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A review on guidelines for management and treatment of common variable immunodeficiency

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Common variable immunodeficiency (CVID) is the most common symptomatic primary immunodeficiency in adults. As symptoms of CVID are usually heterogeneous and unspecific, diagnosis and follow-up of CVID can be challenging. In light of this, a broad review of advances in management and treatment of CVID is performed here in order to reach a distinct protocol. However, it should be noted that owing to the nature of the disease, it can only be treated symptomatically but not cured. There is little evidence to guide appropriate or universal guidelines to improve the current status of management of the disease. The most satisfactory treatments of CVID could be achieved by the use of immunoglobulin replacement, antibiotics, immunosuppressants and hematopoietic stem cell transplantation. This review is written based on the importance of clinical surveillance of asymptomatic CVID cases and early recognition of different clinical complications. Moreover, for each complication, appropriate interventions for improving outcomes are mentioned.

KEYWORDS: clinical phenotypes • common variable immunodeficiency • management • prevention • screening • treatment



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Learning objectives

Upon completion of this activity, participants will be able to:

- Analyze the clinical presentation of CVID
- Assess the practice of exogenous IgG administration to patients with CVID
- Evaluate pulmonary complications of CVID and their management
- Evaluate other potential complications of CVID

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Common variable immune deficiency (CVID) as a heterogeneous group of primary immune deficiencies is characterized by insufficient serum levels of immunoglobulins (Igs), reduced response to specific antigens and higher incidence of repeated infections [1–4]. Autoimmune disorders, lymphoproliferative disorders and gastric complications also have an increased incidence in patients with CVID [5,6]. The prevalence of this predominantly antibody deficiency should not be thought of as being rare (1:10,000–50,000) and CVID is the most common symptomatic human primary immunodeficiency [7–9]. The onset (early or late) and clinical manifestations (distinct phenotypes) of the disease have heterogeneous presentations [10–12]. This variability in clinical phenotype and late onset of disease may lead to delay in CVID diagnosis [13,14].

The molecular basis, both immunologically and genetically, of CVID is still unclear despite huge amounts of evaluation in this field since 1953 [15]. However, during the last 10 years, 10–15% of the patients with a history of CVID manifestations are classified in other primary immunodeficiency categories because of specific identified gene mutations including *ICOS*, *CD19*, *CD20*, *CD81*, *CD21* and *LRBA1* [16–23]. Decreased serum level of IgG, IgA and/or IgM (at least 2 standard deviations below the mean for the age group), hyporesponsiveness to specific antigens, minimum age of 4 years, absence of lymphoid malignancy during the first 2 years of diagnosis and genetic exclusion of other known etiologies for

hypogammaglobulinemia are considered as criteria for diagnosis of CVID (FIGURE 1) [24–26]. Furthermore, approximately 2% of CVID patients may represent clinical or laboratory features that suggest a known severe combined primary immunodeficiency (e.g., opportunistic fungal or viral infections, very low numbers of T cells and/or monocytes). Although this phenomenon is rare, this is important because such patients may need stem cell grafts [27].

Heterogeneity in CVID refers to variability in immunological and genetic defects and diversity in clinical symptoms described in this group of patients [19,28,29]. The main immunological defect is failure of B-cell Ig production, although abnormalities have been described in all other components of the immune system [30,31]. Only some CVID cases are due to monogenic Mendelian diseases and homozygous mutations in that some genes have been reported in some CVID families [17,18,32].

The clinical spectrum of CVID is broad. The main clinical manifestations are recurrent infections occurring in the respiratory tract, GI tract, skin and soft tissues [4,33,34]. However, inflammatory complications occur in varying proportions and include autoimmunity, chronic lung disease, bronchiectasis, gastrointestinal (GI) disease with or without malabsorption, systemic or localized granulomatous disease, liver disease, splenomegaly, lymphadenopathy with or without lymphoma and other malignancies [26,35]. By using data of clinical manifestations and complications from 334 CVID patients

from seven European centers, five different clinical phenotypes were considered for these patients [13]. In the revised phenotyping criteria, lymphoid malignancies were excluded [36].

Over the last few years, advances have been made in the management of CVID, improving outcomes in the patients; these include Ig replacement, antibiotics for treatment and prevention of infections and appropriate therapy for noninfectious complications [37].

IgG replacement is the mainstay of treatment of CVID [35] and it has been shown that long-term Ig replacement therapy for CVID has reduced the rate of infections and their long-term complications [38–41]. However, despite the reduction in the rate of bacterial infections by use of IgG replacement in CVID patients, these patients are still more susceptible to complications because of a dysregulated immune response that attracts the caregiver's attention. Here, the authors review the recent advances in CVID, specifically the clinical features, and focus on the management and treatment of CVID. Other specific classifications based on immunological property of CVID cases (including Freiburg, Paris, EUROclass and severe T-cell defect classification) exist, however their importance for clinical management are under evaluation [42–46]. Moreover, the authors review the recent advances on the management and treatment of CVID.

Clinical manifestations of CVID

The clinical manifestations of CVID constitute six major categories including: infections, pulmonary complications, granulomatous or polyclonal lymphocytic infiltrative diseases, autoimmunity, GI diseases and neoplasias (TABLE 1). These can be established in different periods of life, from childhood to late adulthood, with a bimodal age distribution, demonstrating two peaks between 1 and 5 years and 18 and 25 years [3,4,47].

Management of infectious complications

Virtually all CVID patients encounter chronic or recurrent infections, particularly sinusitis, otitis, bronchitis and pneumonia [47–49]. Approximately 90% of CVID patients have encountered at least one episode of chronic sinusitis and 70% have suffered recurrent otitis media before diagnosis [50–52]. Previously, there had been a history of at least one episode of pneumonia before diagnosis in 75–85% of the CVID patients as well as multiple episodes in many others [38,41]. The majority of morbidities and mortalities of CVID is due to long-term sequelae of recurrent respiratory tract infections including chronic sinusitis, hearing loss (due to tympanic membrane perforation) and bronchiectasis [4]. Encapsulated (*Haemophilus influenzae*, *Streptococcus pneumoniae*) or atypical (*Mycoplasma* spp.) bacteria are the major causative agents for recurrent infections of both the upper and the lower respiratory tract [4,35,53]. Failure of antigen-specific IgG production, which increases susceptibility to encapsulated bacteria, seems to be responsible for recurrent rhinoviral infections in CVID [51].

The GI tract is the second organ that is involved in infections in 10–40% of the CVID cases. Various pathogens can cause GI infections in CVID patients including: *Giardia lamblia*, *Campylobacter jejuni*, *Salmonella* spp., *Cryptosporidium parvum*,

CMV, *Clostridium difficile*, *Helicobacter pylori*, HBV, HCV and so on. Giardiasis is the most prevalent GI infection, especially in those with undetectable serum IgA levels [54]. *H. pylori* is an important pathogen in CVID, resulting in chronic active gastritis involving antrum and corpus, achlorhydria, gastric adenocarcinoma and gastric lymphoma [55,56].

The CNS (meningoencephalitis is especially caused by *Enterovirus* spp.), joints, bones (especially due to *Mycoplasma* spp.), skin and eyes are also affected by CVID and their involvement might be the first and sole presentation of CVID [57]. Fibrotic bladder can develop due to recurrent urinary tract infections due to *Ureaplasma urealyticum* [25,36].

Viral hepatitis (especially HCV transmitted by intravenous Ig [IVIG] administration) and severe *Herpes zoster* infection have been reported in large numbers of patients [4]. Because of recent developments in Ig preparation including careful selection of donors, plasma antibody screening and effective procedures of viral inactivation, the rate of these infections are now very rare in the western world [58]. CMV is involved in many inflammatory complications

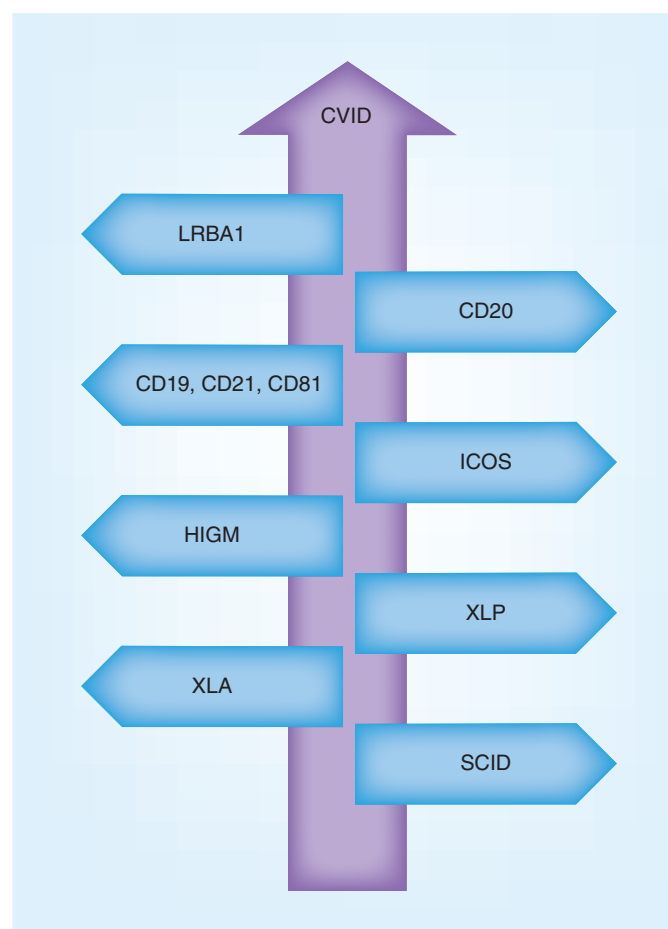


Figure 1. Differential diagnosis for common variable immunodeficiency with definite single defect gene. CVID: Common variable immunodeficiency; HIGM: Hyper IgM syndrome; ICOS: Inducible T-cell costimulator; SCID: Severe combined immunodeficiency; XLA: X-linked agammaglobulinemia; XLP: X-linked lymphoproliferative disease.

Table 1. Abstracted guideline for management of common variable immunodeficiency complications.

Type of clinical complication	Prevention	Screening	Treatment
Infectious	Ig replacment; prophylactic antibiotics; vaccination	Patients' awareness; sputum monitoring; routine visits	High dose Ig; threaputic antibiotics
Pulmonary	Control of infection; high dose Ig	Spirometry; HRCT; routine visits	Endoscopic sinus surgery; inhaled corticosteroids; anti-inflammatory antibiotics; IL-2 therapy; B ₂ agonists; leukotriene receptor antagonists; lung transplantation
Lymphoproliferative		Lymph nodes biopsy; spirometry; imaging; routine visits	Systemic corticosteroids; hydroxychloroquine; immunosuppressive agents
Autoimmunity	Ig replacment?	CBC, diff, PBS; thyroid examination and thyroid function; routine visits	Corticosteroids; anti-CD20 monoclonal antibodies; TNF- α inhibitors
Gastrointestinal	Control of infection, autoimmunity and lymphoproliferative complications	Upper and/or lower endoscopy and yearly ultrasonography; routine visits	Immunomodulators; TNF- α inhibitors
Neopelasis	<i>Helicobacter pylori</i> eradication; decreasing unnecessary irradiation	Routine cancer screening; screening by endoscopy; bone marrow examinations	Routine chemotherapy; rituximab protocols; surgical modalities; allogeneic stem cell transplantation

CBC: Complete blood count; diff: Differentiation of cell blood count; HRCT: High-resolution computed tomography; Ig: Immunoglobulin; PBS: Peripheral blood smear.

of a selected group of CVID patients with special immune cell phenotypes [59]. Enteroviral infection is also currently rare in western CVID patients, however this microorganism being maintained probably due to lack of high-dose treatment and may lead to meningoencephalitis with poor prognosis [60]. The minority of these patients are prone to meningoencephalitis, which usually has a poor prognosis [61]. Human parechovirus type 1 and norovirus were also reported in CVID patients that had severe enteropathy [62].

Prevention

Lifelong Ig replacement therapy (injection of human antibodies harvested from plasma donations) is the mainstay of the therapeutic approach for stopping the cycle of recurrent infections in CVID patients. Both intravenous (3–12% IVIG) and subcutaneous (10–20% subcutaneous Ig [SCIG]) routes provide sufficient amounts of Ig [58,63]. IVIG is used more commonly than SCIG and reduces both the rate of acute and chronic infections and their long-term secondary medical conditions in CVID [38,40,64]. Although the purpose of Ig replacement therapy is to prevent infections, the amounts of administered Ig and individualized dosing can vary depending on baseline level of IgG and presence of chronic lung or GI damage [65]. Furthermore, the optimum trough level of IgG is not universal and clinical response may be a better indicator for dose adjustments in CVID cases [66–68]. Based on this goal, universal IVIG routine protocols recommend typically starting the dose at 400–600 mg/kg every 3–4 weeks, while SCIG is usually started by dosage at 100–200 mg/kg followed by 160 mg/kg every week. In infants and young children, 5–7 ml of SCIG per site is well tolerated; in adults, the volume per site is generally 15–20 ml [69–72].

Although long-term IVIG infusion is an effective treatment for prevention of recurrent infections in CVID patients, it can be complicated by systemic adverse reactions. These side effects may occur up to 72 h after the infusion [73,74].

The majority of IVIG side effects are mild, transient and self-limited and do not require discontinuation of therapy [58]. Predisposing factors responsible for adverse reactions include infection [75], rate of infusion, other comorbidities or patient-related factors such as age (≥ 65 years), cardiovascular impairment, renal dysfunction, thromboembolic risk and the presence of diabetes mellitus, pre-existing renal disease, hypovolemia, sepsis, anti-IgA antibodies and increase of interval since last infusion [76]. One study showed that side effects of IVIG were not significantly correlated with pregnancy [77]. There are different types of Ig products regarding the concentration of antibodies and other plasma proteins such as sodium content, sugar content, osmolality and IgA content. The selection of Ig product must be individualized based on clinical condition of the patient and Ig product-related factors. For patients with congestive heart failure and elderly patients, Ig products with 10% concentration and lower sodium content are more suitable [78].

Monitoring for adverse reactions to IVIG and SCIG must be performed during therapy. Depending on the type of adverse reactions, different managements should be considered.

A very important issue to consider is determination of patients with anti-IgA. Some tests that detect IgG anti-IgA seem to be helpful in predicting adverse reactions. By contrast, some authors disagree with the significant importance of anti-IgA antibodies and they consider it as a rare problem in CVID. Furthermore, many expert centers do not measure these antibodies because

there is little correlation between levels and reactions. However, low-IgA preparations or SCIG should be used in CVID cases who generate anti-IgA antibodies against routine IVIG. After prevention of all predisposing factors for adverse reactions, premedication including paracetamol (500–1000 mg), oral diphenhydramine (25–50 mg), corticosteroids/acetaminophen/anti-inflammatory drugs should be considered prior to treatment for patients who experience adverse reaction following IVIG infusions. If persistent headache symptoms are observed, the patient can switch to SCIG to eliminate the problem and no further premedication is needed [79,80]. Despite this idea, many physicians do not agree with this strategy and they manage headache critically [76].

Most patients tolerate IVIG and SCIG well if administered by an expert nurse. Avoiding infusion during active infection and changing the preparation in those rare patients with repeated reactions usually solves the problem. Moreover, hydration of patient (before, after and during treatment), preparation of Ig product before infusion and using a heating pad or warm blanket because of chilling or local swelling are other strategies to facilitate intravenous replacement therapy [81–83]. Besides preference of SCIG in patients with major adverse events compared with IVIG, this type of replacement reduces fluctuations in serum IgG concentrations, does not require venous access, prepares rapid infusions, decreases risk of fluid overload or hyperosmolarity, is prescribed home-based self-administration requiring minimal skills, improves quality of life and saves travel time, reduces utilization of the healthcare system and eliminates missing work or school. However, local reactions to SCIG are unacceptable for patients with general edema or lack of subcutaneous tissue. Discomfort associated with the needle stick of SCIG can be minimized with local anesthetic creams [58,71].

The second line in prevention of infection in CVID patients is antibiotic prophylaxis, especially in the cases with bronchiectasis, frequent infections (generally more than three per year) or disruptive infections (hospital admission, prolonged period off work, secondary complications such as empyema) [84]. However, this effect of prophylactic antibiotics in CVID patients has not been rigorously assessed [85]. Previous microbiology results, serial sputum testing and antibiotic sensitivity of cultured organisms determine the choice of antimicrobial prophylaxis [86]. Daily use of trimethoprim–sulfamethoxazole or macrolides, which provide substantial anti-inflammatory effects, provide more benefit than much greater doses of Ig therapy in patients with persistent lung diseases [14,87]. Other regimes for prophylaxis consist of azithromycin 250 mg three times/week, cotrimoxazole 960 mg three times/week, amoxicillin 500 mg two times/day and ciprofloxacin 250 mg two times/day [88–90]. By contrast, some authors suggest that the use of prophylactic antibiotics should be avoided because of an increased risk of infection with fungi or other resistant organisms. However, resistant organisms can be treated if they arise by changing of antibiotics according to an algorithm of alternative antibiotics [87].

Immunization by polysaccharide vaccines may be effective in selected CVID patients with normal class-switched memory B cells. Activated vaccine (MMR and varicella) may be neutralized

by antibodies of IVIG and are not recommended in CVID. In contrast, antibody against seasonal influenza virus is not presented in IVIG, therefore yearly recommendation for inactivated influenza vaccine administration is acceptable. Moreover, for indirect protection, close-contact relatives of patients should be vaccinated against influenza [91,92].

Follow-up

Pay attention to educate patients (and parents of children) about alarming signs of infections and the necessity of holding sputum pots themselves before starting antibiotics which is the main step for early detection of infections. Beside patients, raising the awareness of medical and social caregivers for appropriate approach to recurrent infection is critical. Clinical visits and physical examination for early detection of infections in CVID cases that warrant immediate treatment should be carried out every 3–6 months. Sputum monitoring and analysis must be performed for all cases with productive cough. Chronic viral infection is often very difficult to diagnose without a sophisticated virology laboratory. Although with current legislation on the control of Ig products and viral inactivation, no case of viral transmission by Ig administration has been reported since 2000, the HCV viral genome (HCV RNA) must be checked for regularly in all patients already receiving IVIG. Very recently, detection of κ -deleting recombination circles provides a tool for neonatal screening of B-cell formation defects before presentation of infections, but the sensitivity and specificity of this modality should be evaluated in CVID cases [93,94].

Treatment

Early treatment of infections at the first signs and symptoms should be considered an integral part of the treatment of CVID to prevent secondary structural damage. In each type of infection, samples must be collected before oral or intravenous antibiotic therapy if possible. Although culture and sensitivity results help clinicians choose the most effective drugs, this should not lead to delayed empiric therapy. The effective empiric therapy for sinopulmonary infections in patients not taking prophylactic drugs (amoxicillin, macrolide or levofloxacin) differ from cases taking prophylactic drugs (amoxicillin clavulanate, macrolide or ciprofloxacin [90]). Initial treatment in GI microorganisms, the second most important group of infections, is determined on the basis of culture results and biopsy findings and usually includes antibiotics, restoration of nutrients and rehydration.

The use of antiviral agents, such as ganciclovir, pleconaril or ribavirin, appears to be safe and sometimes effective but should be evaluated in controlled clinical trials [60,95].

It should be noted that active infection plays a role in increasing the risk of adverse reaction to IVIG, therefore combination of antibiotic therapy and Ig replacement must be planned in these cases. A prolonged course of treatment should be considered in cases with relapse of infections. Because of the nature of the disease, resistant common organisms and unusual organisms (*Pseudomonas* spp., *Mycobacterium tuberculosis* and opportunistic infections) should be reviewed when treatment fails.

Management of pulmonary complications

As the most frequent manifestation of CVID, pulmonary diseases are present in most patients at the time of diagnosis and they significantly increase morbidity and mortality in CVID patients [47,51]. Recurrent pulmonary infections with pyogenic bacteria among CVID patients can culminate in permanent pulmonary disorders such as air-trapping, ground-glass attenuation, parenchymal opacification, reticular fibrosis, bronchial wall thickening, atelectasis and bronchiectasis (obstructive and restrictive) [48,51]. These complications can develop in various periods of life but are slightly milder among pediatric patients than in adult cases [51]. Of the aforementioned complications, bronchiectasis subsequent to recurrent pneumonia is more prominent and develops in approximately a third of patients [4,96]. Despite regular and adequate treatment in response to the immune dysregulation that occurs in CVID, affected patients may develop inflammatory diseases, which could result in more pulmonary complications, especially bronchiectasis, in this group of patients [47,97].

Prevention

Prophylaxis and treatment of upper and lower respiratory tract infections with greater doses of Ig (600 mg/kg/month) and regular suppressive antimicrobials are the best means for controlling progression of lung disease, however, randomized clinical trials are needed for the exact proof [68,98]. Reducing contact with fungal sources should be noted by patients, especially *Aspergillus* spp.-infected areas [99].

Follow-up

Although there is no consensus for monitoring lung damage in CVID patients, pulmonary lung function tests (spirometry and carbon monoxide diffusion; at baseline and every 1–2 years) and high-resolution computed tomography (gold standard test; at baseline and every 4–5 years) are the best recommended examinations. Plain chest X-ray radiography is of limited value in CVID; however, it should be considered if the patient is febrile, has pleuritic pain and signs of consolidation, effusion or collapse. Moreover, because of the probability of radiosensitivity in some CVID cases, lower intervals with other X-ray procedures should be avoided as screening leads to excessive radiation exposure over time [48,51,100–102]. Biopsy and pathological investigation should be carried out if large or persistent nodules are found in the lungs, which may change our therapeutic strategy to treat for polyclonal lymphocytic infiltrative disease-like granulomatous infiltrates [53,103].

Treatment

Endoscopic sinus surgery may be required in cases of chronic sinusitis. Obstructive airway diseases of CVID patients can be managed with inhaled corticosteroids [99]. There are several studies that report methods for preserving and improving lung function in pulmonary complicated CVID cases, including postural drainage, inspiratory muscle training and pulmonary rehabilitation programs [104,105], advocating higher IgG trough levels (700–800 mg/dl) [27], using anti-inflammatory effects of macrolides with azithromycin [106–108], inhaled corticosteroids

fluticasone or nebulized gentamicin for reduction of sputum production [109,110], using an oral quinolone and aerosolized colimycin or tobramycin for aggressive eradication of colonized *Pseudomonas* spp. [111,112], NSAIDs [113] and mucolytics [114]. Of interest, patients with bronchiectasis required IVIG higher than 600 mg/dl to achieve the same IgG level compared with patients without bronchiectasis [115,116]. Clinical response, lung function and sputum sampling should be performed for respiratory health monitoring after starting the treatment.

In CVID patients with pulmonary diseases, new therapeutic approaches focus on IL-2 therapy [117–120], short and long-acting inhaled B₂-agonists in bronchiectasis [121,122] and leukotriene receptor antagonists [113]. Although most bronchiectatic CVID patients tend to have generalized lung damage, selected cases with highly localized disease may benefit from surgical procedure [123].

Lung insufficiency due to progressive intractable pulmonary disease necessitates continuous oxygen treatment and/or heart or lung transplantation, although overall outcomes of this modality are variable in CVID cases [53,124–126].

Management of polyclonal lymphocytic infiltrative complications

Approximately 10–25% of CVID patients encounter various lymphoproliferative and granulomatous diseases and the mean age at onset of these complications is 20–40 years. Granulomatous lesions can affect any organ in the progression of CVID, but the most common site is the lung, presenting with a pattern of interstitial lung disease (granulomatous lymphocytic interstitial lung disease [GLILD]) [48,103,127,128].

The frequency of multisystemic involvement is unknown and probably underestimated [129]. All CVID patients with pulmonary granulomatous diseases suffer from shortness of breath and persistent cough. Although physiological functions are normal in patients with pulmonary granulomas, it is not excluded that these patients would have eventually developed abnormal tests over time [48]. Lymphoid interstitial pneumonitis (LIP) is another involvement of the pulmonary system in lymphoproliferative disorders without evidence to be related to any known pulmonary infection and it is associated with other connective tissue disorders [36]. LIP and GLILD complications have a poor outcome and many unanswered questions about the pathogenesis and appropriate therapeutic intervention of both complications remain [130].

The lymphoproliferative and granulomatous diseases in CVID seem to be related to severe depletion of switched memory B cells and CD4⁺ native T cells [131]. Splenomegaly and malignancies are also more frequent in this subgroup of CVID patients [48]. Expansion of CD8⁺ cells and lack of CD4⁺ cells has already been shown to be associated with the granuloma formation in tissues [132–134]. Genetic predisposition may have a role in different aspects of granulomatous diseases in CVID patients.

Prevention

Ig replacement therapy has no effect on polyclonal lymphocytic infiltrative diseases as a preventive agent for inflammatory process that is made by an immune dysregulation mechanism [40,135].

Follow-up

Biopsy via open lung or transbronchial surgery may be required for large and persistent lymph nodes. Signs of interstitial lung disease including dyspnea and reduced exercise tolerance should be considered in regular visits. Restrictive ventilatory pattern in pulmonary function test and parenchymal nodules or ground glass opacities in high-resolution computed tomography may alert physicians to consider pulmonary lymphoproliferative diseases. However, other imaging modalities (e.g., MRI, endoscopy) for assessment of progression of granulomatous diseases may be indicated.

Treatment

The optimum therapeutic option for CVID-related lymphoproliferative diseases is not clear, and this complication remains a major clinical challenge. High doses of systemic corticosteroids (10 mg a day or 20 mg every other day or twice-daily inhaled beclomethasone) is the first choice for interstitial lung disease with restrictive ventilatory defect due to lymphoproliferative disease such as pulmonary granulomas and LIP, but their long-term use is limited because of the risk of infections [136,137]. For long-term therapy, hydroxychloroquine is prescribed with dosage of 200–400 mg a day (range: 3.5–6.5 mg/kg) [138–140]. Steroid-sparing immunosuppressive agents have also been recommended in special situations when inflammation is predominantly pulmonary, including cyclosporine A (125 mg a day) [135], methotrexate [141], azathioprine, mycophenolate mofetil and 6-mercaptopurine [136]. All mentioned therapeutic modalities are used in case reports or limited studies and their results for extrapolation to CVID should be tested in clinical trials. Monoclonal antibodies as TNF- α inhibitors, such as etanercept [132,142] and infliximab [143–146], can be used in the case of generalized granulomatous lesions combined with autoimmunity, but no systematic clinical trials have investigated their efficacy and safety. Opportunistic infections like *Pneumocystis jirovecii* pneumonia may result when patients are under treatment for lymphoproliferative diseases [52,115].

Hepatomegaly and lymphadenopathy have also not been proven for treatment recommendations. Splenectomy should be avoided because its efficacy in the treatment of cytopenia is controversial and this surgery predisposes patients to severe infections [4,147,148].

Management of autoimmune complications

Autoimmune-associated disorders, reported in 20–25% of CVID patients, are caused by immune dysregulation due to failed or circumvented specific autoreactivity checkpoints during the B-cell development process [149]. This dysregulation culminates in production of multiple autoantibodies against various self-antigenic targets [150]. Autoimmune thrombocytopenic purpura (ITP) and autoimmune hemolytic anemia (AIHA) are the most common types of autoimmune consequences, occurring in 5–8% of the all registered CVID patients [4,151]. These disorders present in some patients before the diagnosis of CVID. Thus, CVID must be considered as a differential diagnosis in adult-onset ITP and AIHA [152,153]. Other autoimmune disorders

include the presence of anti-IgA antibodies [154], autoimmune neutropenia [36], pernicious anemia [140,150], juvenile rheumatoid arthritis, systemic lupus erythematosus, psoriasis, autoimmune thyroiditis, autoimmune hepatitis, primary biliary cirrhosis, insulin dependent diabetes, sicca syndrome, vitiligo and vasculitis [25,36,155,156].

Prevention

No preventive modalities are presently available, however, IVIG treatment has led to reduction of incidence of the autoimmune diseases especially within cases with ITP and AIHA [153].

Follow-up

General medical vigilance and hematologic laboratory monitoring with intervals of 3–6 months is the way for monitoring of hematologic autoimmunity. Some clinical immunologists recommend annual thyroid examination and thyroid function testing as part of routine follow-up in CVID patients.

Treatment

Common treatment protocols for autoimmunity are used similarly in CVID cases. In case of hematologic autoimmunity, managements are based on intravenous corticosteroids (1 g of methylprednisolone in mild disease) or anti CD-20 monoclonal antibodies (rituximab in severe disorders) [36,157,158]. Persistent autoimmunity can be handled by high Ig immunomodulatory effects (1 g/kg/week) for a short time.

TNF- α inhibitors might be used in overlapped phenotypes of autoimmunity (e.g., infliximab for Crohn's disease and etanercept for rheumatoid arthritis) and polyclonal lymphocytic infiltration [142,159].

Management of GI complications & enteropathy

The GI tract constitutes the largest human immune organ and is therefore expected to be affected by CVID [55,160–162]. Virtually 60% of CVID patients present with diarrhea and 10% develop digestive complications such as idiopathic malabsorption associated with weight loss [163]. Other gut symptoms such as discomfort and bloating are also common [25]. Inflammatory GI disorders are extremely frequent in CVID patients [164]. Approximately 20% of CVID patients have GI symptoms not related to infectious causes [4]. Classical Crohn's disease is probably not seen in CVID, although it has a high incidence in X-linked agammaglobulinemia. Celiac (gluten-sensitive) disease does occur but is very rare. CVID-related enteropathy is a sprue-like illness with villus atrophy and crypt hyperplasia in biopsy but shows no improvement by gluten-free diet [165]. Inflammatory bowel disease (ulcerative colitis, ulcerative proctitis or Crohn's disease), which can cause stricture, lymphocytic colitis and collagen enterocolitis, is more prevalent in CVID patients than the normal population [166]. Intestinal lymphangiectasia, nodular lymphoid hyperplasia and nonspecific malabsorption have also been reported [4]. Defective cellular immunity, rather than antibody deficiency alone, appears to predispose patients to such symptoms [164]. Up to 10% of CVID patients may suffer from liver dysfunctions (abnormal

liver function tests, predominantly increased alkaline phosphatase and nodular regenerative hyperplasia) caused by infections (e.g., HBV and HCV), autoimmunity (e.g., autoimmune hepatitis, primary biliary cirrhosis) and granulomatous diseases [84,160,167]. Previous studies suggested that nodular regenerative hyperplasia has different etiology, including circulating immune complexes or light chain deposits in the sinusoidal walls [168]. Unexplained liver disease with portal hypertension occurs in 5–10% of the patients. Autoimmunity (69.2%) and lymphocyte abnormalities (78.6%) were observed more frequently in CVID patients with hepatic dysfunctions [169–173].

Prevention

No effective preventive modalities are presently available for GI complications. However, prevention of primary hepatic complications (viral hepatitis, autoimmunity and granulomatous diseases) helps progression of CVID cases from regenerative hyperplasia leading to portal hypertension, cholestasis and hepatic dysfunction. It remains to be proven whether fast treatment of intestinal infections improves outcomes for CVID patients [14].

Follow-up

Screening for GI complications is more unclear, unless attention is paid to the patient complaints (diarrhea refractory to antibiotic treatments) and clinical symptoms (especially weight loss) that are key alarm signs [14]. Biannual upper and/or lower endoscopy and yearly ultrasonography may help screening for GI symptomatic CVID cases.

Treatment

The management of severe inflammatory enteropathy in CVID is based on low-dose immunomodulators (azathioprine or 6-mercaptopurine) and TNF- α blockers (infliximab or etanercept) [165,174]. Management in mild inflammatory bowel disease, however, is the same as for immunocompetent patients. The use of long-term high-dose corticosteroids is controversial because of the increased probability of intestinal CMV infection [160,175].

Management of malignancy

CVID patients are at higher risk of neoplasias (hematological or solid tumors) compared with normal population (over ten-times the risk) [176]. The most common type of malignancy is non-Hodgkin's lymphoma (NHL), which is more likely to be of B-cell origin [177]. Lymphoid malignancies (including mucosa-associated lymphoid tissue lymphoma, marginal zone lymphoma and T-cell-rich B-cell EBV-associated lymphoma) are more prevalent in younger patients [5,34,178]; by contrast, CVID adults are more susceptible to GI tract malignancies, especially adenocarcinoma of the stomach [177]. It was estimated that 8.2% of CVID cases are susceptible for lymphoma, however, females and CVID cases with higher levels of serum IgM are more prone to this secondary complication [26]. Polyclonal lymphocytic infiltration is a clinical predictor associated with an increased risk of lymphoid malignancy [51]. Furthermore, in CVID patients, clinical and family histories of neoplasia should be taken accurately along with consideration

of surveillance for malignancy, especially lymphoma and gastric cancer [48]. Risk of gastric cancer, especially gastric adenocarcinoma, may be increased by *H. pylori* infections and chromosomal radiosensitivity [177,179]. Chronic viral infections with CMV and human herpesvirus 8 may predispose CVID patients to develop NHL [176].

Prevention

H. pylori antigen screening in feces and appropriate endoscopy with examination for this microorganism and its eradication may prevent gastric cancer [180]. Moreover, decreasing unnecessary exposure of CVID patients to irradiation can reduce risk of iatrogenic cancer due to chromosomal radiosensitivity [177].

Follow-up

First of all, age-appropriate cancer screening of general healthy population (colonoscopy, prostate examination, cervical smears and mammograms) should be programmed for all CVID patients more tenuously. CVID-specific screening by endoscopy for finding mucosal changes should be performed in symptomatic cases. Histopathological investigation of enlarged nodes via excision of the whole lymph node and periodic complete blood counts and differential white blood cell counts are important means for screening of lymphoid malignancy [181]. Bone marrow examinations for lymphoma screening, however, are not positive, except in the most advanced cases.

Treatment

Management of neoplasia in CVID is similar to routine chemotherapy protocols for cancerous patients as well as standard rituximab protocols. Surgical modalities such as total gastrectomy are lifesaving for early diagnosed cancers [177].

Because of the relation of presentation of malignancy and impaired T-cell immunity in CVID, allogeneic stem cell transplantation is now considered in these selected CVID cases. However, it should be noticed that these potentially curative approaches are experimental and should only be proposed for therapy-refractory life-threatening complications (late-onset combined immunodeficiency subgroup) with careful process for donor selection [182]. The best response of allogeneic stem cell transplantation is seen in the patients with NHL resolving all CVID-related consequences. Graft-versus-host disease should be monitored in these patients [183].

Prognosis & surveillance

Major indicators that affect poor CVID prognosis are structural pulmonary damages, GLILD, severe autoimmunity, malignancy and extent of end-organ damage, which all can be managed by therapeutic strategies [103]. Moreover, implementation of appropriate prevention, screening and treatment protocols during recent years improved mortality rate after 10 years of follow-up from 20–40% [4,33] to 5–10% [13,34]. Respiratory tract insufficiency, especially cor pulmonale, serves as the most frequent cause of death in CVID patients followed by lymphoma and liver failure. Despite clinical manifestations, low levels of IgG, poor

T-cell responses to antigens, and a low percentage of peripheral B cells are laboratory factors that can predict lower survival rates in CVID.

Expert commentary

Ig replacement therapy, either subcutaneous or intravenous, is the mainstay of therapy in patients with CVID, while specific treatment for certain complications associated with disease is needed. In addition to recurrent infections, in which antibiotic prophylaxis might be added to Ig replacement therapy, further pulmonary problems as well as polyclonal lymphocytic infiltrative complications, enteropathy, autoimmune diseases and malignancies require

additional management, and higher doses of Ig replacement therapy can be recommended in certain conditions.

Five-year view

It is to be hoped that underlying genetic defect(s) and precise pathophysiology of CVID will be identified in the near future, considering multicenter international studies in this field, which could provide novel possibilities for treatment of this disease. Moreover, conducting some studies on safety and efficacy of current treatments can help clinicians come to a consensus on treatment of this disease, which definitely can improve the prognosis of the patients.

Key issues

- Education of patients, immunoglobulin replacement therapy, prophylactic and therapeutic antibiotics and complementary vaccinations are the main means for tackling infectious complications of common variable immunodeficiency (CVID) cases.
- Pulmonary function tests and high-resolution computed tomography should be considered in all CVID patients to diagnose secondary lung damages at the earliest time possible.
- Annual ultrasonography and endoscopy every 2 years are the best screening methods for individuals with suspected gut complication.
- Steroid-sparing immunosuppressive agents and TNF- α inhibitors may be useful therapeutic modalities in patients with lymphoproliferative and autoimmune phenotypes.
- Beside routine protocols of chemotherapy, allogeneic stem cell transplantation may have an appropriate result in malignant CVID patients.

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A review on guidelines for management and treatment of common variable immunodeficiency

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Activity Evaluation

Where 1 is strongly disagree and 5 is strongly agree

	1	2	3	4	5
1. The activity supported the learning objectives.					
2. The material was organized clearly for learning to occur.					
3. The content learned from this activity will impact my practice.					
4. The activity was presented objectively and free of commercial bias.					

1. You are seeing an 18-year-old young woman with recurrent upper respiratory and gastrointestinal infections. She was just diagnosed with common variable immunodeficiency (CVID). What can you tell her about this diagnosis?

- ☐ A It may be diagnosed among children as young as 2 years of age
- ☐ B The principal clinical presentation of CVID is recurrent infections
- ☐ C Non-encapsulated bacteria promote most bacterial infections among patients with CVID
- ☐ D Campylobacter species promote most gastrointestinal infections among patients with CVID

2. You decide to initiate immunoglobulin G (IgG) replacement therapy for this patient. What should you consider regarding this therapy?

- ☐ A Only intravenous therapy provides consistently sufficient doses of IgG
- ☐ B Subcutaneous doses of IgG should not exceed 100 mg/kg per week
- ☐ C Subcutaneous administration of IgG provides a more stable serum level of IgG compared with intravenous administration
- ☐ D Side effects are more common among adolescents vs adults over age 65

3. The patient continues to have a cough after 2 courses of antibiotic therapy. What should you consider regarding pulmonary complications of CVID?

- ☐ A Younger age is associated with more severe pulmonary complications
- ☐ B Her dosage of IgG may need to be increased
- ☐ C Plain radiography remains the best means to evaluate chronic pulmonary symptoms among patients with CVID
- ☐ D Corticosteroids are to be avoided in the management of pulmonary disease among patients with CVID

4. What else should you consider regarding the potential complications of CVID?

- ☐ A Autoimmune thrombocytopenic purpura and autoimmune haemolytic anemia are the most common autoimmune complications of CVID
- ☐ B CVID-related enteropathy usually improves after gluten is eliminated from the diet
- ☐ C CVID is associated with a higher risk of hematological but not solid malignancy
- ☐ D The most common malignancy associated with CVID is chronic leukocytic leukemia