in weight-for-age for children between 0 and 6 months (8). This lack of sharp definition between normal and delayed growth can be a source of confusion for junior doctors, and shows the importance of following the child's growth regularly, to observe the rate of their faltering growth. It also highlights the importance of further investigation and examination, particularity when dealing with organic FTT.

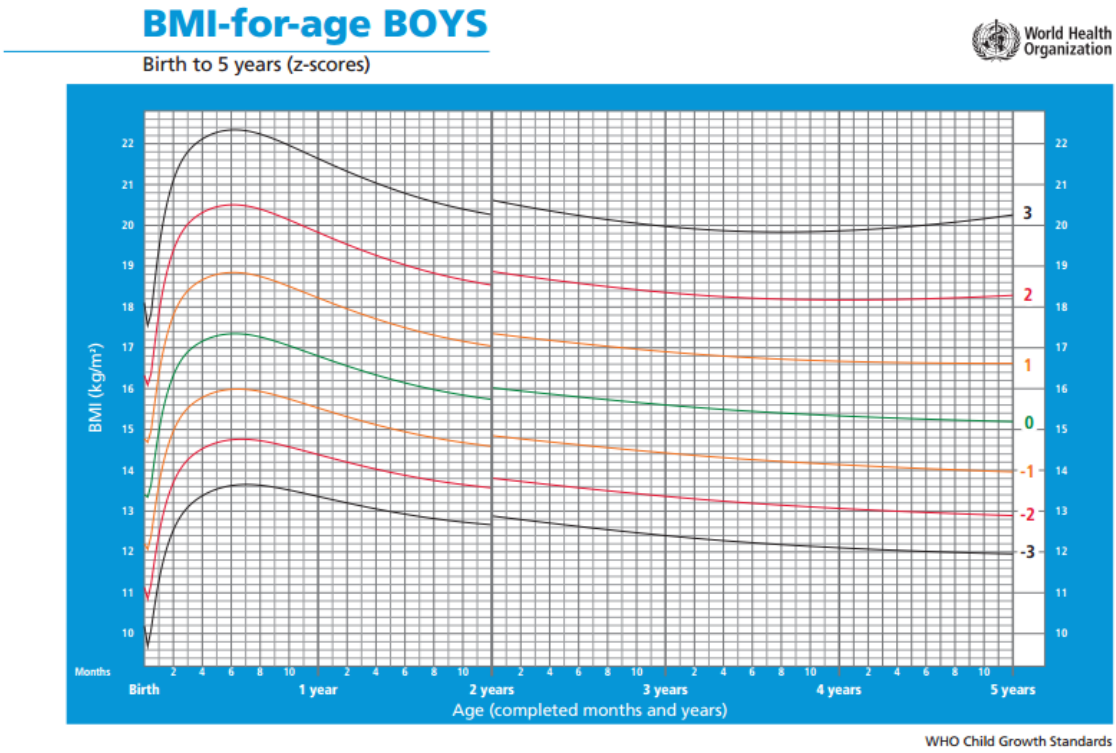


Figure 1. WHO Growth Chart: BMI-for-age for Boys, from birth to 5 years (*z*-scores)

World Health Organization. *BMI for age z-scores: boys. http://www.who.int/childgrowth/standards/bmi_for_age/en/ (accessed 25 March 2014).*

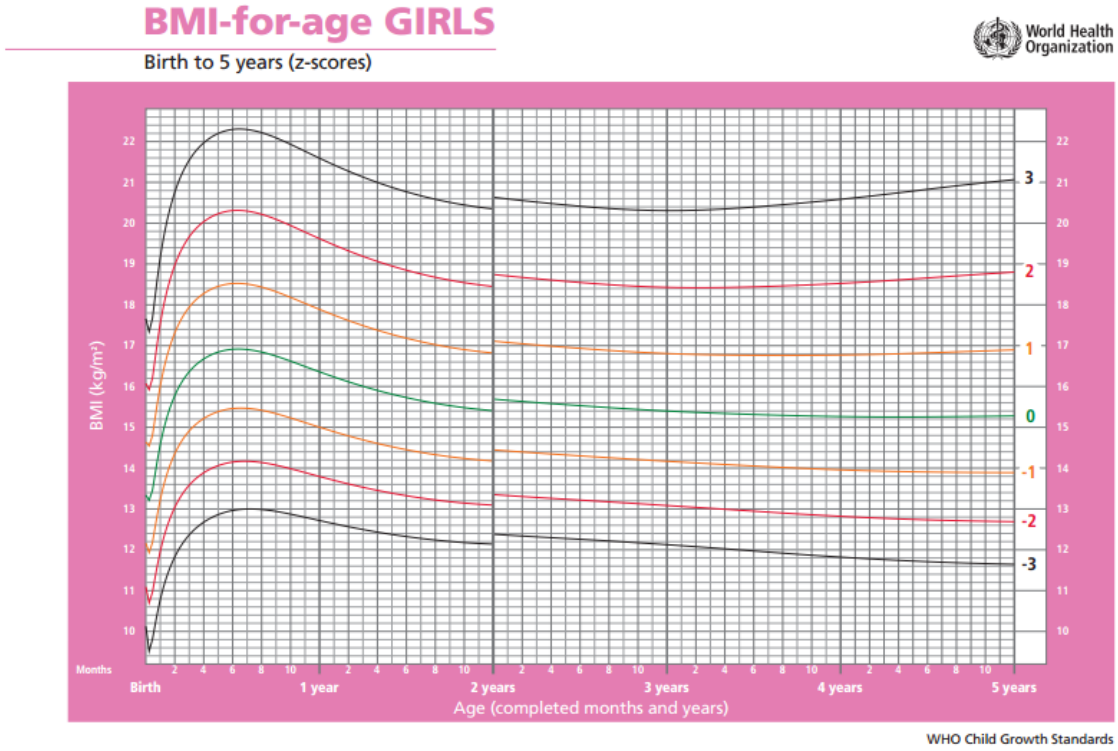


Figure 2. WHO Growth Chart: BMI-for-age for Girls, from birth to 5 years (*z*-scores)

World Health Organization. *BMI for age z-scores: girls. http://www.who.int/childgrowth/standards/bmi_for_age/en/ (accessed 25 March 2014).*

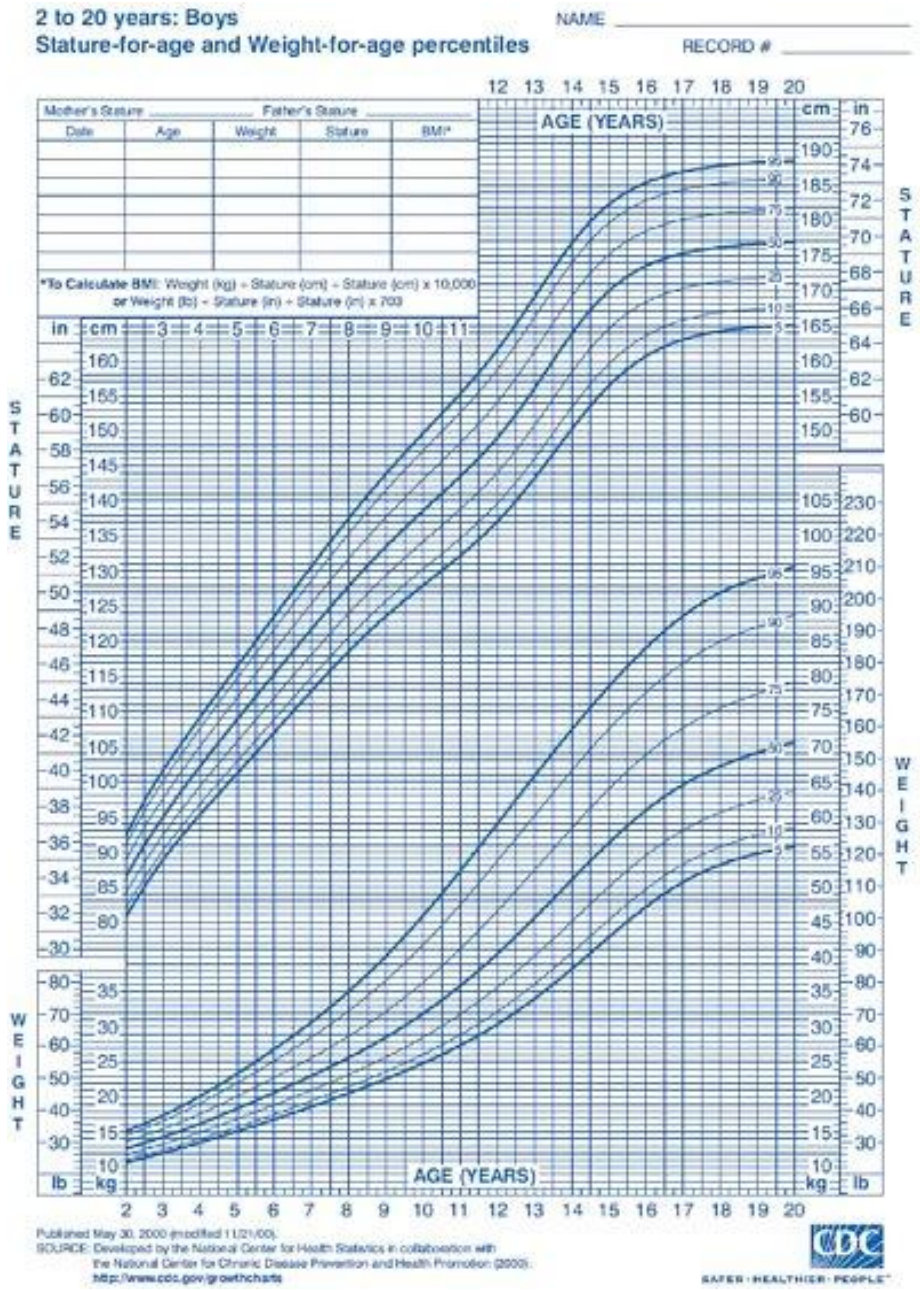


Figure 3. CDC Growth Chart: for Boys aged 2-20 (percentiles)

Centers for Disease Control and Prevention. *Boys Stature-for-age and Weight-for-age. http://www.cdc.gov/growthcharts/clinical_charts.htm (accessed 25 March 2014).*

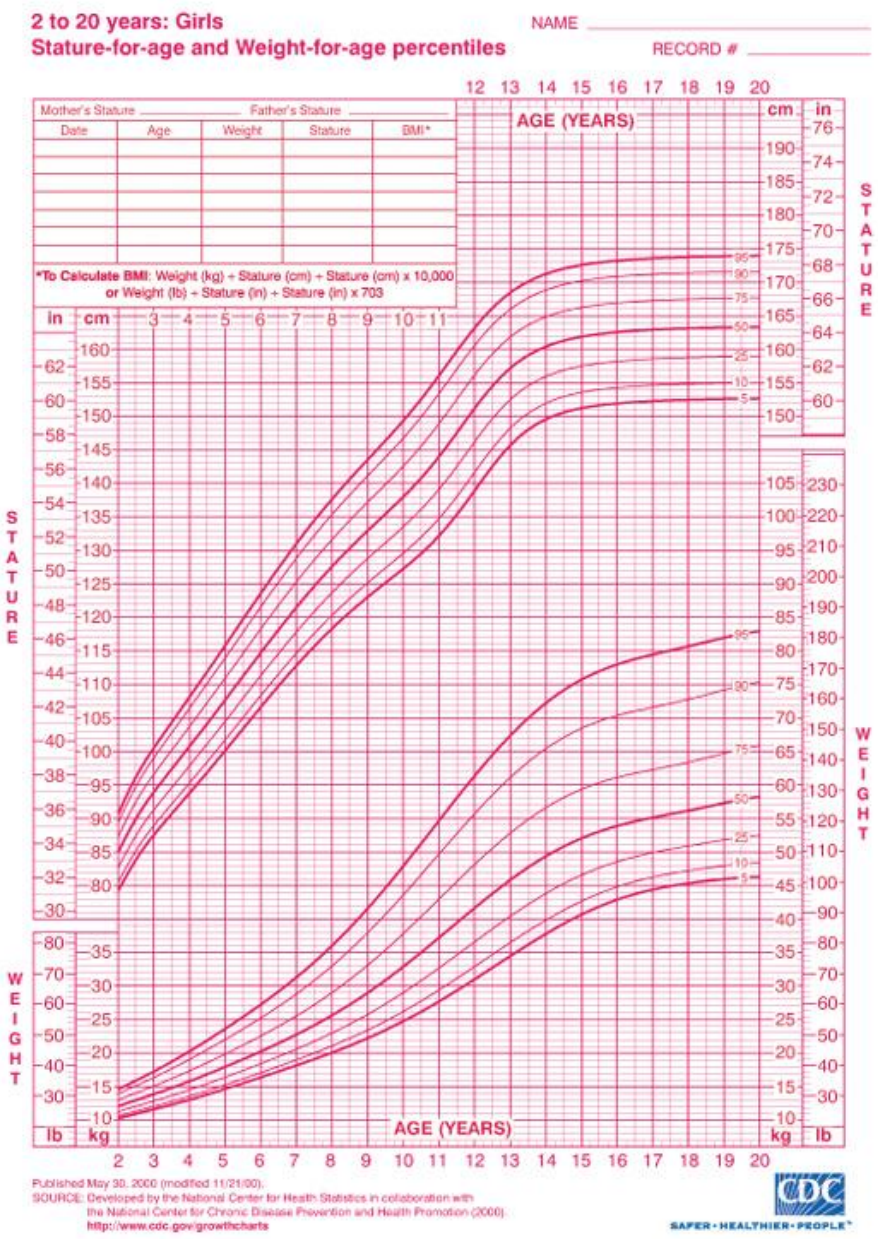


Figure 4. CDC Growth Chart: for Girls aged 2 – 20 (percentiles)

Centers for Disease Control and Prevention. *Girls Stature-for-age and Weight-for-age. http://www.cdc.gov/growthcharts/clinical_charts.htm (accessed 25 March 2014).*

Pathogenesis of FTT

An alternative way to group the causes of FTT is by the general mechanisms which ultimately all lead to malnourishment and are divided into: inadequate caloric intake, inadequate absorption, increased caloric requirements or defective utilization of calories. Based on this caloric organization, *Table 1* shows a differential diagnosis for some of the more common organic causes of FTT.

FTT due to inadequate caloric intake is the most frequently seen mechanism in primary care because it encompasses nonorganic causes which are more common, such as neglect and feeding problems (11). But there are also gastrointestinal conditions which are placed in this group. They include gastroesophageal reflux disease (GERD) and irritable bowel syndrome (IBS). The signs and symptoms of these GI issues appear as the doctor continues to assess the child; when they enquire about their patient's history and complete a physical examination. The amount of calories a child takes in may be sufficient but there may be an issue with the absorption of nutrients. Children affected by short bowel syndrome either due to a severe intestinal disease or after surgical removal of a large portion of intestines have a physically smaller capacity to absorb what they have eaten. Malabsorption also occurs in children suffering from CD, CF and chronic diarrhea. Another scenario is when the child consumes the appropriate calories, utilizes them properly, but because of a chronic condition their caloric expenditure is increased.

Pathologies of the gastrointestinal system can lead to malnourishment and FTT through one or more of these general mechanisms. In the case of cystic fibrosis, exocrine pancreatic insufficiency and the lack of pancreatic enzymes necessary for digestion of fats, is the main reason for inadequate absorption (14). Similarly, the lack of bile and lowered duodenal pH contribute to the same issue (14). These patients may also be suffering from a progressive chronic pulmonary infection, which leads to increased caloric requirements. A high-fat diet is advised in these patients, but a stressed child may exhibit a poor appetite and due to decreased compliance have inadequate caloric intake (14). The number of contributing mechanisms and the overall caloric deficit will determine the speed of faltering growth and the severity of FTT.

Table 1. Main Organic Causes of Failure to Thrive

Main Organic Causes of FTT	
Inadequate caloric intake/ Excessive loss of nutrients	Cleft lip or Cleft Palate, Oromotor Dysfunction, Cerebral Palsy, Parasites, Gastroesophageal Reflux, Irritable Bowel Syndrome, Pyloric Stenosis, Chronic Diarrhea
Inadequate absorption	Food intolerance and allergy, Celiac Disease, Inflammatory Bowel Disease, Inborn errors of metabolism, Cystic Fibrosis, Giardiasis, Short Gut Syndrome
Increased energy requirements	Chronic infection or immunodeficiency, Chronic pulmonary disease, Malignancy, Cystic Fibrosis, Heart Failure, Hyperthyroidism, Infection, Endocrine disorders
Defective utilization of calories	Trisomies 21, 18, and 13, Diabetes Mellitus, Classic Galactosemia Inborn errors of metabolism, Fructose Intolerance

Diagnostic Evaluation of the Patient: History

Once establishing a child's development as faltering with their anthropometric measures plotted on growth charts, a complete patient history is done. It is the next important component of a thorough investigation into a child with organic FTT due to a gastrointestinal cause. A doctor needs to obtain a detailed history by questioning the primary care-giver, ideally a family member, and they should also involve the child if they are age-appropriate. This should take place in a relaxed, quiet environment to promote cooperation with the child and to hold a constructive conversation with the care-giver.

The history should be extensive and, as seen in *Table 2*, should cover the following areas:

Prenatal History**:** The mother should describe her pregnancy and if she was exposed to any teratogens, drugs or medication. Any complications during child-birth and whether or not the child was born prematurely should also be noted. A premature infant's growth should be compared on growth charts and percentiles using their corrected age for the first two years of life (1). The doctor needs to differentiate FTT from small for gestational age (SGA). Causes of SGA, such as chromosomal disorders, pre-eclampsia, and congenital infections, should be noted while talking with the mother.

Nutritional History: Feeding habits are to be characterized; the amount and frequency of meals should be documented, as well as the type of food and liquids consumed. A decrease in appetite or anorexia is important to note. Alternatively, if the care-giver finds that the child is extremely hungry and not gaining weight even with frequent meals, numerous diseases should be considered, including PS, CD, GERD, IBD and CF (4). The doctor should enquire about any postprandial symptoms such as vomiting, heartburn, and acid reflux, which are common complaints in a child that may be suffering from GERD. The consistency, quantity and frequency of stools should be noted. A three-day food diary is a way of accurately documenting the child's dietary history; parents are encouraged to write down everything the child consumes at home and at school over the course of several days. In consultation with a dietician, the child's caloric intake can be calculated along with a breakdown of meal components including carbohydrates, proteins, fats, vitamins and minerals. If the child is being breast fed, the mother should measure the amount of milk that she is able to produce and feed to the child. The age of the patient should also be noted; some symptoms may

coincide with the introduction of new food, such as weaning from breast milk to cow's milk. Since gluten-containing foods are added to a child's diet between the ages of 4-6 months, CD will usually only start to show symptoms around this period (15). Any earlier symptoms or faltering growth might be suggestive of other gastrointestinal causes of FTT such as GERD or CF (15).

Medical History (Past and Present): The care-giver should be asked to describe all of the child's previous illnesses. Recurrent infections, fever or respiratory symptoms such as a chronic cough should be queried by the doctor, as should any recent or sudden weight loss. Abdominal pain should be described thoroughly; the location, duration, and any aggravating factors should be mentioned. Any bloating, diarrhea or constipation could be indicative of gastrointestinal disturbances and any steatorrhea, blood or mucus in stools could be the signs of malabsorption or IBD (13). The patient may complain of nocturnal diarrhea or noticed gross or occult rectal bleeding present for the last 4-6 weeks, in which case; the doctor must lead further investigations into CrD (16). A complaint of chronic diarrhea alone could again be due to malabsorption disorders (CD, CF and lactose intolerance) or infections such as giardiasis (9). Persistent vomiting may be a sign of an anatomical abnormality of the bowels or of GERD and should be further explored (9). With reported signs and symptoms along with serial anthropometric measurements, the doctor will begin to build a full clinical picture of the patient.

Socioeconomic History: The doctor should enquire about the family's employment and financial stability, along with the parent's level of education and mental health. Any possible socioeconomic causes of stress in the family should be investigated in case there is a NOFTT superimposed on an organic cause of FTT.

Family History: The medical history of the family is also an essential part into the investigation of the child's FTT. The anthropometric measures of both parents and of any siblings should be carried out; the child's size may be due to constitutional factors. Doctors should ask about previous pregnancies, if any siblings were born prematurely, or were born SGA. In addition, any familial cases of developmental delay may give important clues to the child's FTT (9). Included in this part of the history should be any family member's significant illnesses affecting the respiratory, gastrointestinal or endocrine systems as they may be connected to the child's current condition. In the case of IBD, an individual has a 10-15 times greater risk if a first-degree relative is affected by the disease (16). Other autoimmune

diseases also show a high prevalence in some families. Genetic factors increase an individual's risk of CD to between 5-18% when a first-degree relative is affected (17). This shows the importance of asking detailed questions about each family member. Keeping these familial factors in mind will place a priority on certain disorders which need to be further investigated and excluded first. This helps narrow the differential diagnosis for the doctor.

Once each component of the patient's history and information about the other family members has been gathered, all noteworthy information will direct the doctor's subsequent evaluations. Collected from the history above, a doctor should start to suspect a gastrointestinal cause in a child with a history of vomiting, diarrhea, or constipation, abdominal pain, a positive family history and of course faltering growth.

Table 2. Main Topics in the Evaluation of Patient History

Evaluation of a Patient's History	
General History (Prenatal and Postnatal)	Obstetric events Nutritional intake Three-day food diary Postprandial symptoms Stool (consistency, frequency, amount)
Medical History (Past and Current)	Previous illnesses Meconium ileus or delayed pass of meconium Respiratory, gastrointestinal or endocrine issues Recurrent infections or fever Persistent signs or symptoms (vomiting, constipation, diarrhea, etc.) Recent or sudden weight loss
Socioeconomic History	Income Level of education Stress factors Abuse or neglect
Family History	Anthropometric measures Major illnesses Autoimmune diseases Constitutional factors (small parents, maternal ethnicity, BMI)

Diagnostic Evaluation of the Patient: Physical Examination

After questioning the child and care-giver, and completing the patient's history, a meticulous physical examination is the next fundamental step in investigating the causes of organic FTT. A general physical evaluation is only the precursor to a more focused examination of the patient's complaints, as well as signs and symptoms that were discovered during history taking. Focus should then be put on understanding the physical findings which could be linked to the child's gastrointestinal complaints, and eventually the origin of the child's FTT.

The doctor should start by inspecting the child's general appearance. The patient should be undressed and observed from head to toe. Does the child look undernourished? Is the child agitated or weak? The doctor should search for any signs of neglect or abuse. Again, NOFTT should be excluded or it could be simultaneously present with an organic cause of FTT. The doctor's role is to investigate, diagnose and treat the organic cause. The child's skin should be evaluated for rashes. If malnutrition is longstanding, its effects will be quite evident. The child might have dry, pale and cracked skin, diminished amounts of subcutaneous fat, a swollen abdomen, sparse hair and signs of vitamin deficiencies (9,13). The doctor should inspect for any dysmorphic features, as the child may be affected by a genetic abnormality, or by a syndrome, which can affect the gastrointestinal system. The mouth should be checked for cleft palate, quality of sucking movements and tooth status to rule out any feeding issues and for any lesions which might be clues to a gastrointestinal disease. Auscultation of breathe sounds is important for detecting respiratory infections, while the heart should be checked for murmurs to exclude congenital heart defects. Continuing the systematic exam, the abdomen should be palpated for any masses or tenderness. If the doctor is considering lysosomal storage disorders, palpation for hepatomegaly and/or splenomegaly should be done (1). Also, the perianal area and rectum should be examined.

Once the physical examination has been completed, the doctor should take into consideration all of the physical findings and relate them back to the patient's history. Gastrointestinal causes of FTT can manifest in a wide spectrum of clinical findings. The child can show a variety of extraintestinal manifestations, such as perianal fissures, fistula openings abdominal distention, or exhibit nothing but faltering growth. The latter is then quite challenging. In the case that neurological, endocrine, cardiac and other organic causes have

been ruled unlikely, the doctor's focus should continue to search for a gastrointestinal cause. The patient's history and physical findings will suggest which further diagnostic investigations need to be done.

Disease-specific Investigations and Diagnostic Criteria

As previously mentioned, FTT may be due to a variety of underlying diseases. Depending on the age of the patient, a doctor should suspect some causes more than others. Newborns with FTT will be affected by genetic disorders, anatomical abnormalities and congenital resorption defects (9,13). Short bowel syndrome following surgery for necrotizing enterocolitis is also a common cause of FTT in newborns (13). With infants and young children, a doctor should investigate causes such as an intestinal allergy to cow's milk protein and esophagitis with gastroesophageal reflux (GER), and should consider the risk of CF and CD (13). Causes in older children and adolescents may include chronic inflammatory intestinal diseases, and psychiatric disorders, particularly anorexia nervosa (13).

A systematic approach is encouraged to ensure a thorough evaluation, as working on the basis of exclusion may be easier for a junior doctor. Clinicians may have patients referred from other departments because of predominantly gastrointestinal symptoms. As the underlying causes of FTT are associated with multiple organ systems, they should all be explored. Neurological problems, such as hypotonia, cranial nerve palsy, Arnold-Chiari malformation, or neuromuscular weakness cause feeding difficulties and an inadequate caloric intake. Negative investigations for malignancies and examinations for congenital heart defects help to exclude oncological and cardiac origins of FTT. The child should be evaluated for a possible renal source contributing to their FTT, such as kidney chronic renal disease or renal tubular necrosis, which causes an increase of energy expenditure. Subsequently, the endocrine system could be the origin of the underlying problem. Diseases including hyperthyroidism, diabetes mellitus, and growth hormone deficiency should have a place in the differential diagnosis. Investigations concerning the gastrointestinal system will complete a systematic evaluation of the child for the remaining possible causes of FTT.

A clinician's working diagnosis is strongly based on a patient's history and examination (3). Each disease has specific investigations and criteria which must be fulfilled for a definitive diagnosis of FTT.

CrD

CrD is chronic, relapsing and one of the most frequently diagnosed IBDs, which can affect the whole digestive tract. Doctors should be aware that one quarter of patients with IBD will present in childhood (18). After gathering the patient's history and completing the physical examination, the doctor should have sufficient information to suspect CrD, as the diagnosis is primarily clinical (16). Furthermore, the diagnosis is later supported with investigations such as measuring laboratory inflammatory parameters, radiology, endoscopy and histology (16).

The child will have a history of gastrointestinal problems such as abdominal pain, diarrhea with blood and/or mucus, which may be nocturnal. There may be gross or occult rectal bleeding, and a fever may be reported. Depending on the age of the patient, along with faltering growth there may be a delay in puberty, which is assessed with Tanner staging. There can also be a positive family history for IBD. The physical examination in a child with CrD can yield a variety of extraintestinal manifestations (EIM), because the gastrointestinal system is not that only one that can be involved. 6% of children will present with at least one EIM before being diagnosed and are found more frequently in children older than five (19). If present, dermatological issues such as erythema nodosum, psoriasis, and pyoderma gangrenosum will found during a thorough inspection of the skin. Ophthalmologic findings may include iritis and uveitis. On further inspection, joint pain, swelling and redness indicate musculoskeletal involvement. Arthritis, more commonly found peripherally than axially, along with aphthous stomatitis are the most frequent EIMs found before diagnosis of IBD (16). Finally, fissures, fistulae, perirectal abscesses and skin tags may be present when the perianal region is checked.

With this history and these physical characteristics, further diagnostics are warranted. The first imaging technique used is usually transabdominal ultrasound. This is used to search for thickening of the bowel wall and mesenteric lymphadenitis. For proper diagnosis, endoscopy, colonoscopy and gastroduodenoscopy, is mandatory (16). This allows for histological confirmation of transmural inflammation, which is chronic and skips areas of bowel. Granulomas and pyloric gland metaplasia can also be seen. At least two biopsies from at least five colonic segments should be taken and should include a sample from the ileum (16). Extramural inflammation, abscesses, and fistulae can be detected with non-radiating

techniques such as magnetic resonance enterography. In pediatric patients, it is suggested to use alternative diagnostics instead of methods which use ionising radiation (small bowel follow through and CT), as the latter increases the risk of cancer later on in life (16). Once strictures are ruled out, capsule endoscopy can be preformed to look for inflammation or other changes in the small bowel.

As for laboratory findings used for the diagnosis of CrD, unfortunately, there are no disease specific markers. A complete blood count (CBC) may show anemia and thrombocytosis, there may be an increase in the erythrocyte sedimentation rate (ESR) and deficiencies of iron, and vitamin B12 may also be present. Non-specific inflammatory markers, such as C-reactive protein, fibrinogen, fecal calprotectin and lactoferrin are the best-investigated markers as they can signify active disease (16). Serum proteinogram should also be evaluated. Serological markers most frequently used in CrD include antibodies against mannan of Saccaromyces cerevisiae (ASCA) and antineutrophil-cytoplasmic antibodies (ANCA). Combinations of ASCA and ANCA along with pancreatic autoantibody and goblet cell antibodies are used to indicate whether CrD or UC is a more likely diagnosis (16).

Once CrD has been established, it is classified according to the Montreal Classification. In the case of a pediatric patient, a modified Paris classification is used which considers age at diagnosis, location of the disease, behavior (structuring, penetrating, neither or both) (16). Lastly, the Paris classification takes into account whether or not there is a growth delay, which is clearly present in a child that first presented with FTT.

CD

CD is an enteropathy which becomes apparent with the introduction of the protein gluten into the child's diet, usually around the age of six to eight months. The care-giver will document gluten-containing foods, such as wheat, barley, rye in the child's dietary diary. They may also mention family members affected by CD. Due to its high prevalence, CD is believed to be the most common genetically predetermined condition (20). Based on European and American studies, approximately 3–13/1,000 children between the age of 2.5 and 15 years are affected (21). With this large number of children involved, doctors should be familiar with the variety of clinical presentations of CD. Symptoms can range from classical clinical features to asymptomatic children with silent CD identified on screening. Clinicians

should be familiar with the appropriate diagnostic guidelines including serology, endoscopy and biopsy.

CD most commonly presents with abdominal distention, and less often with chronic diarrhea (20). Classically, other symptoms include abdominal pain, anorexia, irritability, vomiting and naturally FTT. Hypoproteinemia is present in approximately half of the children with CD, which may or may not develop into evident ascites seen on physical examination (20). The doctor should be aware of the increasing trend of atypical variants of CD, now seen more often in older children (20).

With these patients, EIMs are more apparent on physical examination. Rather than the classical gastrointestinal complaints, children with atypical CD may present with arthritis, dental enamel hypoplasia of permanent teeth and although rare, may exhibit dermatitis herpetiformis. Anemia is almost always present and is due to an iron deficiency (20). Children with CD are also at an increased risk of osteopenia, osteoporosis, and concurrent autoimmune diseases.

On completion of history and physical examination, criteria for the diagnosis of CD follow guidelines focused on patients presenting with clinical symptoms or asymptomatic individuals with associated risks factors. Clinicians are to begin further investigations by first doing serological tests for IgA tissue transglutaminase antibody, and IgA antiendomysial antibody. Some CD patients may be affected by IgA deficiency; it is beneficial to measure total serum IgA to ensure accuracy of earlier tests. If an IgA deficiency is not present, either test shows a sensitivity and specificity of 95% (22). Because of less accuracy, antigliadin antibody tests are not recommended (21). With positive serologic testing, doctors should confirm the diagnosis of CD with small bowel biopsies. Four to six biopsies should be taken from the small bowel, including samples from the second portion and distal duodenum (17). The patient should be on a gluten diet to ensure histological changes such as mucosal inflammation, villous atrophy, hyperplasia of crypts, and increased intraepithelial lymphocytes.

Along with positive serology and characteristic biopsy findings, the child should immediately be placed on a gluten-free diet (GFD) to impede previously mentioned symptoms. If the response to treatment is uncertain, repeat biopsies should be done. Clinicians should keep in mind that histological improvements lag behind clinical response (22). With proper education and strict enforcement of a GFD with the help of the care-giver, children

previously suffering with FTT will show an increased appetite and eventually begin to gain weight.

GERD

The involuntary passage of gastric contents into the esophagus is called GER. Also known as "spitting up", GER is considered physiological. 70-85% of infants under the age of two months experience innocent regurgitation, and the majority resolve (23). A child is considered to have pathological GER or GERD if there are worrying symptoms or complications associated with reflux, such as FTT. A doctor should monitor the child with persistent GER and must be ready to investigate if GER does not cease or begins to cause serious problems.

There are a variety of clinical presentations of GERD, and symptoms depend of the age of the child. In infantile GERD, regurgitation with occasional projectile vomiting is the most common feature (24). Even with sufficient quantities of food and frequent feeding noted in a dietary diary, recurrent regurgitation will eventually lead to FTT. The child is unable to retain enough food needed for normal growth and development. The care-giver will note an infant with persistent hiccups, mention nonspecific symptoms such as irritability and back-arching or complain of excessive crying. In older children and adolescents, GERD presents with symptoms seen more commonly in adults, the most common being heartburn (24). Heartburn is described by the patient as being a retrosternal burning sensation. They may mention excessive burping, abdominal pain, and refusal to eat. Doctors should be understanding of other concomitant extraesophageal symptoms, such as dental erosions, hoarse voice, recurrent otitis media and sinusitis. Respiratory symptoms are also linked with GERD such as chronic coughing, aspiration pneumonia and 'gastric asthma' (24).

Further diagnostic evaluation is needed in GERD as none of the symptoms are specific for the disease. Additional investigations include radiography, endoscopy with biopsy, esophageal pH monitoring, and esophageal impedance monitoring. Parents may be asked to complete a GER questionnaire. This helps to support a doctor's decision to investigate further, but unfortunately, there is no 'gold standard' investigation for GERD (24). An upper gastrointestinal series with the use of barium is done to rule out anatomical abnormalities which may mimic GER. Endoscopy with biopsy and histology is useful to examine

esophageal damage and to exclude other conditions, such as eosinophilic esophagitis (23). Endoscopy can classify GERD as either nonerosive reflux disease, or erosive esophagitis depending on the extent of mucosal damage (2). Macroscopic lesions associated with GERD include erosions, exudate, ulcers, strictures, and hiatal hernia. Furthermore, 24-hour pH probe monitoring can be done which counts "GERD episodes" or the amount of time the esophageal pH is below 4. The percentage of time in 24 hours with this low pH is referred to the Reflux Index and considered the most valid measure of reflux, because it is the total acid exposure time in the esophagus (23). In infants, a reflux index of more than 11% and more than 7% in older children is considered abnormal (23). Alternatively or in combination with a pH probe, impedance monitoring records the flow of gastric contents based on changes in electrical current.

For uncomplicated GER, a clinical diagnosis is often sufficient enough for children with regurgitation since 95% of cases will resolve by the age of 1 without intervention (23). It is when the child presents with GERD with complications so severe that the growth is faltering, that a doctor must quickly organize further diagnostic investigations and therapeutic interventions.

Food Allergy

Adverse reactions to food can be divided into immune and nonimmune reactions. These can be distinguished by the timing of clinical reactions in relation to food ingestion (10). Delayed reactions, which are non-IgE mediated, consist of mainly gastrointestinal or cutaneous manifestations (10). The onset of signs and symptoms are seen several hours or even days after food ingestion. This creates a challenge for junior doctors. Additionally, it is common for a child to have multiple food allergies, which further complicates the diagnosis (10). Various gastrointestinal allergic disorders which may be the cause of a child presenting with FTT include food protein-induced enteropathy, proctocolitis and chronic food protein enterocolitis syndrome (FPIES).

Children with food allergies may present with a variety of clinical manifestations. Gastrointestinal complaints may include persistent diarrhea, profuse vomiting, steatorrhea and low-grade rectal bleeding. A careful history should establish the time interval between the ingestion of offending foods and the onset of symptoms. A diary will show if new foods have

been introduced to the diet, and help identify the amount of food needed to cause symptoms. Also, doctors should confirm if the child is breastfed as some disorders, such as FPIES, do not occur in these infants (10). In the case of FPIES, chronic exposure to allergens including cow's milk, soy, grains (wheat, rice) and chicken will lead to FTT (22). Acute complications may occur in FPIES, especially on re-exposure following a period of elimination (22). A doctor might be faced with a severely dehydrated child, possibly in hypovolemic shock. This should not be mistaken for sepsis or gastroenteritis (10).

With a complete history, doctors should continue the clinical workup with radioallergosorbent test (RAST) and skin prick testing (SPT) to differentiate IgE from non-IgE-mediated food allergies. Negative RAST and SPT warrant further investigation to confirm causes of delayed allergic reactions. Endoscopy should be performed with the examination of intestinal biopsies. In the case of proctocolitis, the rectal mucosa will show increased lymphocytes and eosinophils, with focal epithelial ulceration (10). Care-givers should be strongly encouraged to promptly change the child's diet and to closely observe the response to allergen elimination. Since children may develop tolerance to the food allergen; re-assessments should be conducted on a regular basis.

A child with food hypersensitivity is at high risk of FTT because of persistent vomiting and diarrhea, especially if there are associated feeding difficulties (10). Doctors will encounter children clearly allergic to certain allergens, who exhibit reactions such as urticaria, angioedema and anaphylaxis. For children who do not demonstrate such obvious systemic symptoms, doctors should be aware of the necessary diagnostic investigations for non-IgE-mediated reactions.

CF

CF is an autosomal recessive disorder involving the mutation of the cystic fibrosis transmembrane regulator (CFTR) gene. With this comes a change in the body's sweat glands, pancreatic secretions and makes a child more prone to airway infections. CF is a chronic and progressive disease, and as previously mentioned, leads to malnutrition and FTT through numerous mechanisms. Nutritional deficits arise because of malabsorption from pancreatic insufficiency, increased caloric expenditure due to chronic lung infections and fever and inadequate dietary intake can occur due to anorexia. The seriousness of CF complications

calls for prompt diagnosis; especially in countries which do not include newborn screening of CF. Doctors should be familiar with the signs and symptoms to recognize when to order diagnostic tests.

A portion of infants will present to the doctor with meconium ileus. Clinicians should immediately include CF in their differential diagnosis as 80% of cases of meconium ileus are associated with the disorder (24). For the remainder affected by CF, signs might not point so obviously to this cause. Older children may present with distal intestinal obstruction syndrome, with symptoms of crampy abdominal pain and distention, nausea and vomiting. They may also have delayed puberty. The care-giver may have noticed a salty taste when kissing the child's skin, which is a sign of excessive levels of sodium and chloride in the sweat. Doctors should ask about any familial cases of CF. When asked about other symptoms, care-givers may mention the child's persistent or recurrent cough or pneumonia which indicates a chronic respiratory infection. Any hemoptysis should be alarming. Chronic sinusitis and nasal polyposis are common, and any child under the age of 12 with nasal polyps should be evaluated for CF (22). Steatorrhea will occur due to fat malabsorption, and unexplained peripheral edema may be present if there is an issue with protein absorption. Cholestatic jaundice in infancy or prolonged, direct-reacting neonatal jaundice may also be a sign. Laboratory findings will show hyponatremia and hypochloremic metabolic alkalosis due to the failure of sweat ducts to conserve electrolytes (22). Tests will also show additional nutritional deficiencies of fat-soluble vitamins (A, D, E, and K), while hypoproteinemia and hypoalbuminemia are responsible for the edema. The presence of *Pseudomonas aeruginosa* in the respiratory tract, unexplained by any other factors, such as prolonged intubation or tracheostomy, requires further testing.

Newborn screening is the first test done during the first 48-72 hours of life. It is a heel-prick test which measures the level of immunoreactive trypsinogen. If this is elevated, it is an indication for DNA testing for CFTR mutations. Two known CF mutations confirmed by DNA analysis is diagnostic for CF. Unfortunately, not all countries include CF in neonatal screening, in which case the variety of signs and symptoms mentioned above is an indication for performing a sweat test. Certain criteria should be established in order to diagnose CF. One or more typical clinical features of CF must be indentified in the child. This includes chronic pulmonary disease, gastrointestinal and nutritional abnormalities, and salt loss syndromes. Alternatively, the child must have two positive sweat tests and then prove CF through DNA analysis. Sweat tests must be confirmed at a CF Foundation certified laboratory

and results > 60 mEq/L are considered positive, borderline is 40-60 mEq/L and negative if below 40 mEq/L.

CF is a complex disorder with a vast number of severe complications. Diagnosis is complicated, especially in countries that do not screen for CF regularly. A doctor will be faced with a child with an array of symptoms on top of malnutrition and FTT. Vitamins, fat and protein deficiencies, along with liver, pancreatic or respiratory issues should influence a clinician's differential diagnosis. Two reproducible sweat tests and confirmation of two CFTR gene mutations, through DNA analysis, are criteria to satisfy the diagnosis of CF.

Giardiasis

Giardia lamblia, a parasite involved in the diarrheal disease Giardiasis, is found in contaminated water and food. It is the most commonly reported intestinal parasite worldwide and affects children from the age of 2-12 more frequently than adults (25). Most infections are self-limiting, but because of the risk of re-infection, chronic infections with *G. lamblia* are possible. Gastrointestinal manifestations in symptomatic children such as diarrhea and abdominal complaints are due to microbial overgrowth (26), while direct damage to intestinal mucosa is found to show a spectrum of clinical presentations (27). Through mechanisms of malabsorption, maldigestion and malnutrition, giardiasis has been shown to affect anthropomorphic factors (28), and over time affected children can develop growth disturbances and FTT.

An ill child with giardiasis will present to the doctor with a range of gastrointestinal troubles. Clinical symptoms include abdominal pain, diarrhea, bloating, and nausea. Patients may also have steatorrhea and a mild fever. Rarely, an infection with *G. lamblia* can be associated with symptoms of cholecystitis and cholangitis (27). Through a conversation with the care-giver, the duration of the illness will be established and if the diarrhea has been acute or chronic. Both of these are key factors associated with growth disturbance and FTT (28). They should also be questioned about recent travels, especially to developing countries. Travelers are a susceptible group which are at greater risk of giardiasis, as are children in daycare centers (26). Socioeconomic conditions are important factors and should be explored; along with poor sanitation and improper housing, they contribute to the high prevalence of this parasite (25). Doctors should enquire about any other disorders the child may have.

Giardiasis is more likely to become chronic in patients with common variable immunodeficiency and Bruton's X-linked agammaglobulinemia (28).

Additional investigations should be ordered by the clinician to identify and confirm *G. lamblia* as the causative agent. Stool samples should be collected from the child and examined for cysts and trophozoites. Multiple samples collected over several days are required for diagnosis because of intermittent shedding of organisms (29). Stool antigen detection is highly sensitive and specific (30) and is done by enzyme immunoassays (EIAs), also direct fluorescent-antibody tests can be done to detect intact organisms (29). Alternatively, microscopic examination can be used and most often detects cysts (30). Other diagnostic methods include sampling of the small bowel but are more expensive, invasive, and uncomfortable for the child (30).

Doctors should be prepared to order additional tests when faced with a child with predominantly gastrointestinal symptoms and FTT. The child with giardiasis may present with a range of clinical manifestations, from asymptomatic to a fatigued patient with chronic diarrhea. Most infections of *G. lamblia* are self-limiting (28), but because of the risk of re-infection and chronic illness, the child may be prone to complications such as impaired cognitive function, chronic fatigue syndrome and IBS (28). A doctor must quickly make a diagnosis with the identification of parasite antigens in the child's stool to decrease the risk of these chronic gastrointestinal consequences of giardiasis, and to ultimately treat the child's FTT.

Other Causes

In certain patients, some conditions may not be as obvious as others. A child may have difficulties in consuming adequate or proper nutrition by mouth. This is considered a feeding disorder. A doctor should still consider special conditions and diseases such as anorexia nervosa and bulimia nervosa, as they may present independently or concurrently with other organic causes of FTT (31). Once recognized in patients, a multidisciplinary approach with nutritionists and psychiatrists is necessary for the diagnosis and appropriate treatment.

HIV infections also have nutritional consequences on a child. Infected children have difficulties gaining weight, and may present with stunting or wasting. This is due to decreased caloric intake, increased caloric utilization and due to gastrointestinal malabsorption (10).

Infants affected by the vertical transmission of the virus have lower birthweights and are prone to micronutrient deficiencies (10). Deficiencies of vitamin A, selenium and zinc may accelerate the progression of the disease. A high viral load is also associated with a greater risk of growth failure. Doctors should immediately consider HIV as the underlying cause of FTT in any child born to a HIV-positive mother.

An additional cause of malnutrition is cholestatic liver disease. Clinicians will encounter children affected by FTT with poor dietary intake. The child will also present with organomegaly, ascites and vomiting, all of which affect the child's gastric volume (10). Contributing to the malnutrition is the decreased absorption of macronutrients, particularly of fats and fat-soluble vitamins, because of the lack of bile acids (10). Furthermore; energy expenditure is increased in these children. Cholestatic liver disease negatively affects a child's nutritional status through multiple mechanisms, and should be investigated promptly.

Conclusion

Although a concrete definition for FTT does not exist, there are many anthropometric measurements, such as height and weight, which can be used to monitor a child's growth and development. Measurements should be taken each time the child visits the general practitioner; plotting a series of values allows for easy monitoring and for accurate assessment of FTT. Any rapid decrease across two major percentile lines or values under certain percentages on standardized growth cards created by the CDC and WHO are a cause for concern.

FTT is a common problem for practitioners, and so they should be familiar with the diversity of patients that present with FTT. With a significant portion affected with faltering growth, a doctor should know how to approach the issue in a strategic manner. This helps ensure quality in routine practice, as it may be difficult for an inexperienced clinician to identify a cause. FTT is responsible for 5-10% of children under the age of five seen in primary care in the United States, with even higher rates in developing countries (1,11). FTT may be found incidentally on systematic physicals examinations especially if is the only symptom, or it may be identified secondarily in a child brought in for other symptoms. There are more visible issues a child may have coexisting with FTT, such as anorexia, diarrhea, or persistent respiratory infections. It is a doctor's responsibility to find the explanation. As

previously mentioned, the causes of FTT are numerous, and the majority of reasons are non-organic; doctors should not forget the possibility of organic causes. When considering organic causes of FTT, it is vital for the doctor to be aware of the gastrointestinal reasons. These small numbers of cases carry along with them very serious complications, which not only hinder a child's growth and development, but can also affect their quality of life.

When faced with a child with FTT, a physician must start with a thorough and structured patient history, including any prenatal and obstetric events. With the help of the child's care-giver, the severity of issues can be assessed and a timeline of the length of symptoms and chronicity of the problem can be established. Along with co-existing diseases, the doctor will be informed of any prevalent family illnesses or siblings with similar complaints, which may play a factor in the child's current symptoms. The physician should also keep in mind of the possibility of co-existing NOFTT. This will be evident through conversation when developing a relationship with the care-giver. A three-day food diary will give insight to the child's nutritional intake. A doctor should then consult a dietician to help in the assessment of the patient's diet.

After documenting the patient's history, the doctor should do a complete physical examination. The child should be looked at from head to toe, for any signs or clues that will assist with the diagnosis. Extraintestinal manifestations of gastrointestinal causes of FTT may be present on the skin or inside the mouth; additionally any other organ system in the body can be involved. A systems-based approach demonstrates a doctor's professional expertise (3) and ensures nothing is overlooked. The importance of a proper patient history and physical examination must be stressed. It will guide the clinician's decisions in regards to further investigations.

A variety of diagnostic procedures may be indicated depending on the previous findings. It may include imaging such as transabdominal ultrasound to look for intestinal changes in the case of CrD, or look for hypertrophic changes seen in pyloric stenosis. Test such as serological testing for IgA antibodies is done in CD and diagnosis is confirmed with small bowel biopsies. Biopsies are also done in suspected cases of CrD and to exclude other diseases presenting similarly to GERD. Gastrointestinal issues such as infections involving *G. lamblia* are investigated and confirmed through stool analysis. Samples should be collected on numerous occasions because of intermittent shedding. Routine laboratory findings are not generally recommended (11). Some studies have shown that only 1.4% of lab investigations

are diagnostically useful (9). This mean they serve only to support of the doctor's suspicions, in light of the patient's history and findings on physical examination.

Children presenting with FTT are often challenging to junior clinicians, as the number of possible causes may be overwhelming. An organized approach to the issue, along with the patient's history and physical exam, are all important pieces in solving the underlying cause of the child's FTT. Doctors should be prepared to assess very young children as 80% present themselves before the age of 18 months (11). In these cases, collaboration with the care-giver is imperative. It is a doctor's responsibility to diagnose and confirm the underlying cause swiftly, as some may be life threatening if not immediately managed. Most importantly, prevention of FTT may help stop these complications from developing. This is done through parental education, neonatal screening, and regular anthropometric measurements (1). Hygiene interventions, hand washing promotion and provision of safe water is also crucial for the growth and development of children (10). Because patients are at a fragile age, a proper diagnosis is crucial for the immediate treatment of gastrointestinal causes of FTT in children.

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Biography

Loren Ida Zelic is a sixth year medical student at the University of Zagreb, in Croatia. Her previous education was in Canada, where she completed the Extended French Program, both in elementary and secondary school. Since enrolling in medical school in 2008, Loren has actively attended a variety of conferences in Zagreb. She is an active member with the European Medical Students' Association, and volunteers at the Zagreb International Medical Summit annually. She is also an active member of the Student Section of Pediatrics in Zagreb. Loren is on the organizing committee and a presenter at the Dubrovnik Summer School, which is centered on educating medical students on important topics in Emergency Medicine. Loren is focused on orientating her professional career in Pediatrics once she completes her medical degree.