Idiopathic CD4 Lymphocytopenia Diagnosis and Management of

Lead Author: Dr Hana Alachkar, Immunology consultant
Additional author(s) Dr Archana Herwadkar, Immunology Consultant
Division/ Department: Immunology, Tertiary Medicine
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It is your responsibility to check on the intranet that this printed copy is the latest version.
1. **What is this policy about?**

1.1 This protocol describes the evaluation and management of patients with suspected idiopathic CD4 lymphopenia, to ensure that diagnostic tests and treatment meets the needs and requirements of such patients and conforms to accepted national guidelines.

If you have any concerns about the content of this document please contact the author or advise the Document Control Administrator.

2. **Where will this document be used?**

2.1 Immunology Consultants, medical and nursing staff who are involved in the care and management of patients with immunodeficiency and Idiopathic CD4 lymphocytopenia. Other medical and nursing staff Trust-wide managing patients with Idiopathic CD4 lymphocytopenia. As a guidance to other medical teams caring for patients with Idiopathic CD4 lymphocytopenia.

2.2 Applies to adults only.

3. **Why is this document important?**

3.1 The purpose of this protocol is to ensure that a correct diagnosis is made and the reader made aware of the complex condition and management. To be used as guidance and increase the awareness of other health professional involved in their care.

3.2 There are no published guidelines for monitoring patients with ICL.

4. **What is new in this version?**

4.1 Guideline has been re-formatted in line with trust guidelines and content reviewed by the immunology team.

5. **Policy**

Idiopathic CD4 lymphocytopenia (ICL) is a rare heterogeneous cellular immune deficiency condition, of unknown aetiology, diagnosed typically in middle age, usually after an opportunistic infection and characterized by a low CD4 cell count that is unexplained by HIV infection or other medical conditions. ICL is defined by a CD4+ absolute count <300 cells/μL (0.3 x 10^9/l), a CD4+ cell percentage <20% of total T cells, and a CD4+:CD8+ cell ratio of less than one on at least two successive laboratory determinations, together with confirmed absence of an underlying HIV disease, and
without a known cause of immunodeficiency or treatment with immunosuppressives. Transient, unexplained decreases in CD4 cells may occur in healthy persons.

In addition to the CD4+ lymphocytopenia, several patients also display a CD8+ lymphocytopenia, while low B or NK cell counts have also been reported in others. Studies demonstrate increased spontaneous and activation-induced apoptosis in more than half of the patients, while other studies report proliferative T cell defects to mitogens.

The pathogenesis of ICL is unknown, there several hypotheses:

1. diminished generation of T-cell precursors;
2. Increased T-cell apoptosis;
3. Biochemical failure of the CD3-T-cell receptor (TCR) pathway by p56 Lck kinase alteration;
4. Defective production of cytokines;
5. CD4 T-cell antibodies.

**Possible genetic factors** — a small number of specific mutations have been identified in patients with ICL:

- Hypomorphic mutations in the recombination activating gene 1 (RAG1)
- Mutations in the human uncoordinated 119 gene (UNC119), which codes for a signalling adaptor protein that is essential for normal T cell signalling through the TCR
- Mutation in the magnesium transporter gene, MAGT1
- Somatic chimerism in JAK3

**Clinical Presentations**

The broad spectrum of presentations varies from a completely asymptomatic immunological disorder, to the occurrence of opportunistic infections (OIs), lymphoproliferative disorders and solid malignancies, neurological disorders, and autoimmune diseases.

**Infections** - In spite of the very low CD4 count, these patients have fewer OIs than AIDS patients for a given CD4 level. The predominant OIs associated with ICL are cryptococcosis (cryptococcal meningoencephalitis or cerebral cryptococcoma, osteomyelitis and pulmonary infection), molluscum, pulmonary histoplasmosis, disseminated prolonged human papilloma virus (HPV) infection (persistent genital HPV infection with or without perianal and/or hand/plantar disease), mycobacterium pneumonia or various localisation infection, salmonella sepsis and Fusobacterium nucleatum hepatic abscess.
Other infections include recurrent sinopulmonary infections, oesophageal and vaginal candidiasis, *Pneumocystis jirovecii* pneumonia (PCP), aspergillosis, cytomegalovirus and dermatomal varicella zoster (VZV).

Although the clinical follow-up of ICL patients is dominated by HPV, VZV, and mucosal candidiasis, more serious and potentially lethal subsequent opportunistic infections may occur, such as PCP, progressive multifocal leukoencephalopathy (PML) caused by Polyomavirus/JC virus, and EBV-related lymphoproliferative disease leading to B-cell lymphoma.

**Malignancy** - Lymphomas are prevalent in the ICL population, including: Non-Hodgkin's lymphomas, Leptomeningeal lymphomas, Intravascular cerebral lymphomas and EBV related Burkitt's lymphomas, Cervical or perineal neoplasias and other virally-mediated malignancies such as Kaposi’s sarcoma of the digestive tract or skin have been reported.

**Autoimmune disorders** - A number of autoimmune conditions, particularly those involving skin and mucous membranes have been associated with ICL. Reported conditions include the following: Sjogren’s Syndrome, Polyanarthritides/vasculitis, antiphospholipid antibody syndrome (associated with deep venous thrombosis and pulmonary embolism), psoriasis, autoimmune thyroiditis, SLE, arthritis, autoimmune haemolytic anaemia, ulcerative colitis, vitiligo, Erosive lichen planus of the scalp and Bechet’s-like syndrome.

The CD4 T-cell counts in ICL patients remain less than 300/mm3 for several years, demonstrating absence of progression of lymphocytopenia over time, however, up to one-fifth of patients may resolve their lymphocytopenia within few years of diagnosis. Low CD8 T-cell counts at diagnosis represent a subgroup of ICL with a worse prognosis and increased risk for a serious opportunistic infection or death.

**The differential diagnosis** –

- HIV infection
- Chronic infections (EBV, CMV, TB, Toxo, others)
- Drugs.
- Sarcoidosis
- Other primary immunodeficiencies,
- Immunosuppressive states induced by chemotherapy, radiation
- Autoimmune disorders
- Lymphoproliferative disorders

Because infections and lymphoma may also cause CD4 lymphocytopenia, the distinction between cause and effect may evolve only during follow-up.

**Diagnosis**

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Diagnosis is made according to World Health organisation (WHO) criteria, by excluding retroviral infections or other known causes of primary or secondary immunodeficiency.

Case definition criteria include:

1) CD4 less than 300 cells/mm³ or a CD4 percent less than 20% of lymphocytes on two or more measurements, two or three months apart;
2) Lack of laboratory evidence of HIV infection; and
3) Absence of alternative explanation for the CD4 cell lymphocytopenia including Sjogrens Syndrome, sarcoidosis, radiation, atopic dermatitis, collagen vascular disease, steroid therapy, or lymphoma.

The immune evaluation of a patient with suspected ICL includes the following tests:

- Complete blood cell count and differential.
- Determination of lymphocyte subpopulations by flow cytometry.
- In vitro studies of T cell function, including response to mitogens and response to specific antigens. Lymphocyte transformation may be depressed or normal.
- Tests for HIV-1. Serologic and PCR tests.
- Tests for HIV-2 infection, EBV and CMV
- Testing for tuberculosis (Chest x-ray and Quantifern test).
- Measurement of serum immunoglobulins (IgG, IgA, and IgM).
- Measurement of serum specific antibodies; such as anti-tetanus, antidiphtheria, and anti-pneumococcal antibodies to assess the functional status of the humoral immune system. If titers are low, the patient should be vaccinated and post-vaccination titers measured one month later. Vaccination response may be normal or weak, depending upon the degree of immune derangement. Results are usually normal if the only detectable defect is CD4 lymphopenia.

**Immunologic characteristics of ICL**

The decrease in CD4 cell counts of patients with ICL is slow or even absent for a long period. Unlike HIV patients, patients with ICL do not show an increase in CD8 cells. ICL patients have higher proportion of activated (HLA-DR) CD4, but not CD8 T cells. The studies of patients with ICL showed that among CD4 T-cells, naive CD45RA T-cells are more severely diminished than the memory CD45RO population. Some reports described a high percentage of gd TCR cells in ICL patients.

OKT4 epitope deficiency — Patients who appear to have low or absent CD4 cells should be evaluated for OKT4 epitope deficiency, a condition in which the antigen recognized by the monoclonal antibody most commonly used to detect CD4 cells by flow cytometry, OKT4, is deficient or absent. Individuals with OKT4 epitope deficiency usually have normal CD4+ T cell number and do not develop infections, although there may be an association with autoimmune conditions.
Management

There is no standard treatment for ICL, except for management of the associated conditions and the prompt treatment of infections. Infections (such as mycobacteria) further deplete the CD4 cell pool, and treatment may improve the degree of CD4 specific lymphopenia.

Patients who present with an opportunistic infection should be treated and then started on secondary prophylaxis for that particular organism. If CD4 counts improve subsequently, the need for prophylaxis can be revisited.

Prophylaxis against infections

There is insufficient evidence to guide primary infection prophylaxis.

The current recommendations are based mainly on experience with HIV-infected patients. Prophylaxis should be considered for a subset of ICL patients with the worst prognosis, such as those with CD4+ T cell counts below 200 cells/uL and those with low CD8 counts or patients presenting with an "AIDS defining condition."

Antimicrobial prophylaxis for opportunistic infections is suggested for most patients with ICL and Cryptococcus as well as relapsing herpes infection may require lifelong secondary prophylaxis.

Prophylaxis against opportunistic infections in patients with AIDS
Successful primary treatment of HPV-associated intraepithelial neoplasia with the quadrivalent vaccine has been recently reported. The role for HPV vaccination in the setting of immunodeficiency is undefined but is likely reasonable.

WARTS TREATMENT: Non-surgical interventions with topical 5-fluorouracil, 5% imiquimod, tacalcitol, systemic retinoids combined with interferon (IFN)α, cimetidine, and topical 5-aminolevulinic acid photodynamic therapy

Therapies to increase CD4 cell counts —

A small number of reports of the use of IL-2, IL-7 and hematopoietic cell transplantation in ICL.

IL-2 — The use of IL-2 (aldesleukin) in patients with ICL would only be considered in individuals with significant refractory infections (mycobacterial disease, cryptococcal meningitis, and generalized herpes zoster and gastrointestinal candidiasis) and CD4 counts that remained very low (eg, less than 100 cells/uL).

RECOMMENDATIONS FOR MINIMIZING EXPOSURE TO SELECTED PATHOGENS

- **Pneumocystis carinii**: Avoid close contact with patients who have active PCP (e.g., avoid sharing hospital room).
- **Toxoplasma gondii**: Avoid eating undercooked red meat and exposure to cats that scavenge for food outdoors.
- Cryptosporidium: Avoid drinking unprocessed ground water (e.g., from lakes or streams); use properly boiled, bottled, or filtered water; avoid household pets less than 6 months of age, especially those that were obtained from commercial breeders or pet shelters, that were previously strays, or that have diarrhoea; emphasize good hygiene in child care.
- **Mycobacterium tuberculosis**: Avoid high-risk occupational settings, such as correctional facilities, homeless shelters, and certain health care situations.
- CMV: if patient is seronegative for cytomegalovirus, avoid transfusion with CMV-seropositive or unfiltered blood products; avoid unprotected sexual exposure. Emphasize good hygiene in child care.
- Human papillomavirus, herpes simplex virus, and hepatitis B: Avoid unprotected sexual exposure.
- *Histoplasma capsulatum*: In areas of endemic disease, avoid high-risk activities such as exploring caves or cleaning chicken coops; avoid exposure to faeces of wild birds.

Monitor and review:

There are no published guidelines for monitoring patients with ICL. For patients who are well, measurement of CD4 subsets every three to four months would suffice.

Patients who become ill must be assessed for likely infections and treated accordingly.

As chronic HPV infections may predispose patients to squamous cell carcinomas, appropriate cancer screening should be done (cervical neoplasia every 6 months).

6. **Roles and responsibilities**

It is the responsibility of the Consultant Immunologist in consultation with Specialist registrar and Immunology Specialist nurse to implement and review this protocol.

7. **Monitoring document effectiveness**

7.1 Complete the following:

- **Key standards**: see below references. Auditing against guidelines, the small population of patients within our cohort.
- **Method(s)**: Clinical audit,
- **Team responsible for monitoring**: Immunology department
- **Frequency of monitoring**: Auditing every 2 years in regards to standard with blood tests every 3-4 months
- **Process for reviewing results and ensuring improvements in performance**: every 2 years we will audit against the blood results as to whether the patients have had bloods every 3-4 months.

8. **Abbreviations and definitions**

All terms and definitions are explained in the text.

9. **References and Supporting Documents**

9.1 **References**


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10. Document Control Information

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Remove instructions once completed.

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<th>Name</th>
<th>Role</th>
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<tr>
<td></td>
<td>Dr Hana Alachkar</td>
<td>Consultant Immunologist</td>
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| Lead author contact details: | Full contact telephone number 0161 2065576 | Full trust email address Hana.alachkar@srft.nhs.uk |

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<th>Lead Author’s Manager:</th>
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<tr>
<td></td>
<td>David Fitzgerald</td>
<td>Clinical Director</td>
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| Document developed in consultation with: | Immunology Team |

| Keywords/ phrases: | Immunology, CD4, Lyphotocopenia, cellular immune deficiency, HIV |

| Communication plan: | Available on the intranet. Latest version shown to all staff in the department at the clinical meeting |

| Document review arrangements: | This document will be reviewed by the author, or a nominated person, at least once every three years or earlier should a change in legislation, best practice or other change in circumstance dictate. |

| Approval: | Add name of Committee and Chairpersons name and role: Immunology Team/Department, Dr Hana Alachkar |

| How approved: | Chair’s actions: Agreed locally within team | Formal Committee decision | Discussed within clinical meetings. |

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11. Equality Impact Assessment (EqIA) screening tool

Legislation requires that our documents consider the potential to affect groups differently, and eliminate or minimise this where possible. This process helps to reduce health inequalities by identifying where steps can be taken to ensure the same access, experience and outcomes are achieved across all groups of people. This may require you to do things differently for some groups to reduce any potential differences.

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<thead>
<tr>
<th>1a) Have you undertaken any consultation/involvement with service users, staff or other groups in relation to this document? If yes, specify what.</th>
<th>Yes</th>
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<td>1b) Have any amendments been made as a result? If yes, specify what.</td>
<td>No</td>
<td>Outline changes made</td>
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2) Does this policy have the potential to affect any of the groups listed below differently? 
Place an X in the appropriate box: Yes, No or Unsure

This may be linked to access, how the process/procedure is experienced, and/or intended outcomes. Prompts for consideration are provided, but are not an exhaustive list.

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<th>Protected Group</th>
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<td><strong>Age</strong> (e.g. are specific age groups excluded? Would the same process affect age groups in different ways?)</td>
<td>X</td>
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<td><strong>Sex</strong> (e.g. is gender neutral language used in the way the policy or information leaflet is written?)</td>
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<td><strong>Race</strong> (e.g. any specific needs identified for certain groups such as dress, diet, individual care needs? Are interpretation and translation services required and does staff know how to book these?)</td>
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<td><strong>Religion &amp; Belief</strong> (e.g. Jehovah Witness stance on blood transfusions; dietary needs that may conflict with medication offered.)</td>
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<td><strong>Marital status/civil partnership</strong> (e.g. would there be any difference because the individual is/is not married/in a civil partnership?)</td>
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<td><strong>Gender Reassignment</strong> (e.g. are there particular tests related to gender? Is confidentiality of the patient or staff member maintained?)</td>
<td>X</td>
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<td><strong>Human Rights</strong> (e.g. does it uphold the principles of Fairness, Respect, Equality, Dignity and Autonomy?)</td>
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<td><strong>Carers</strong> (e.g. is sufficient notice built in so can take time off work to attend appointment?)</td>
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<td><strong>Socio/economic</strong> (e.g. would there be any requirement or expectation that may not be able to be met by those on low or limited income, such as costs incurred?)</td>
<td>X</td>
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<td><strong>Disability</strong> (e.g. are information/questionnaires/consent forms available in different formats upon request? Are waiting areas suitable?) Includes hearing and/or visual impairments, physical disability, neurodevelopmental impairments e.g. autism, mental health conditions, and long term conditions e.g. cancer.</td>
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Are there any adjustments that need to be made to ensure that people with disabilities have the same access to and outcomes from the service or employment activities as those without disabilities? (e.g. allow extra time for appointments, allow advocates to be present in the room, having access to visual aids, removing requirement to wait in unsuitable environments, etc.)

| 3) Where you have identified that there are potential differences, what steps have you taken to mitigate these? |
| (what action has been taken or will be taken, who is responsible for taking a future action, and when it will be completed by – may include adjustment to wording of policy or leaflet to mitigate) |

| 4) Where you have identified adjustments would need to be made for those with disabilities, what action has been taken? |
| (what action has been taken or will be taken, who is responsible for taking a future action, and when it will be completed by – may include adjustment to wording of policy or leaflet) |

Will this policy require a full impact assessment? No
(a full impact assessment will be required if you are unsure of the potential to affect a group differently, or if you believe there is a potential for it to affect a group differently and do not know how to mitigate against this - Please contact the Inclusion and Equality team for advice on equality@pat.nhs.uk)

Author: Type/sign: Melanie Fernandez – Immunology CNS Date: 06/08/2018
Sign off from Equality Champion: Date: