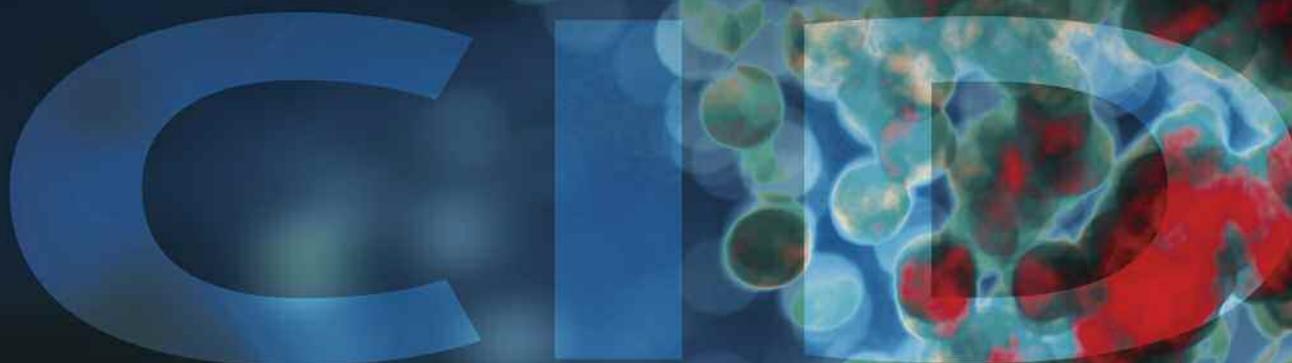


Understanding Combined Immunodeficiencies

While knowledge about this complicated disease has advanced over time, it is still often misdiagnosed and treatment must be individualized for each patient.



By Terry O. Harville, MD, PhD, D(ABMLI), D(ABHI)

AS THE NAME implies, combined immunodeficiencies (CIDs) encompass a category of immunodeficiencies in which T and B lymphocytes fail to function as normally expected. What is not clarified in the name is whether B lymphocytes fail to function due to lack of T lymphocyte assistance or whether the underlying gene mutations affect the functions and numbers of both T and B lymphocytes. Additionally, it is unclear at what point CID is severe enough to become classified as severe combined immunodeficiency (SCID); what the varieties of CID are; whether some have more T lymphocyte dysfunction and less B lymphocyte dysfunction and vice versa; and how CID is diagnosed and treated.

Historical Perspective of CID

In the past, most immunologists understood what the term CID meant. For instance, many years ago (and still today), it was believed SCID was diagnosed in infancy and required bone marrow transplantation (BMT) or hematopoietic stem cell transplantation (HSCT) for infant survival. Furthermore, it was believed CID was diagnosed later in children with less-severe disease that did not require BMT/HSCT. Indeed, lymphocyte deficiencies at that time

were basically divided into five categories: 1) pure T lymphocyte deficiency (e.g., DiGeorge syndrome), 2) pure B lymphocyte deficiency (e.g., X-linked agammaglobulinemia [XLA]), 3) SCID, 4) common variable immunodeficiency (CVID), defined as primarily B lymphocyte deficiency with possibly some T lymphocyte deficiency and 5) CID, defined as primarily T lymphocyte deficiency with corresponding B lymphocyte deficiency, but not as severe as SCID (e.g., Wiskott-Aldrich syndrome [WAS]). The latter is now what we refer to as classical CID.

Rebecca Buckley, MD, a pioneer in immunodeficiencies, used the term SCID to describe those with such severe T and B lymphocyte immunodeficiency that they would not survive without BMT/HSCT. Further, infants with SCID could undergo successful BMT/HSCT without the need for chemotherapy. This distinguished them from patients with CID who require chemotherapy to suppress the meager immunity present, enough to prevent engraftment of donor cells if BMT/HSCT were performed. Indeed, this description remains a good differentiator between SCID and CID. Unexpectedly, the category of CID expanded over the years, which complicated its definition.

In Between Past and Present Considerations of CID

Between the definition of CID described above, and the latest definition to be discussed below, CID had become an all-encompassing disease process (Table 1). CID was divided, essentially, based on the severity of T lymphocyte dysfunction into 1) SCID (the most severe), 2) classical CID (less severe than SCID) and 3) CVID (less severe than classical CID with T lymphocyte function ranging from fundamentally normal to some dysfunction).

However, the medical profession began recognizing that some conditions were not as pure as previously thought. For example, there were infants who initially appeared to have SCID, but the evaluation demonstrated their bodies were capable of making some T lymphocytes. Therefore, their disease was worse than classical CID but not as severe as classical SCID. These cases became known as leaky SCID to distinguish them from classical SCID. Leaky SCID could be considered a CID since these patients require BMT/HSCT for treatment and typically require chemotherapy for conditioning for the transplant. Further, in some infants, T lymphocytes were present and functioning to some extent (as expected in CID), but the disease process still required BMT/HSCT for the infant to survive (e.g., Omenn syndrome). Thus, according to Dr. Buckley's definition, patients with some level of T lymphocyte numbers and function, and who require chemotherapy conditioning, should be diagnosed with CID rather than SCID.

Molecular DNA techniques also led to further clarifications of the definition of CID. As these techniques identified which mutations were responsible for different immunodeficiencies, classifications based on which DNA mutations were present could be performed.

The Recent Past of CID

In 2016, the World Health Organization (WHO) released a reorganization of the International Classification of Diseases (ICD-10) (Table 2) that includes a specific category of CID (D81). Yet, the conditions listed were previously considered mostly in the SCID category, requiring BMT/HSCT for treatment, rather than in classical CID. Interestingly, conditions with milder than SCID T lymphocyte dysfunction, which were included previously as classical CID diagnoses, are not listed under the CID category. These are now primarily listed in separate categories based on additional features associated with the disease process. For example,

Table 1. Former Categorical Hierarchy of Combined Immunodeficiencies (CID)

CID		
SCID	Classical CID	CVID

In the past, CID was considered to be all conditions with T and B lymphocyte dysfunction. The T lymphocyte severity and overall severity increased to the left, with SCID being the worse. The classical CID category included conditions such as DiGeorge syndrome, Wiskott-Aldrich syndrome, ataxia-telangiectasia and WHIM syndrome. CVID was considered primarily a B lymphocyte deficiency with normal or near-normal T lymphocytes to conditions in which some T lymphocyte dysfunction was present but not as severe as what was considered to be associated with CID.

Table 2. 2016 Reorganized ICD-10 Classifications of Combined Immunodeficiencies

- D81 Combined immunodeficiencies
Excluding autosomal recessive agammaglobulinaemia (Swiss type) (D80.0)
- D81.0 Severe combined immunodeficiency (SCID) with reticular dysgenesis
- D81.1 Severe combined immunodeficiency (SCID) with low T- and B-cell numbers
- D81.2 Severe combined immunodeficiency (SCID) with low or normal B-cell numbers
- D81.3 Adenosine deaminase (ADA) deficiency
- D81.4 Nezelof syndrome
- D81.5 Purine nucleoside phosphorylase (PNP) deficiency
- D81.6 Major histocompatibility complex class I deficiency
Bare lymphocyte syndrome
- D81.7 Major histocompatibility complex class II deficiency
- D81.8 Other combined immunodeficiencies
Biotin-dependent carboxylase deficiency
- D81.9 Combined immunodeficiency, unspecified
Severe combined immunodeficiency disorder (SCID)
not otherwise specified

The World Health Organization ICD-10 classification of combined immunodeficiencies primarily includes conditions that were mostly previously considered SCID due to the need for BMT/HSCT. It does not include classic CID considerations such as DiGeorge syndrome and Wiskott-Aldrich syndrome, which fall into specific categories based on additional features present. Further, CVID is placed into its own separate category.

Source: icd.who.int/browse10/2016/en#/D81

WAS is listed as “D82.0, immunodeficiency with thrombocytopenia and eczema” rather than as a CID.

The use of ICD-10 is helpful from the standpoint of hospital billing and reimbursement, but it does little to promote understanding the immunologic relationships of the disease processes.

Further Considerations for the Recent Past of CID

It can now be recognized that there is not a single form of CID, but instead a complex category of immunodeficiencies, with the name acting as a catch-all for a myriad of conditions that share both T and B lymphocyte dysfunctions. Thus, the International Union of Immunological Societies Expert Committee for Primary Immunodeficiency published a more comprehensive classification for CID.¹ This classification divided CID into 77 types and subtypes. These include the various SCID types due to different mutations, as well as the classical CID diagnoses such as DiGeorge syndrome and WAS, all of which are placed into specific classifications based on clinical, laboratory and genetic features, with many of the types classified based on specific known mutations of genes associated with immunodeficiencies. CVID is no longer in the main CID category, but is placed into a category defined by “primary antibody dysfunction.”

Ultimately, the goal of classification systems of immunodeficiencies is to have all the types and subtypes categorized based on the specific clinical features, expected laboratory test results and underlying DNA gene mutations. UpToDate.com published a review of CID last updated in 2019, in which Luigi D. Notarangelo, MD, states: “Combined immunodeficiency syndromes are somewhat arbitrarily distinguished from severe combined immunodeficiency (SCID) in that they do not characteristically lead to death from overwhelming infection in the first year of life. In addition, combined immunodeficiency syndromes frequently have associated clinical features.”² This definition parallels Dr. Buckley’s.

What Is CID?

CID is a broad categorical name for immunodeficiencies with T lymphocyte and B lymphocyte dysfunction that have at least 77 types and subtypes. In most cases, the T and B lymphocyte counts are low, along with abnormal function. For most, mutations are present affecting both T and B lymphocytes, although there may be some in whom the mutation primarily affects T lymphocyte function, which causes a reduction in B lymphocyte function due to the lack of T lymphocyte help.

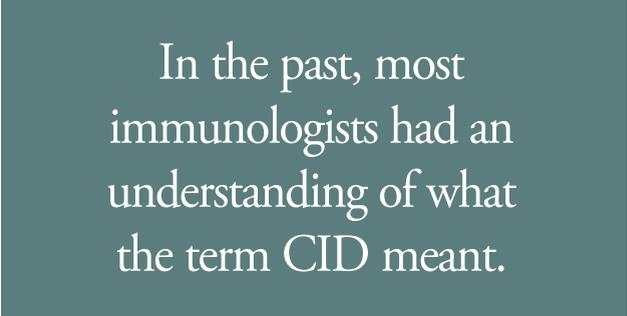
Patients with CID whose primary dysfunction occurs in the B lymphocytes with less effect on the T lymphocytes may now be in the CVID category. Patients with CID who have the most severe T lymphocyte dysfunction are in the SCID category. Patients with SCID are typically infants who require

BMT/HSCT for treatment to survive and usually do not require chemotherapy conditioning for successful transplantation.

Some forms of CID are not recognized until the person is older. In some of these cases, BMT/HSCT may still be helpful, but the risks of transplantation have to be weighed against the risks of not transplanting due to the potential morbidity and mortality associated with the chemotherapeutic conditioning regimen versus those caused by the disease itself.

Some cases of CID are not diagnosed until adulthood. Some of these patients were initially diagnosed with CVID and were subsequently changed to a diagnosis of CID after DNA testing revealed mutations more associated with CID (e.g., milder forms of adenosine deaminase deficiency).

Thus, CID represents a collection of diseases with significant T and B lymphocyte dysfunction, where the T lymphocyte dysfunction is the primary root of the problem. This results in susceptibility to viral, bacterial, fungal and opportunistic infections (infections not expected to occur in persons with normal functioning immunity), in addition to susceptibility to autoimmune disorders.



In the past, most immunologists had an understanding of what the term CID meant.

How Is CID Diagnosed?

Diagnosing CID can be difficult and involved. Those who have symptoms similar to SCID will likely be evaluated in infancy for recurrent, severe and/or opportunistic infections. The lymphocyte count of the white blood count is expected to be low, and assessment of the specific numbers of T and B lymphocytes is expected to be low. Specific markers of T lymphocytes, for example CD45RO expressed on the cell surfaces of CD4 T lymphocytes, may be disproportionately elevated (high percentage, when a lower percentage is expected for age). Additionally, T lymphocyte function is expected to be subnormal, but not to the relative absence observed in SCID. Quantitative antibody levels may be low, and if

assessed, the ability to make antibodies to specific antigen-vaccine challenge is expected to be impaired. Thus, for infants, the difficulty may be determining whether the diagnosis should be SCID or CID. Currently, DNA analysis for specific mutations is also helpful for determining the diagnosis.



For older infants, children, teenagers and adults, diagnosis can be delayed. For younger children and some school-aged children, their illnesses may be perceived as bad luck and due to viruses acquired in a daycare or school setting. In this scenario, since there appears to be a reason for having recurrent illnesses, there is a delay in laboratory evaluation and a potential immunodeficiency is not considered. However, when an evaluation is initiated, it would likely look for an antibody deficiency due to its relative commonality versus CID.

A less-than-expected improvement with immune globulin (IG) replacement therapy for a putative antibody deficiency could prompt a further evaluation for CID. This is because even when treated with IG, patients with CID may continue to become ill due to the presence of more pronounced T lymphocyte deficiency. Unfortunately, more bad luck rather than treatment failure is often considered, resulting in further delaying a CID diagnosis. Once again, DNA analysis for specific gene mutations that cause immunodeficiencies can help to better delineate the actual condition present.

How Is CID Treated?

There is no one best treatment option for CID. Treatment should be individualized and optimized for each patient. Those with more severe disease (more infections) or other

features such as autoimmunity should be considered as candidates as soon as possible for BMT/HSCT, with all the risks and benefits considered. Earlier transplantation may help prevent the accumulation of infectious organisms that can make later transplantation more difficult since these organisms may result in severe infections after chemotherapy has further compromised the immune system in preparation for BMT/HSCT.

An example of complications due to accumulation of infectious organisms occurs in WAS. Even though early-in-life symptoms could be relatively mild and manageable, commonly at about 5 years of age, Epstein Barr virus (EBV) infection may occur. Once infected, EBV remains in the B lymphocytes for the rest of the life. Patients with WAS are at significant risk for EBV to cause B lymphocytes to grow abnormally due to their underlying immunodeficiency. Initially, there may be lymphoproliferative disease (abnormal growth and expansion of B lymphocytes), but it can evolve into B lymphocyte leukemia or lymphoma. If this happens, more drastic therapy may be required, including BMT/HSCT. Therefore, early BMT/HSCT should be an important consideration in CID.

As noted, some patients have an illness more akin to CVID that causes milder T lymphocyte dysfunction than the more severe cases of CID. These individuals may respond reasonably well to IG replacement therapy. Daily antibiotics may be required by some, whereas others may need only courses of antibiotics, particularly during the winter months. Ongoing evaluations are required to denote if there is progression in T lymphocyte dysfunction, especially onset or worsening of autoimmune disease features. Again, DNA analysis for specific gene mutations can help toward a decision of undergoing earlier BMT/HSCT for definitive treatment.

It is recognized that autoimmune processes (which can occur in patients with CVID) are potentially the most significant issue in some patients with CID. Their infections may be controlled with IG replacement and antibiotic therapies, but patients may remain quite ill from autoimmune disease. Determining which genes are responsible can be helpful. For example, if the PI3K δ protein has a mutation causing increased activity, immunodeficiency and autoimmunity may be present.³ In these persons, the use of rapamycin, a so-called mTOR inhibitor, can result in dramatic improvement in symptoms. This form of therapy may help re-establish a balance in immune system function, resulting in good outcomes.

While patients may be treated for a long time with these

treatments, it remains unknown whether these patients should proceed to BMT/HSCT for a more definitive treatment of the underlying disease. The mTOR inhibitor can only establish a certain level of homeostasis, and disease breakthroughs may occur. By determining the underlying genetic process resulting in CID, it may be possible to individualize treatment with specific medications as described above. Overall, though, BMT/HSCT should be considered as early as possible as a potential cure for the underlying disease.

A Complicated Immunodeficiency

CID is complicated. There are multiple individually named disorders, in addition to unnamed ones, which have both T and B lymphocyte dysfunction and are thus CIDs. In patients with CID, T lymphocyte dysfunction can range from being less severe like CVID to extremely severe such as with SCID. Some patients may respond to treatment with IG replacement and antibiotics. But, those with additional

conditions such as autoimmunity will likely require further individualized therapies and therapeutic options. Some of these may actually work well, but it is unknown if they can provide the needed long-term benefit. DNA studies for mutations responsible for immunodeficiencies can help with diagnosis and, potentially, with individualized treatment options. BMT/HSCT should be considered as early as possible for definitive treatment in most patients with CID. ■

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