The immunodeficiency of chronic lymphocytic leukaemia

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Introduction: Patients with chronic lymphocytic leukaemia (CLL) have progressive immunodeficiency and infection is the commonest cause of death. This review seeks to identify the extent of the abnormality, its cause, clinical significance and any possible remedy.

Sources of data: TJH has studied CLL for the past 40 years and has scanned or read every paper he could find published on the topic since 1970 and most of those of historical importance published before that date. He has read around the subject, covering relevant articles on immunology, cell biology, oncology and genetics. Furthermore, he has attended most major meetings dealing with CLL in this time and has written many reviews to update the state of knowledge about the topic. He receives weekly updates of papers published on CLL from PubMed and Science Direct with the keywords ‘chronic lymphocytic leukaemia’.

Areas of agreement: The immunodeficiency chiefly manifests as hypogammaglobulinaemia but involves all elements of the immune system. It is caused by the interpolation of tumour cells among immunological cells and mediated by bi-directional cell contact and secretion of cytokines, which both sustain and invigorate the tumour and suppress immunity. CLL treatment generally makes the immunodeficiency worse. Intravenous immunoglobulin is clinically effective but not cost-effective, while prophylactic antibiotics are useful in appropriate circumstances. Vaccination against infectious disease is usually ineffective.

Areas of controversy: Exactly how the presence of tumour cells in the immune organs renders the patient immunodeficient is controversial as is the clinical significance of minor degrees of immunodeficiency in early or indolent cases. The immunosuppressive effect of most forms of treatment is agreed, but how much this should figure in the choice of treatment is a matter of dispute.

Growing points: The study of tumour–stromal interactions is an area of intense research.

Areas timely for developing research: There has been little done to develop better vaccination strategies in patients with CLL, and although effective antimicrobials have been developed to protect against opportunistic infections,
Introduction

Patients with chronic lymphocytic leukaemia (CLL) are all to a degree immunodeficient. The most obvious and well-known abnormality is hypogammaglobulinaemia, which is present in up to 85% of patients. Serum immunoglobulin levels may be suppressed in other lymphoid malignancies, but in CLL the suppression is far greater. Profound defects of cell-mediated immunity also occur, and although these are most obvious in patients who have been treated with purine analogues, even untreated patients have abnormalities of T-cell numbers and function. This review will seek to explore the extent of the immune defect in CLL, its causes, clinical significance and possible remedies.

Extent of the immune defect

Infections are the major cause of death in between a quarter and a half of patients with CLL. Bacterial infection of the respiratory tract, skin or urinary tract is the commonest problem, and before the use of purine analogues for treatment, the usual organisms were *Streptococcus pneumoniae, Staphylococcus aureus, Streptococcus pyogenes* and *Escherichia coli*. Protection against these organisms is provided principally by antibody, but only 15% of patients with CLL have completely normal serum immunoglobulins. It is likely that the only patients with CLL who do not have hypogammaglobulinaemia are those in whom it will occur in the future.

The extent of hypogammaglobulinaemia depends on the stage and duration of the disease. It occurs in patients with mutated and unmutated immunoglobulin heavy chain (*IGHV*) genes. Although older papers described serum IgA as the first immunoglobulin to be reduced followed by IgM and IgG, this is by no means invariable and most patients have or will have depression of all classes of immunoglobulin. It should be stressed that the hypogammaglobulinaemia is not confined to patients who have been treated. In one study of an untreated patient with stage B disease without a detectable paraprotein, the hypogammaglobulinaemia was so profound that over 90% of the detectable immunoglobulin in the serum was idiotypic, and thus derived from the tumour.
Despite the low levels of serum immunoglobulins, most patients suffer no clinical consequences from this, and in one study, 65% of bacterial infections occurred with serum IgG levels below 300 mg/dl\(^3\) (reference ranges vary from lab to lab). In patients with primary immunodeficiency, it is recommended that immunoglobulin replacement therapy should only begin when the serum IgG falls below this level.

The non-malignant B-cell population in CLL is not well characterized.\(^4\) The proportion and overall number of non-malignant B cells are often significantly reduced, and clearly their function is impaired as the normal immunoglobulins are suppressed. What is not clear is whether they are directly suppressed by the tumour or indirectly as a consequence of inhibitory effects elsewhere in the immune response.

Apart from bacterial infections, patients with CLL also suffer from the reactivation of herpes viruses. Most commonly this involves \textit{herpes zoster}. In one series from before the era of treatment with purine analogues, the incidence of herpes zoster was given as 28.6%, with 3.5% having recurrent attacks.\(^1\) Particularly important is the observation that attacks of shingles frequently precede the clinical diagnosis of CLL,\(^1\) suggesting that the underlying immune defect does not depend on either hypogammaglobulinaemia or the physical overwhelming of immune organs by infiltrating tumour cells.

Recurrent attacks of \textit{herpes simplex} also occur in some untreated patients. Both HSV1 and HSV2 may be involved. The recent recognition that \textit{herpes simplex} is implicated in many cases of Bell’s palsy may explain the association of Bell’s palsy, including recurrent attacks, in patients with CLL.\(^1\)

Treatment greatly increases the risk of the reactivation of herpes viruses. Reactivation of cytomegalovirus (CMV) is, of course, particularly associated with treatment with alemtuzumab. In one clinical trial, symptomatic infections occurred in 15% of patients and asymptomatic reactivation occurring in more than half.\(^5\) However, in our experience, symptomatic reactivation may occur after treatment with fludarabine and asymptomatic reactivation has been reported even after treatment with chlorambucil.\(^5\) Reactivation of the Epstein-Bar virus (EBV) occurred in four out of 24 patients treated with the combination of fludarabine, cyclophosphamide and dexamethasone, and in this series and others, treatment with fludarabine has been associated with transformation to EBV-positive high-grade lymphoma or the Hodgkin disease.\(^6\)

Human herpes virus 8 (HHV8) is the cause of Kaposi’s sarcoma in immunodeficient individuals. It has been reported in CLL both in untreated patients and those treated with fludarabine. An American Surveillance, Epidemiology and End Results (SEER) report noted nine cases between 1973 and 1996 among 16 367 patients observed, a statistically significantly increased hazard ratio of 5.09.\(^7\) Human herpes
virus 6 causes roseola, the childhood exanthem, but in adults it has been suggested as an initiating agent in both chronic fatigue syndrome and multiple sclerosis. Fatigue is a common symptom in CLL often dismissed by physicians yet much discussed on patient websites. Multiple sclerosis has been reported as occasionally coexisting with CLL.1

A systematic study of herpes viral copy number in haematological diseases has been carried out using real-time quantitative polymerase chain reaction. Occasional patients with CLL had high copy numbers of EBV, CMV and HHV6A, but not HHV6B, HHV7 and HHV8.8 Although interesting, the use of leukaemic B cells as a source of DNA means that T-cell lymphotropic viruses would be missed, and no indication was given as to the stage of the patients or the degree of immunosuppression.

In most patients with CLL, T-cell numbers are increased. This increase mainly affects CD8+ cells, but CD4+ cells are also increased, though the CD4/CD8 ratio is reversed.4,9 Analysis of the expanded CD8+ cell population demonstrates that they are also positive for CD45RA and CD57, and negative for CD27,9 indicating that they have a cytotoxic effector function. Moreover, both CD4+ and CD8+ T-cells appear to have restricted clonality when examined for T-cell receptor V gene usage and length of the CDR3,9 and display an activated phenotype with upregulation of CD69, CD16, CD56, CD71 and HLA-DR with loss of CD62L and CD28 (reviewed by Mackus et al.9). These findings were originally interpreted as evidence that there is an autologous T-cell response against the tumour, but convincing evidence of such a response is still lacking.

A T-cell lymphocytosis with a similar marker profile is seen during some viral infections and, in patients latently infected with CMV, increased senescence of the immune system with age is associated not with a falling away of CMV-reactive T-cells, but with a marked increase of such cells, which tend to be oligoclonal and have the same immunophenotype as those seen in CLL.10 In elderly individuals, CMV-specific cytotoxic T-cells may comprise more than half the CD8+ repertoire10 and the figure is similar in CLL.9 Indeed, in patients with CLL who are seronegative for CMV, there is no increase in T-cell numbers and the CD4/CD8 ratio is not reversed.9

There are other changes in T-cell function, many of which will be explored with the discussion of interactions between CLL cells and host T-cells, but it seems clear that many of the changes observed in the T-cell population in CLL are a consequence of the immune system having to ‘work harder’ to control latent herpes virus infections, especially CMV. Investigators envisage that the anti-CMV response might be harnessed and redirected to attack the CLL itself.11
In addition to viruses, patients with defects of cell-mediated immunity are also susceptible to other opportunistic infections such as *Listeria, Nocardi a, Candida, Aspergillus, Pneumocystis jirovecii, Histoplasmosis, Cryptococcus* and atypical mycobacteria, although these seldom occur in untreated patients. Such infections are often seen in patients with other haematological conditions who are treated with myelosuppressive drugs and in our estimation usually require the added feature of failure of effector function in the immune system.

In CLL, neutropenia may be a consequence of any cytotoxic therapy, though it is usually short-lived. Autoimmune neutropenia is exceedingly rare, but patients with stage C disease frequently have severe and prolonged neutropenia to accompany their anaemia and thrombocytopenia. Because the often very high lymphocyte counts in such patients interfere with automatic differential counting, the neutropenia is often not observed. Prolonged neutropenia also sometimes occurs after treatment with fludarabine-based regimens. The reason for this is not clear, although unexpected cases of secondary myelodysplastic syndrome following treatment with purine analogue and alkylating agent combinations are being reported.

Early papers identified defects in phagocytic function and cytotoxic activity of neutrophils, monocytes and NK cells. Although some authors were seeking to establish a common lineage between the CLL cells and other blood elements, just as exists for chronic myeloid leukaemia, the fact that features like deficient levels of β-glucuronidase, myeloperoxidase and lysozyme in neutrophils and monocytes were corrected after treatment had removed most of the CLL cells from the circulation strongly suggests that the tumour cells themselves affect effector cell function either by their secretions or cellular contact. The NK cell function is similarly restored by the removal of the CLL cells and it has been shown that treatment with fludarabine not only spares NK cells but may actually enhance their activity. More recent papers have identified defects in the production of pro-inflammatory cytokines by CLL monocytes, and of chemotaxis, but not of phagocytosis or intracellular killing in CLL granulocytes.

Another prominent and important factor in the suppression of lymphocyte and monocyte function and thus the occurrence of opportunistic infections is the use of corticosteroids. Early trials showed no benefit to their use with alkylating agents, and trials of their addition to purine analogues were halted because of a higher incidence of infection, but they remain the drug of choice in treating the autoimmune complications of CLL. Corticosteroids are also used, often without the knowledge of the physician directing therapy, to suppress transfusion reactions and reactions to infusions of rituximab. More recently, high-dose steroids have found favour in the treatment of bulky and drug-resistant disease.
Early studies suggested that the deficiency of the complement components C1 and C4 was a regular occurrence in CLL. Although this has not always been confirmed, there is undoubtedly an abnormality of complement function in many patients, resulting in an inability to coat bacteria with C3b, and perhaps most frequently involving the alternative pathway.\textsuperscript{14,15}

One further piece of evidence of immunodeficiency should be mentioned: it has long been believed that second malignancies are commoner in CLL than in the general population and this has been attributed to a defect of immune surveillance. A recent review\textsuperscript{16} goes into painstaking detail of all reported studies. The risk is particularly great for skin cancers and virally induced cancers but less convincing for other tumours. There are difficulties in assembling accurate statistics, as CLL frequently goes unreported or undiagnosed in old people. Patients with cancer are more likely to have blood tests than normal individuals, so that asymptomatic CLL is more likely to be diagnosed in them. Similarly, patients with CLL are more likely to be seen by doctors than individuals without it, and other cancers, especially skin cancers, are thus more likely to be diagnosed. Nevertheless, there almost certainly is an increase in some cancers, which might be attributed to a defect in cell-mediated immunity.

\section*{Causes of the immune defect}

Although the precise mechanism is not yet clear, the immune defect in CLL is mediated by the presence of the tumour cell in the midst of the lymphoid organs and by the attempts of the physician to remove them. Exactly how this is mediated is unclear. Some have suggested a role for the non-polymorphic human leukocyte antigen G (HLA-G), which counteracts the cellular immune response of T- and NK cells by several pathways. Certainly, patients expressing greater amounts of HLA-G have poorer immunity and shorter survival, but the precise mechanism of its action remains to be worked out.\textsuperscript{17}

In the normal immune response, T-cell activation involves interactions with antigen presenting cells (APCs)—dendritic cells and B-cells. T-cells encounter antigen as APC-processed peptides requiring cell–cell contact via a low-affinity interaction between CD11a and CD54 (LFA-1 and ICAM-1), which facilitates antigen recognition between the T-cell receptor/CD3 complex and MHC class II and CD4. This signals the upregulation of certain surface markers and the secretion of specific cytokines. The activation of helper T-cells in an immune response may have a defined polarity depending on what cytokines are produced. Th-1 polarity with secretion of interferon-\gamma
favours cell-mediated immunity; Th-2 polarity with secretion of interleukin-4 (IL-4) favours antibody production. In a Th-2 response, the activated T-cells are able to ‘help’ activate normal B cells and induce them to mature and secrete antibody. The upregulated activation marker CD28 interacts with the CD80/CD86 receptors on B-cells and the increased expression of CD154 on T-cells binds to its ligand CD40 on B-cells. The cytokine interleukin-2 (IL-2) is produced, which facilitates proliferation and clonal expansion of T-cells. Activation of the T-cell has a built-in ‘off switch’: a late activation molecule on the T-cell surface is CTLA-4 (CD152), which on engaging with the CD80/CD86 complex on the B-cells inactivates the T-cell response.18 It should be noted that stimulation of the T-cell receptor without interaction between CD28 and CD80/CD86 leads to T-cell anergy.4

CTLA-4 is also present on a subpopulation of regulatory T-cells that suppress antigen-specific T-cell immune responses. These naturally occurring cells play a central role in the maintenance of peripheral tolerance by suppressing autoreactive T-cell populations. Apart from CTLA-4, regulatory T-cells are characterized by the expression of CD4 and CD25 together with Forkhead box P3 (FOXP3), CD62L, glucocorticoid-induced tumour necrosis factor-related protein (GITR), transforming growth factor β1 (TGF-β1) and interleukin-10 (IL-10).19

In CLL, dendritic cells that are phenotypically and functionally normal may be derived from peripheral blood monocytes,20 however, the CLL B-cells themselves are poor APCs.4 A direct suppression of bone marrow plasma cells by CLL B-cells has been reported by one group.21 This appeared to be mediated by the interaction of Fas ligand (CD178) molecules which are expressed on CLL cells with the Fas death receptor CD95, which is upregulated on patients’ plasma cells. However, this has not been replicated by other groups and it seems more likely that the immunodeficiency stems from the interaction between B-cells and T-cells.

The peripheral lymphoid organs host the proliferative core of CLL. The chemokine stromal-derived factor 1α, also known as CXCL12, recruits CLL cells towards the secondary lymphoid organs via their specific CXCR4 receptor.22 Within the secondary lymphoid organs, they form proliferation centres or pseudofollicles. These are indeed parodies of lymphoid follicles in which the CLL cells are able to subvert the normal helper function to their own use while denying it to normal B-cells. Experiments suggest that T-cells expressing CD154 interact with CLL B-cells through their CD40 receptor activating them and upregulating CD38 and ZAP-70.22,23 The effect of this interaction on CLL cells in the proliferation centre is to increase proliferation rate24 (though it remains less than that of normal B-cells in normal
individuals) but also to induce cell cycle arrest and resistance to apoptosis.25

However, the T-cells do not come through the encounter unscathed. It is important to separate the effects of low-grade reactivation of herpes viruses on T-cells from the effects of their interaction with the tumour cells, but it seems clear that this interaction induces a state of relative T-cell anergy with poor responses in mixed lymphocyte reactions, poor delayed hypersensitivity reactions, Th2 polarization and reduced expression of CD154. How this comes about is a matter of dispute, but CLL cells express a wide variety of cytokines including IL-1β, -2, -4, -5, -6, -8 and -10; interferon-α and -γ; G-CSF and GM-CSF; TNFα and TGF-β. A good case has been made recently for interleukin-6 being responsible for many of the effects.26 It is an unexplained paradox how T-cells can be at the same time unable to react with normal B-cells yet able to stimulate CLL B-cells. The confocal microscope studies reported by Patten et al.23 were unable to demonstrate CD154 on T-cells in proliferation centres in lymph nodes and bone marrow.

Regulatory T-cells are increased in number in CLL, and the increase is greatest in patients with the most advanced disease.19 It is not clear whether this contributes to the immune deficiency, but what is most noticeable is that this population is exquisitely sensitive to treatment with fludarabine as opposed to treatment with alkylating agents. It has been suggested that this might be one of the mechanisms that favours the development of autoimmune haemolytic anaemia after treatment with fludarabine.12

The suppression of T-cells generally by fludarabine is so profound and persistent6,27 that it overwhelms the immunodeficiency of the disease itself. The numbers of CD4+ T-cells fall to the levels seen in AIDS, and they remain low for up to 2 years following therapy. Although there were early suggestions that achieving a complete remission might restore the integrity of the immune system and while it is certainly true that some patients have fewer infections following complete responses, the general rule is that patients continue to have a severe immunodeficiency after treatment and in many cases they also have more severe infections. The immune suppression following treatment with alemtuzumab is more severe in that reactivation of herpes viruses is more likely, but tends not to be so long lasting. The suppressive effects of corticosteroids have already been mentioned. Other treatments such as alkylating agents, while less immunosuppressive, tend to be less effective and do not ameliorate the disease-related immune defect. A single small study has reported on any improvements in the serum immunoglobulin levels following treatment with fludarabine, chlorambucil and prednisolone and rituximab. The responses to
the first two regimens were trivial and not statistically significant, but at the time of maximum clinical response to rituximab, serum immunoglobulins rose by a mean of 17.3%, which was significant at a $P$-value of 0.001. Higher doses of rituximab were more effective, but further studies will be necessary to confirm this result.

**Potential remedies for the immunodeficiency**

As has already been discussed, just treating the CLL does not restore immunity and guidelines do not recommend immunodeficiency as a reason for beginning treatment. There have been three attempts to restore cell-mediated immunity using low-dose IL2, with mixed results, though further studies in earlier disease are probably warranted.

*Intravenous immunoglobulin*

The chief means of improving the immune defect has been the use of intravenous immunoglobulin (ivIg) infusions. It should be remembered that immunoglobulin infusions only contain significant amounts of IgG and will not restore deficiencies of other immunoglobulin classes. The use of ivIg in CLL is controversial. Several clinical trials have demonstrated that it reduces the incidence of mild and moderate bacterial infections but none have shown a decrease in mortality. When the need to regularly attend hospital is taken into consideration, there may be no improvement in quality of life. One study estimated that the cost of one quality adjusted life year was $6 million. IvIg only becomes cost effective if it is better targeted. Our own practice is to confine treatment to patients whose serum IgG is $<300$ mg/dl and who have had at least two bacterial infections in a 12-month period. We recommend a dose of 250 mg/kg given every 4 weeks. Arrangements are available for patients to self-administer the immunoglobulin infusions at home.

*Prophylactic antimicrobial agents*

There are no clinical trials of prophylactic antimicrobial agents in CLL. Although the use of cycling antibiotics to prevent infections is very common in patients with recurrent chest infections due to bronchiectasis, or recurrent urinary tract infections, there are no studies of the efficacy or cost effectiveness of this approach in CLL. Nevertheless, some patients with recurrent sinusitis clearly benefit from this sort of approach.
There are similarly no trials or prophylactic antimicrobials in patients with low CD4+ T-cell levels following treatment with purine analogues or alemtuzumab.\(^29,31\) The current practice derives from what has been used in patients with AIDS. Prophylaxis against *Pneumocystis jirovecii* is normally with cotrimoxazole 960 mg on alternate days continued for a minimum of 6 months after stopping therapy. Some authorities recommend monitoring the count of CD4+ T-cells and continuing the cotrimoxazole until the count is greater than \(0.2 \times 10^9/l\). For patients who cannot tolerate cotrimoxazole, pentamidine 300 mg by inhalation every 4 weeks is available. Alternatives are dapsone 100 mg daily or atovaquone 750 mg twice daily, though this is an unlicensed indication in the UK.

In patients with a history of herpes simplex or herpes zoster prophylaxis with aciclovir should certainly be given following treatment with either fludarabine or alemtuzumab.\(^29,31\) The dose that should be used has not been established; between 400 and 1600 mg per day have been variously recommended on the basis of experience with AIDS patients or those undergoing stem cell transplantation. Again, anti-viral treatment usually continues for 6 months after treatment stops, though some would advocate monitoring the count of CD4+ T-cells. In patients who receive treatment with alemtuzumab, though not in those receiving purine analogues, monitoring for CMV reactivation should be undertaken weekly. Evidence of reactivation should be treated with either ganciclovir 5 mg/kg iv twice daily or oral valganciclovir 900 mg twice daily.

Antifungal prophylaxis is also indicated in some patients receiving either purine analogue or alemtuzumab treatment and, of course, in some patients receiving stem cell allografts. The commonly used fluconazole has no activity against *Aspergillus* species, and when this fungus is considered to be a hazard, the choice of agent should be between itraconazole, voriconazole, posaconazole and caspofungin. Itraconazole is the cheapest of these options but it is unpleasant to take and compliance may be poor. Because of the high cost of the remaining options, many units prefer to limit their use to those at the greatest risk of infection with *Aspergillus* species and other fluconazole-resistant fungi. Particular risk factors would be previous systemic fungal infection, severe and prolonged neutropenia, the use of high-dose steroids and several previous rounds of immunosuppressive therapy.

**Vaccines**

Patients commonly ask whether they should receive vaccinations. Their enquiries have two purposes; they want to know if vaccination is safe and if it is effective. Although vaccination may sometimes transiently
raise the peripheral lymphocyte count, there is no evidence that it triggers an exacerbation of the CLL. On the other hand, patients with CLL should be regarded as immunodeficient as far as vaccination with live attenuated organisms is concerned and these should be avoided. A list of such vaccines is given in Table 1.

Patients with CLL respond very poorly to vaccination. Even newly diagnosed Rai stage 0 patients with normal serum immunoglobulins fail to mount a primary response against a previously unseen antigen, though on repeated injection about half the patients are able to mount a secondary response though at a level substantially less than in normal individuals.\(^{33}\) Vaccination studies in CLL have been comprehensively reviewed by Sinisalo.\(^{34}\) Over the past 50 years, there have been numerous investigations of vaccination against *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, influenza, tetanus, diphtheria, mumps and *Salmonella typhi*. In general, antibody responses to vaccines have been weak. Protein vaccines have produced weak to moderate responses in up to 50% of patients, chiefly in early-stage patients with normal serum immunoglobulin levels, but responses to polysaccharide vaccines have been virtually zero.\(^{34}\) There have been several attempts to enhance responses.

Histamine exerts a complex influence on the immune response via receptors on dendritic cells, macrophages and T and B lymphocytes. It is involved in the regulation of helper T-cell polarity and through the

Table 1 Vaccination against infectious disease in CLL.

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<th>Vaccines that should be avoided in CLL</th>
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<tr>
<td>BCG</td>
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<td>MMR</td>
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<td>Poliomyelitis (oral)</td>
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<td>Rotavirus</td>
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<td>Typhoid (oral)</td>
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<tr>
<td>Vaccinia</td>
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<td>Varicella-zoster</td>
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<td>Yellow fever</td>
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<th>Vaccines that are permissible</th>
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<td>Anthrax</td>
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<td>Cholera (oral)</td>
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<td>Diphtheria</td>
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<td>Haemophilus influenzae type b</td>
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<td>Influenza</td>
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<td>Pertussis</td>
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<td>Pneumococcus</td>
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<td>Poliomyelitis (injection)</td>
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<td>Rabies</td>
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<td>Tetanus</td>
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<td>Tick-borne encephalitis</td>
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<td>Typhoid (injection)</td>
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type 2 histamine receptor interferes with regulatory T-cell function. Attempts have been made to enhance antibody responses to vaccines using the H-2 antagonist, ranitidine. One such study used ranitidine 300 mg twice daily for 90 days in an attempt to enhance antibody production to *Haemophilus influenzae* type B (Hib) conjugated to tetanus toxoid and influenza virus with vaccines given on day 0 and boosted on day 45. The study showed a significantly increased response rate of 90% compared with 43% for controls in patients receiving the ranitidine with the Hib vaccine, though no significant difference could be seen for the influenza vaccine. Improved responses to the tetanus toxoid-conjugated Hib vaccine against both Hib and tetanus were also reported following ranitidine treatment by an independent group, but ranitidine failed to induce any responses to an unconjugated pneumococcal polysaccharide vaccine. Patients receiving ranitidine had higher levels of interleukin-18, a pro-inflammatory cytokine that induces T-cells to produce interferon-γ.

The problem of poor response to polysaccharide vaccines can be partially overcome by conjugation to protein antigens. In the case of Hib, conjugation to tetanus toxoid is effective. For pneumococcal vaccines, conjugation to diphtheria CRM197 carrier protein produces an more effective vaccine capable of eliciting antibody responses in 40% of patients with CLL, most effectively in Binet stage A patients. Studies using this vaccine with ranitidine are awaited.

Patients with CLL undergoing splenectomy will almost certainly not benefit from vaccination with pneumococcal polysaccharide vaccines. Vaccination with the conjugated vaccine might be tried, but prophylaxis with appropriate antibiotics should be considered mandatory.

**Conclusion**

Patients with CLL are prone to infection. Even those with very early and small volume disease have a degree of immunodeficiency. Although this is most obviously manifested as hypogammaglobulinaemia, the interpolation of tumour cells within all secondary immunological organs interferes with almost all aspects of immune function. Exactly how this is mediated is still unclear, but it seems to be multifactorial and involves both cell to cell contact and the secretion of cytokines. This interaction is bi-directional, and while it inhibits immunity, it sustains and invigorates the tumour. There is no obvious remedy for the immunodeficiency. Treatment of the CLL usually makes the immunodeficiency worse. IvIg has some benefit but is very expensive. Prophylactic antibiotics have specific roles. Vaccination against
infections is generally ineffective, but various manoeuvres can improve performance.

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References


