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Stages of type 1 diabetes in children and adolescents

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What's new

- ‘Phases’ of diabetes have been renamed as ‘stages’ to align with the new classification of stages 1-3
- Tools for prediction of type 1 diabetes, including genetic risk scores
- Updated information on intervention trials, including primary prevention, and at stage 1 and 2 diabetes

Recommendations and principles

- Individuals with a first degree relative with type 1 diabetes have an approximately 15-fold increased relative risk of type 1 diabetes¹⁻³ **A**
- Individuals with two or more islet antibodies are classified as having the first stage of type 1 diabetes.⁴ and the American Diabetes Association **A**
- The majority of children at risk of type 1 diabetes with multiple islet antibodies progress to diabetes within the next 15 years, compared to ~10% who have a single islet antibody.⁵ **A**
- Screening and intervention before the symptoms of type 1 diabetes should be conducted within the context of defined research studies. **E**
- Individuals who screen positive for genetic or immunological markers of type 1 diabetes should have access to appropriate counseling and information regarding current prevention studies. **E**
- Features suggesting the diagnosis of type 2 or monogenic rather than type 1 diabetes include but are not limited to a family history of diabetes in first degree relatives, obesity, acanthosis nigricans, high-risk racial or ethnic group and undetectable islet autoantibodies. **E**

Stages of Type 1 diabetes

Type 1 diabetes is characterized by four stages as shown in Figure 1.

Stage 1 Multiple islet antibodies, normal blood glucose, pre-symptomatic

Stage 2 Multiple islet antibodies, raised blood glucose, pre-symptomatic

Stage 3 Islet autoimmunity, raised blood glucose, symptomatic

Stage 4 Long standing type 1 diabetes

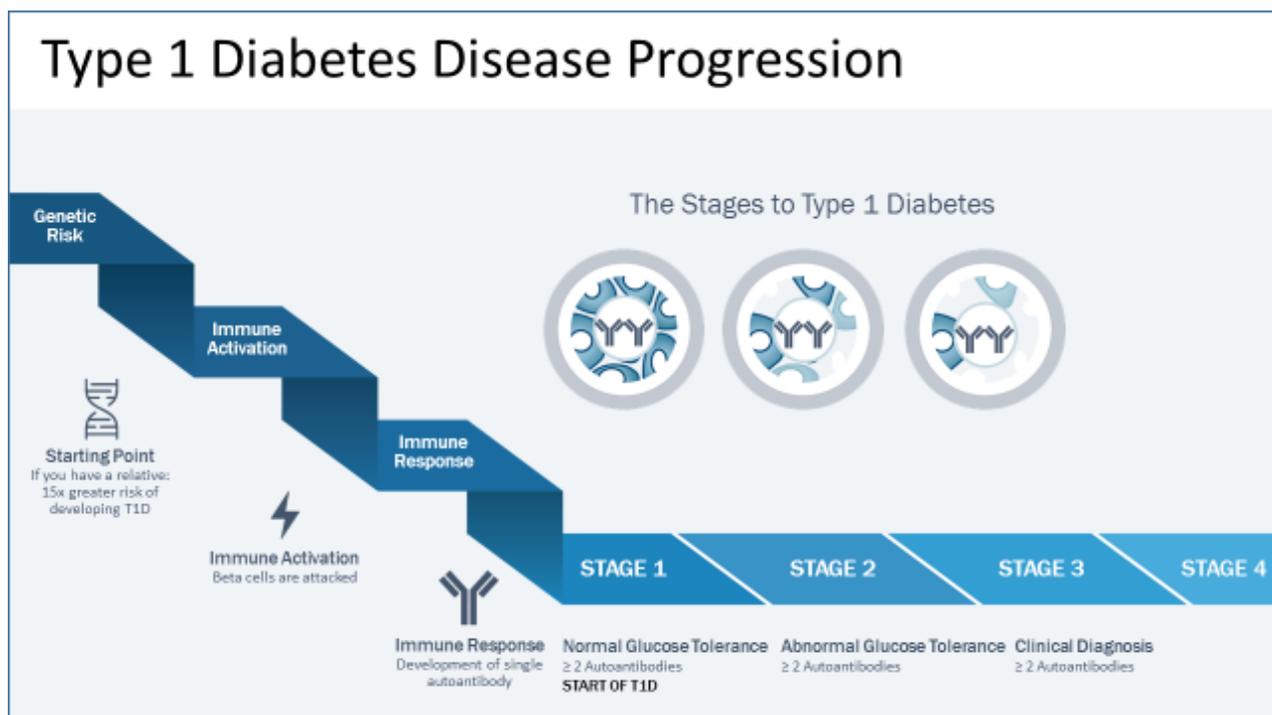


Figure 1: The Stages of type 1 diabetes (T1D) (DiabetesTrialNet.org).

A proportion of individuals who have increased genetic risk of type 1 diabetes progress at variable rates to immune activation and the development of islet autoimmunity. The development of two or more islet antibodies (Stage 1) ultimately progresses to dysglycemia (Stage 2) and then to symptomatic type 1 diabetes (Stage 3).

Risk

Individuals with a first degree relative with type 1 diabetes have an approximately 15-fold increased relative life time risk of type 1 diabetes^{1,3,6}. However at least 85% of children who develop type 1 diabetes do not have a family history of type 1 diabetes. The prevalence of type 1 diabetes in the general population by age 20 years is ~0.3%, compared with ~5% of those with a first degree relative with type 1 diabetes. More than 60 genetic variants have been identified in association with type 1 diabetes by genome-wide association studies⁷. The HLA genotype confers approximately half of the genetic risk for type 1 diabetes^{8,9}. Specific combinations of DR and DQ alleles at the HLA loci confer increased or decreased risk¹⁰. The highest-risk haplotypes are DRB1*03:01-DQA1*05:01-DQB1*02:01 and DRB1*04-DQA1*03:01-DQB1*03:02 (also expressed as DR3/DR4 or DQ2/DQ8 which are in strong linkage disequilibrium). In the general population heterozygotes for DR3/DR4 (DQ2/DQ8) have a 30-fold increased risk of islet autoimmunity and type 1 diabetes¹¹. First-degree relatives carrying DR3/DR4 (DQ2/DQ8) have a further increase in risk consistent with a contribution of non HLA risk loci¹². The highest non-HLA genetic contribution arises from the INS, PTPN22, CTLA4, and IL2RA genes¹³. Genetic risk scores that also incorporate non-HLA genes improve risk estimates for islet autoimmunity and type 1 diabetes^{14,15} and discrete non-HLA genetic markers exist for the risk of progression from islet autoimmunity to clinical type 1 diabetes¹⁶⁻¹⁸.

Immune Activation and Islet (Beta-cell) Autoimmunity

Stages 1 and 2 refer to the months or years preceding the clinical presentation of type 1 diabetes when two or more islet antibodies to proteins associated with secretory granules in β -cells can be detected as markers of β -cell autoimmunity¹⁹: glutamic acid decarboxylase 65 autoantibodies (GAD), tyrosine phosphatase-like insulinoma antigen 2 (IA2) antibodies, insulin autoantibodies (IAA) and β -cell-specific zinc transporter 8 autoantibodies (ZnT8).

Islet autoimmunity and β cell dysfunction begin months to years before the diagnosis of type 1 diabetes. Islet antibodies usually appear in early life whereby over 90% of children who develop type 1 diabetes before puberty have islet antibodies by 5 years. Natural history studies consistently show that nearly all individuals with two or more islet antibodies eventually develop type 1 diabetes, with a rate of diagnosis of ~11% per year amongst two or more antibody positive patients²⁰. The majority of children at risk of type 1 diabetes with two or more islet antibodies progress to diabetes within the next 15 years, compared to a rate of ~10% in those who have a single islet antibody. Progression in children with multiple islet antibodies is faster when

seroconversion to islet autoimmunity is before age 3 years and in children with the HLA DR3/DR4-DQ8 genotype⁵. It is important to note that antibodies can also first appear later in childhood. Thus, genetically at-risk individuals (i.e. family members) who do not have antibodies on initial screening in research studies should be tested annually for development of antibodies until their adult years (DiabetesTrialNet.org).

Loss of β - cell function is often stepwise and non-linear. In addition to immune and genetic markers, the risk of type 1 diabetes may be refined further by measurement of β - cell function as insulin release in response to an intravenous glucose load (IVGTT). Impaired first phase insulin release on IVGTT (defined as an insulin response less than the 10th percentile for age and sex-matched controls) confers a 60% risk of developing type 1 diabetes over the next 5 years²¹. That said, IVGTT does not add prognostic information to the risk of progression; in antibody positive first degree relatives with normal glucose tolerance in the Diabetes Prevention Trial (DPT)-1 trial, the two-hour glucose level on OGTT demonstrated the greatest accuracy for predicting progression to type 1 diabetes²². In those with abnormal glucose tolerance, the combination of 2-hr glucose, peak c-peptide, and area under the curve c-peptide significantly improved the prognostic accuracy compared with a single measure²³. More sensitive predictors of β - cell function, such as elevations in the serum pro-insulin to c-peptide ratio, are under investigation²⁴. Interestingly, antibody positive individuals may experience episodes of hypoglycemia likely due to asynchronous release of insulin in response to meals²⁵. Consistent with this, continuous glucose monitoring detects increased blood glucose variability before the onset of insulin therapy and before progression to symptomatic dysglycemia^{26,27}.

The role of the environment in the pathogenesis of type 1 diabetes

The global increase in the incidence of type 1 diabetes over the last 30 years, in parallel with a reduction in the proportion of individuals with high risk HLA haplotypes²⁸⁻³⁰, confirms the role of the modern environment in its pathogenesis; this is likely through complex gene-environment interactions³¹. There is heightened interest in the interaction of the environment with biological systems (including the microbiome and metabolome), which in turn can regulate immune tolerance. Congenital rubella is a long standing recognized environmental trigger^{32,33}. Other putative exposures are enterovirus infections during pregnancy and childhood^{34,35}, and the introduction of multiple foreign antigens in the infant diet³⁶⁻³⁸. In at-risk children, concurrent breast milk feeding at the time of cereal introduction may be protective³⁷. Omega 3 fatty acids may also have a small protective effect³⁹. Vitamin D metabolism may play, as yet, an undetermined role⁴⁰⁻⁴². The modern environment provides for excess nutrition in mothers during

pregnancy and for rapid growth and weight gain in children in early life with an accompanying reduction in insulin sensitivity. This may accelerate both development of islet autoimmunity and progression to type 1 diabetes⁴³⁻⁴⁵ International networks following children at increased genetic risk from pregnancy or birth are investigating these questions^{5,46,47}.

Prevention of type 1 diabetes and interventions to preserve β - cell function

Care for children living with other autoimmune diseases, such as juvenile idiopathic arthritis, has shifted from symptom treatment to disease-modifying interventions. This is an over-riding goal for type 1 diabetes also. Interventions to preserve β - cell function involve clinical trials before islet autoimmunity (pre-stage 1, primary prevention studies), after the development of islet autoimmunity and before the symptoms of diabetes (Stages 1 and 2), and soon after clinical diagnosis in recent onset diabetes (Stage 3).

Neither screening of any population nor intervention in the preclinical phase should occur outside the context of defined research studies. Individuals who screen positive for genetic or immunological markers of type 1 diabetes should have access to timely counseling and appropriate information about relevant research studies. Families and their at-risk children are generally enthusiastic about entering intervention trials and may benefit from being more prepared if their child is diagnosed with diabetes through participation in follow-up studies⁴⁸. It is our position that unproven treatments that are believed by the medical and research communities to have clinical potential should only be prescribed to patients in the context of carefully monitored clinical trials. The therapeutic value and safety of all treatments and agents must be evaluated rigorously, and human subject (patient) protections must be in place.

Primary prevention trials

Primary prevention trials begin prior to development of islet autoimmunity, typically in young children at increased genetic risk of type 1 diabetes. Since the majority of genetically identified participants would not be expected to progress to clinical disease, the safety of the intervention must be heavily weighed.

- The BABY DIET study showed no benefit from delaying gluten exposure until 12 months of age in 150 at-risk children⁴⁹.
- The FINDIA study, involving 1104 babies, showed that weaning to a cow's milk formula free of bovine insulin reduced the cumulative incidence of islet autoantibodies by age 3 years in

children at genetic risk of type 1 diabetes⁵⁰.

- The international, placebo controlled, randomized TRIGR trial involving 2160 at-risk infants showed no benefit of weaning to an extensively hydrolyzed milk formula on the development of islet autoantibodies by 6 years of age nor the development of type 1 diabetes by 11 years of age⁵¹⁻⁵³.
- The Pre-POINT pilot study demonstrated immune response to high dose oral insulin in a small number of at-risk children⁵⁴. Two studies are further investigating the effects of high-dose oral insulin: one testing whether oral insulin induces an immune response in antibody positive relatives (TrialNet Immune Effects of Oral Insulin Trial; clinicaltrials.gov NCT02580877), and the other testing whether oral insulin results in mucosal tolerance in children in the general population at increased genetic risk, the POINT trial⁵⁵.
- Future primary prevention targets that are being considered include the development of other vaccines that induce immune tolerance in β -cells, an enterovirus vaccine⁵⁶, and use of microbiota and their products (pre or pro-biotics) to induce immune-regulation.

Intervention at stages 1 and 2 of type 1 diabetes

These trials intervene after the development of islet autoimmunity, prior to the onset of symptomatic disease. Since those with multiple antibodies will eventually develop clinical disease, intervention can be considered treatment of early type 1 diabetes, as distinct from prevention. Many consider that intervention at this stage will require combination approaches to multiple targets in the pathogenesis of type 1 diabetes: islet inflammation and autoimmune destruction, β -cell function, and metabolism.

- Type 1 Diabetes TrialNet provides an international network of intervention trials to preserve β -cell function at the different stages^{57,58}. The TrialNet Pathway to Prevention study screens and follows relatives of type 1 diabetes probands. Oral Insulin, CTLA-4 Ig (Abatacept) and anti-CD3 monoclonal antibody (Teplizumab) are currently under investigation in Stage 1 and Stage 2.
- The European Nicotinamide Diabetes Intervention Trial (ENDIT) demonstrated, in a placebo controlled randomized trial of 552 participants, that nicotinamide did not delay or prevent the onset of type 1 diabetes in high-risk first degree relatives⁵⁹.

- The National Institute of Health Diabetes Prevention Trials (DPT-1) demonstrated that neither low dose subcutaneous nor oral insulin therapy delayed or prevented the onset of clinical diabetes in high-risk (N=339) and intermediate-risk (N=372) relatives respectively^{21,60}. However, in post-hoc analysis of those subjects with high insulin autoantibody titers, oral insulin delayed progression to type 1 diabetes⁶⁰. This observation was prospectively retested in the TrialNet Oral Insulin study⁶¹ which failed to prevent type 1 diabetes in the primary cohort of 389 relatives. However, in a second independent cohort of 55 individuals with reduced first phase insulin release there was a detectable delay in progression to type 1 diabetes (unpublished data).
- The Australian intranasal insulin trial II (INIT II) involving 110 antibody positive individuals, which also aimed to induce mucosal tolerance^{62,63}, showed no benefit in delaying progression to type 1 diabetes.
- The adAPT trial currently in progress will test whether metformin can slow the progression to clinical diabetes in children with islet autoimmunity⁶⁴
- Autologous cord blood transfusion does not provide benefit in recent onset type 1 diabetes and is now being investigated in islet autoimmune children in the CoRD study⁶⁵.

Intervention at Stage 3 type 1 diabetes

These trials enroll children generally within 100 days of diagnosis. The aim is to preserve some β -cell function to potentially delay the complications of type 1 diabetes. Cyclosporin transiently preserved β -cell function several decades ago⁶⁶, but was not pursued due to toxicities associated with chronic use. Randomised controlled trials of GAD alum vaccine have produced inconsistent results. Bayesian meta-analysis indicated a high probability that GAD with alum administered twice in Stage 3 diabetes reduces the loss of C-peptide by 15 – 20% at 1 year after treatment⁶⁷.

Short term administration of immune modulation therapies which can delay the loss of β -cell function (rate of decline of C-peptide) in patients with recent onset type 1 diabetes include the anti-CD3 monoclonal antibodies Teplizumab⁶⁸ and oteelixizumab, Abatacept (CTLA4-Ig)^{69,70},

Alefacept⁷¹, and the anti-CD20 monoclonal antibody, rituximab^{72,73}. Children and adolescents were participants in these trials and in general had a better c-peptide response to the intervention than adults.

Combination immune therapy via autologous non-myeloablative hematopoietic stem cell transplant has had the most success in restoring β -cell function in the short term⁷⁴. Trials were designed to deconstruct the therapy with more acceptable risk profiles using anti thymocyte globulin and granulocyte colony stimulation factor. Anti-thymocyte globulin (ATG) and granulocyte colony stimulation factor (GCSF) combination therapy preserved β -cell function for at least 12 months in a pilot study in established type 1 diabetes, with distinct responders and non – responders⁷⁵. A fully powered, randomized placebo- controlled trial of low dose ATG vs placebo and low dose ATG/GCSF versus placebo in new onset type 1 diabetes demonstrated significant reduction in HbA1c in both ATG and ATG/GCSF treated subjects with significant preservation of C-peptide in the low-dose ATG group at one year outcome (clinicaltrials.gov identifier NCT02215200)⁷⁶.

In contrast, multiple other therapies tested in phase 2 fully powered, randomized placebo controlled trials in recently diagnosed individuals have demonstrated no effect on preservation of β -cell function. These include antigen therapies⁷⁷, anti-inflammatory agents⁷⁸, the GLP-1 agonist sitagliptin in combination with a proton pump inhibitor⁷⁹, the combination of mycophenolate mofetil and daclizumab⁸⁰ and many others. Yet with the certain knowledge that controlling the immune system is essential to preserving β -cell function, multiple other agents are under study or being considered either alone or in combination including agents that are already approved for use in other autoimmune diseases in children. Studies are also testing agents aimed at stimulating β cell repair and regeneration.

Ultimately a targeted and combination approach with individualized treatment according to the patient's genetic make-up and other biomarkers of response is likely to be the most effective ^{81,82}.

Clinical presentation of type 1 diabetes

Prospective follow-up of high-risk individuals shows that diagnosis of type 1 diabetes can be made before persistent hyperglycemia and symptoms ²¹ and that their risk of diabetic ketoacidosis is substantially reduced ^{83,84}. Individuals with islet autoimmunity who are followed regularly until clinical diagnosis present with lower HbA1c and a lower risk of diabetic ketoacidosis ⁸⁴⁻⁸⁶. This, taken together with the emerging evidence that children who present with diabetic ketoacidosis have poorer long term control ⁸⁷ has provided impetus to justify general population screening programs for islet autoimmunity. Such general population screening programs are in progress in Germany ⁸⁸ and US. They seek to provide evidence of cost effectiveness and benefit and stimulate active intervention strategies in the pre-symptomatic stages of disease.

A child presenting with a classical history of increasing polyuria, polydipsia and weight loss over 2 – 6 weeks (Stage 3) presents a straightforward diagnosis. However, failure to consider the possibility of diabetes or atypical presentations may result in late diagnosis and an increased risk of diabetic ketoacidosis ⁸⁹. Some children have a rapid onset of symptoms and present within days in diabetic ketoacidosis; others have a slow onset of symptoms over several months. Clinical presentation of diabetes can range from non-emergency presentations to severe dehydration, shock and diabetic ketoacidosis (Table 1).

Urinary 'dipstick' testing for glucosuria and ketonuria, or measurement of blood glucose and blood ketones using a bedside glucometer, provides a simple and sensitive tool for excluding diabetes with less typical presentation. A blood glucose measurement (plasma glucose ≥ 11.1 mmol/L / 200 mg/dL) confirms the diagnosis; this should be based on a laboratory glucose oxidase

estimation rather than a capillary blood glucose monitor.

If a child has symptoms of diabetes, immediate referral to a center with expertise in the care of such children is mandatory, since prompt diagnosis and treatment of diabetes in children is important in preventing rapid deterioration into ketoacidosis. Severe ketoacidosis if untreated is fatal. Therapy is urgent and referral to specialized services is essential. See Chapter 10 – Diabetic Ketoacidosis ⁹⁰.

Differentiating between type 1, type 2 diabetes or monogenic diabetes at diagnosis

Features suggesting the diagnosis of type 2 diabetes rather than type 1 diabetes at diagnosis include:

- Overweight or obesity
- Age greater than 10 years
- Strong family history of type 2 diabetes
- Acanthosis nigricans
- High-risk racial or ethnic groups
- Undetectable islet autoantibodies

The overweight epidemic in many countries has resulted in up to one third of children presenting with overweight or obesity at diagnosis of type 1 diabetes ⁹¹⁻⁹³, with accompanying insulin resistance. Raised islet autoantibodies confirm the diagnosis of type 1 diabetes and the need for insulin therapy. It is noteworthy that some racial or ethnic groups have a higher risk of DKA at presentation of type 1 diabetes.

Partial remission or honeymoon phase in type 1 diabetes

In approximately 80% of children and adolescents, insulin requirements decrease transiently following initiation of insulin treatment ⁹⁴; this reflects partial β -cell recovery with increased insulin secretion and improved peripheral insulin sensitivity before the decline in insulin production begins ^{95, 96}. Parents and children with type 1 diabetes should be counseled that the remission phase of diabetes is transient and does not indicate total remission of diabetes. At present no therapy is known to restore β -cell function for an extended period of time.

Nevertheless, any preservation of β -cell function decreases the risk of developing vascular complications and the risk of severe hypoglycemia^{97,98}, so this remains an important research goal.

Some have defined partial remission as an insulin requirement of < 0.5 units per kg of body weight per day and $HbA_{1c} < 7\%$ ⁹⁴. The phase commences within days or weeks of the start of insulin therapy and may last for weeks to years. However, an unusually prolonged “honeymoon phase” should alert the treating physician to the possibility of a form of monogenic diabetes such as MODY or milder manifestation of genes commonly responsible for NDM (see chapter on Monogenic Forms of Diabetes). During this period, blood glucose levels are frequently stable within the normal range, despite fluctuations in diet and exercise. Ketoacidosis at presentation⁹⁹, and younger age at diabetes onset reduce the likelihood of a remission phase^{100,101}.

Chronic phase of lifelong dependence on insulin

The progression from the partial remission phase into the chronic phase of dependence on exogenous insulin is usually a gradual decrease in residual β -cell function. The rate of loss of c-peptide production is similar in children and adolescents, and faster than that in adults; few children and adolescents have significant residual β -cell function by 4 years after clinical diagnosis¹⁰². However ultra-sensitive c-peptide assays show that a small amount of long term endogenous insulin production persists in up to 75% of patients¹⁰³; the presence of persistent c-peptide in long standing disease is much less in those diagnosed as children as compared to diagnosis as an adult¹⁰⁴.

Table 1: Clinical characteristics at presentation of type 1 diabetes

Non- Emergency Presentations

- Recent onset of enuresis in a previously toilet-trained child, which may be misdiagnosed as a urinary tract infection
- Perineal candidiasis, especially in pre-pubertal girls
- Chronic weight loss or failure to gain weight in a growing child
- Irritability and decreasing school performance
- Recurrent skin infections

Emergency presentations (Diabetic ketoacidosis or hyperosmolar hyperglycemia)⁹⁰:

- Moderate to severe dehydration

- Frequent vomiting and in some cases, abdominal pain, which may be misdiagnosed as gastroenteritis
- Continuing polyuria despite the presence of dehydration
- Weight loss due to fluid loss and loss of muscle and fat
- Flushed cheeks due to ketoacidosis
- Acetone detected on the breath
- Hyperventilation of diabetic ketoacidosis (Kussmaul respiration), characterized by an increased respiratory rate and large tidal volume of each breath, which gives it a sighing quality
- Disordered sensorium (disoriented, semi-comatose or rarely comatose)
- Shock (rapid pulse rate, poor peripheral circulation with peripheral cyanosis)
- Hypotension (a very late sign and rare in children with diabetic ketoacidosis)

Diagnostic difficulties that may delay diagnosis

- Very young children may present in severe ketoacidosis because of a more rapid onset of severe insulin deficiency and because the diagnosis was not considered earlier.
- The hyperventilation of ketoacidosis may be misdiagnosed as pneumonia or asthma (cough and breathlessness distinguish these conditions from diabetic ketoacidosis) and in the case of asthma treated with glucocorticoids that exacerbate the severity of hyperglycemia.
- Abdominal pain associated with ketoacidosis may simulate an acute abdomen and lead to referral to a surgeon.
- Polyuria and enuresis may be misdiagnosed as a urinary tract infection.
- Polydipsia may be thought to be psychogenic.
- Vomiting may be misdiagnosed as gastroenteritis or sepsis.

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