Secondary immunodeficiency associated with haematological malignancies

SECONDARY IMMUNE DEFICIENCY

The Burden of Immune deficiency following Chronic Lymphocytic Leukaemia

SECONDARY IMMUNE DEFICIENCY

Objectives of this module

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- To describe the pathogenesis of SID in chronic lymphocytic leukaemia
- To highlight the treatment algorithm in CLL with a focus on drugs compromising the immune system
- To outline risk factors for developing infections in patients with CLL
- To list infections specifically associated with CLL
- To illustrate the impact of SID and infections on the course of CLL, through describing
  - Infection incidences
  - Associated mortality

SID, secondary immunodeficiency; CLL, chronic lymphocytic leukaemia.

Infections associated with SID in Patients with CLL

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- The majority (up to 80%) of patients will experience an infectious complication at some point during their disease[1]
- 20% of CLL patients have severe/major infections[2]
- Infectious complications account for up to an estimated 60% of deaths[1]
- Patients are predisposed to infection due to inherent immune defects related to the primary disease, and as a result of therapy[1]
- The range of infectious complications has evolved alongside therapeutic advances in the treatment of CLL[1]
- Novel targeted therapies have been recently introduced, whose unique safety profiles have an impact on the prophylaxis and management of infectious complications in these patients[1]
- Hypogammaglobulinaemia is a key clinical parameter that correlates with infection risk[1]
- Infection risk correlates with disease progression[3]

1. *Tadmor, T. et al., Expert Review of Hematology 2018; 11:1, 57-70.*
2. *Hensel, M. et al., Br J Haematol. 2003; 122:600.*
3. *Gale, R. P. et al., N Engl J Med. 1988; 319:902.*

Chronic Lymphocytic Leukaemia pathogenesis impacts differentiation and function of blood cells

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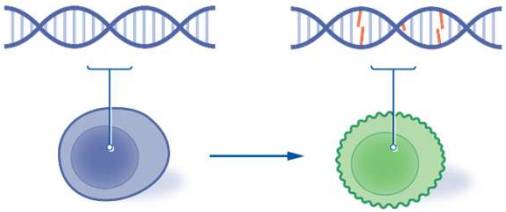
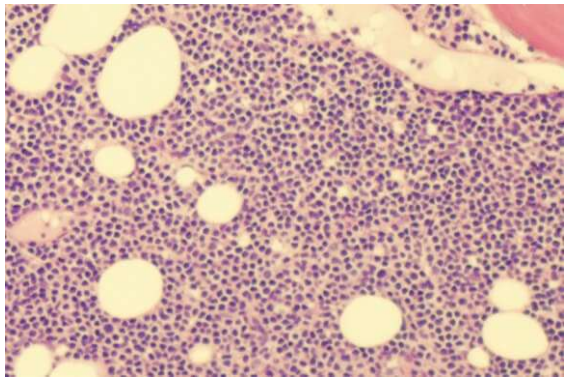


Antigen-experienced B cell

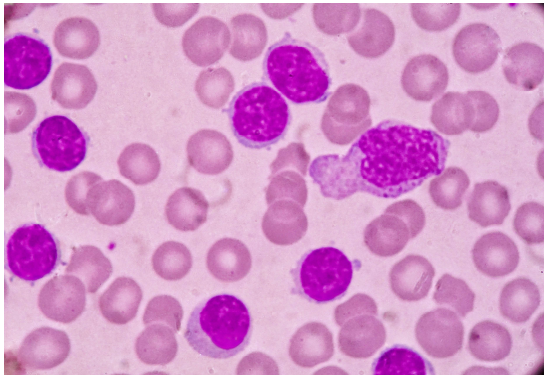
CLL cell

Proliferation of CLL cells, crowding the bone marrow and blood stream

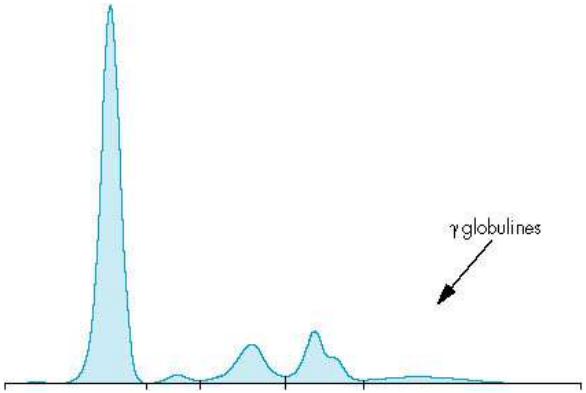
Anaemia,
Lymphocytosis,
Lymphadenopathy,
Splenomegaly,
Hepatomegaly
Thrombocytopenia
Hypogammaglobulinaemia



CLL cells crowding the bone marrow*



Lymphocytosis*

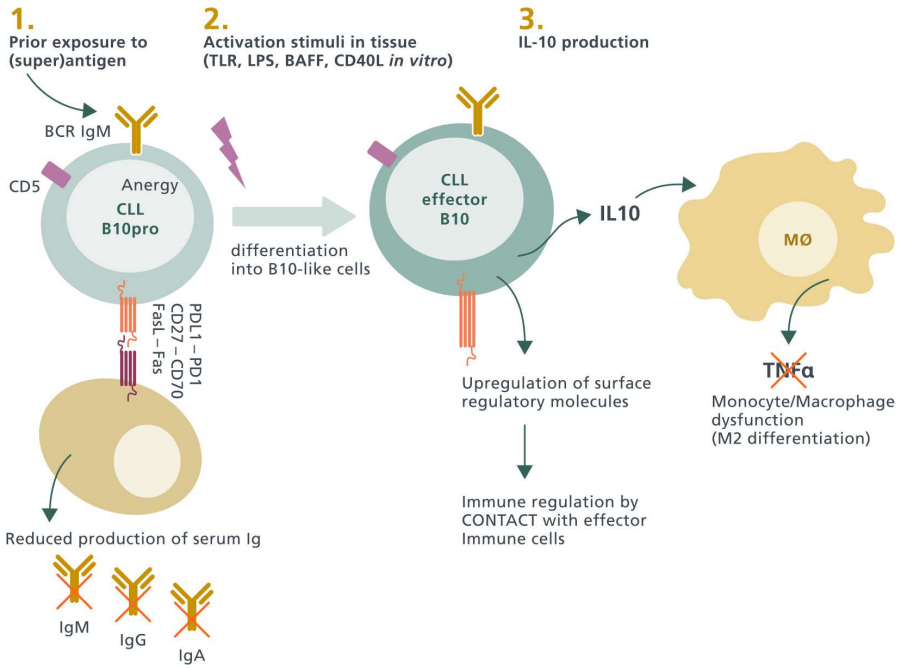


CLL, chronic lymphocytic leukaemia.

Frenzel, L. P. et al., Oncol Res Treat 2016;39:9; American Cancer Society. Chronic Lymphocytic Leukemia Early Detection, Diagnosis, and Staging. Available at: https://www.cancer.org/content/dam/CRC/PDF/Public/8681.00.pdf (accessed July 2019).

Chronic Lymphocytic Leukaemia pathogenesis impacts differentiation and function of blood cells

SECONDARY IMMUNE DEFICIENCY

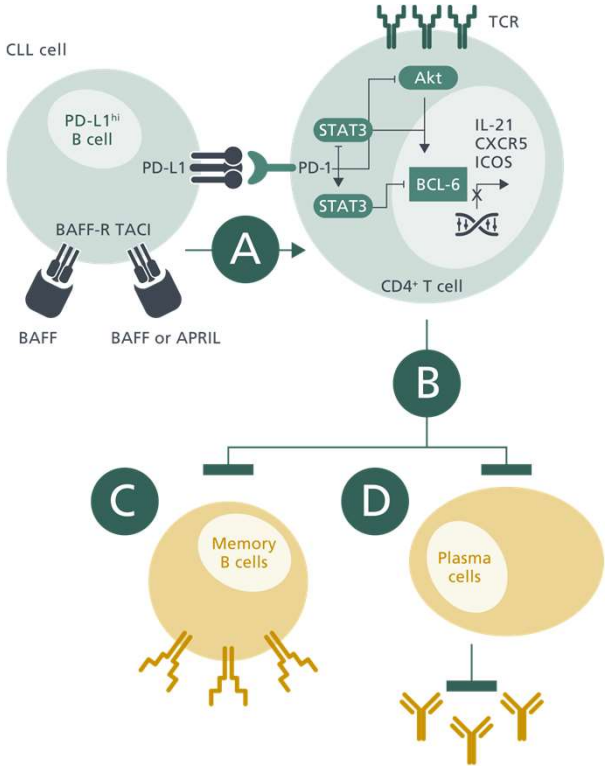


Hypothetical model of immune regulation in CLL[1]

- Circulating CLL cells are anergic B cells with low surface IgM levels after exposure to (super)antigen.
- CLL cells express several molecules that may have regulatory activity on plasma cells either by cell contact (eg, FasL, CD27, and/or PD-L1 via T_{FH} cells) or by deprivation of soluble factors essential for plasma cell survival (eg, BCMA). This reduces the production of serum Ig and induces hypogammaglobulinaemia. Note: High PD-L1 expression on CLL cells defines a mechanism for potent suppression of humoral immunity through the regulation of T_{FH} cells.
- Upon activation in tissue, CLL cells differentiate into B10 cells to produce immunosuppressive IL-10 and upregulate molecules with regulatory activity on other effector arms of the immune system. Among the targets of IL-10 monocytes/macrophages are suppressed in their activity to produce tumor necrosis factor-α (TNF-α).

CLL, chronic lymphocytic leukaemia; FasL: Fas ligand; PD-L1: programmed death-ligand 1 ; T_{FH} cells: T follicular helper cells. 1; BCMA: B-cell maturation antigen; IL-10: Interleukin 10; TNFα: tumor necrosis factor-α.
Adapted from: Forconi F. et al., Blood 2015; 126: 573-581.

Chronic Lymphocytic Leukaemia pathogenesis impacts differentiation and function of blood cells



Hypothetical model of immune regulation in CLL[2]

- CLL cells have an elevated expression of PD-L1. This might cause hypogammaglobulinaemia via the following mechanism:[1]
  - PD-L1^{hi} B cells (which express higher levels of BAFF-R and TACI) interact with PD-1 on activated T cells (A).[2]
  - For T_{FH}-cell differentiation, activation of Akt and Stat3 lead to increased transcription of Bcl-6. Interactions with PD-L1^{hi} B cells cause an increase in Stat5 expression, a known suppressor of T_{FH}-cell development and expansion (B).[2]
  - A reduction in T_{FH} cells limits B-cell fate by limiting both memory B-cell development (C) and terminal differentiation to plasma cells (D).

CLL, chronic lymphocytic leukaemia; PD-L1: programmed death-ligand 1; PD-1: programmed cell death protein 1 ; BAFF-R: B-cell activating factor receptor; TACI: transmembrane activator and calcium-modulating cyclophilin ligand interactor; T_{FH} cells: T follicular helper cells; Akt: protein kinase B; Bcl-6: B-cell lymphoma 6.
1. Forconi F. et al., Blood 2015; 126: 573-581. 2. Khan et al. Nature Communications 2019. 6:5997.

Characterisation of CLL-associated immunodeficiency – extends beyond antibody deficiency

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Defects in innate immunity

- Reduced levels of several complement proteins, with specific reductions of the C1-C4 components in ~ 40% of patients - implications for opsonisation with C3b
- Defects in neutrophils: impaired phagocytic killing of nonopsonized bacteria and a reduction in C5a-induced chemotaxis
- Defects in monocyte cells: increased circulating monocyte count by >60% but with a gene expression profile associated with immunosuppressive properties
- Natural killer cell defects: increased number in the circulation but with several functional defects including an impaired cytotoxic activity

Defects in adaptive immunity

- T cells: impaired immunological synapse formation with antigen presenting cells as a result of defects in actin polymerisation
- Hypogammaglobulinaemia with impaired antibody responses to test immunization

Forconi F. et al., Blood 2015; 126: 573-581.

T-cells immune defects in CLL (1)

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- Paradoxical increase of circulating T-cells, primarily accounted for an increased number of CD8+ T-cells resulting in a fall in the CD4:CD8 ratio.[1-3] These CD8+ T-cells show abnormalities, such as increased secretion of IL-4.[4]
- IL-4 producing CD8+ T-cells from CLL patients show increased expression of CD30[5]. Ligation of CD30L on the surface of the CLL B-cells has been shown to stimulate their production of TNF-α, resulting in their proliferation.[6] IL-4 is also able to protect CLL B-cells from apoptosis by upregulating expression of the anti-apoptotic molecule Bcl-2.[7-9]
- In contrast, **ligation of CD30L on the surface of the nonmalignant B-cells impairs isotype class switching, and increases their sensitivity to FasL-mediated cell death, potentially contributing to the hypogammaglobulinaemia seen in CLL** [10]
- CLL B-cell derived IL-6 has been suggested to contribute to these T-cell defects. Healthy T-cells stimulated in the presence of tumour supernatant containing high levels of IL-6 have been shown increase their production of IL-4, and show impaired upregulation of CD40L.[11] Furthermore, IL-6 has been shown to be increased in the serum of patients with CLL, with higher levels correlating with poorer survival.[12,13]

IL-4: interleukine 4; CLL: chronic lymphocytic leukaemia; TNF- α: tumor necrosis factor α; Bcl-2: B-cell lymphoma 2; FasL: Fas ligand; IL-6: interleukine 6.

1. Catovsky D et al. Lancet 1974; 2: 751-2. ; 2. Platsoucas CD et al. J Immunol 1982; 129: 2305-12. ; 3. Herrmann F, et al. Clin Exp Immunol 1982; 49: 157-62. ; 4. Mu X et al. Br J Haematol 1997; 96: 733-5. ; 5. de Totero D et al. Br J Haematol 1999; 104: 589-99. ; 6. Riches et al. Hematol Oncol Clin N Am 2013; 27: 207–235. ; 7. Dancescu M, et al. J Exp Med 1992; 176: 1319-26. ; 8. Panayiotidis P et al. Br J Haematol. 1993; 85: 439-45. ; 9. Kay NE et al. Br J Haematol 2001; 112: 760-7. ; 10. Cerutti A et al. Nat Immunol 2001; 2: 150-6. ; 11. Buggins Aget al. Leukemia 2008; 22: 1084-7. ; 12. Fayad L et al. Blood 2001; 97: 256-63. ; 13. Kurzrock R et al. Cancer Res 1993; 53: 2118-22.

T-cells immune defects in CLL (2)

SECONDARY IMMUNE DEFICIENCY

- CD4+ T-cells are also abnormal in CLL. Absolute numbers of CD4+CD25+ regulatory T-cells (Tregs) are increased, with the largest increases being found in patients with the most clinically advanced disease.[1-3]
- **Higher frequencies of Tregs have been shown to correlate with decreased T-cell responses against viral and tumor antigens, and Tregs may also decrease cellular immunity by secretion of soluble IL-2 receptor resulting in inhibition of Th1 differentiation.** [2-4]
- However, the role of Tregs is not completely straightforward in CLL as other evidence suggests that CD4+ cells may be important in immune-related disease control. Both nonregulatory CD4+ T-cells and Tregs have been shown to express higher levels of the cytolytic markers FasL and CD107a, and could kill autologous leukemic B-cells in vitro.[5] The expansion of Tregs in CLL may be due to both a combination of decreased sensitivity to apoptosis as a consequence of higher expression of Bcl-2, and increased formation facilitated by intra-nodal CD27-CD70 interactions.[6]
- Other studies suggest that numbers of CD3+CD16+ CD56+ NKT-cells might also be important, as a reduction in percentage (of CD3+ lymphocyte compartment) was associated with disease progression and a higher risk of death in CLL patients.[7]

Tregs: regulatory T cells; IL-2: interleukine 2; Th1: T helper cell type 1; FasL: Fas ligand; NKT-cells: natural killer T cells; CLL: chronic lymphocytic leukaemia.

1. Beyer M et al. Blood 2005; 106: 2018-25. ; 2. Giannopoulos K et al. Oncology reports 2008; 20: 677-82. ; 3. D'Arena G et al. Leuk Res 2011; 35: 363-8. ; 4. Lindqvist CA et al. Immunology 2010; 133: 371-6. ; 5. Lindqvist CA, et al. Immunology 2010; 133: 296-306. ; 6. Jak M et al. Leukemia & lymphoma 2009; 50: 788-801. ; 7. Bojarska-Junak A et al. Oncology reports 2010; 24: 803-10.

T-cells immune defects in CLL (3)

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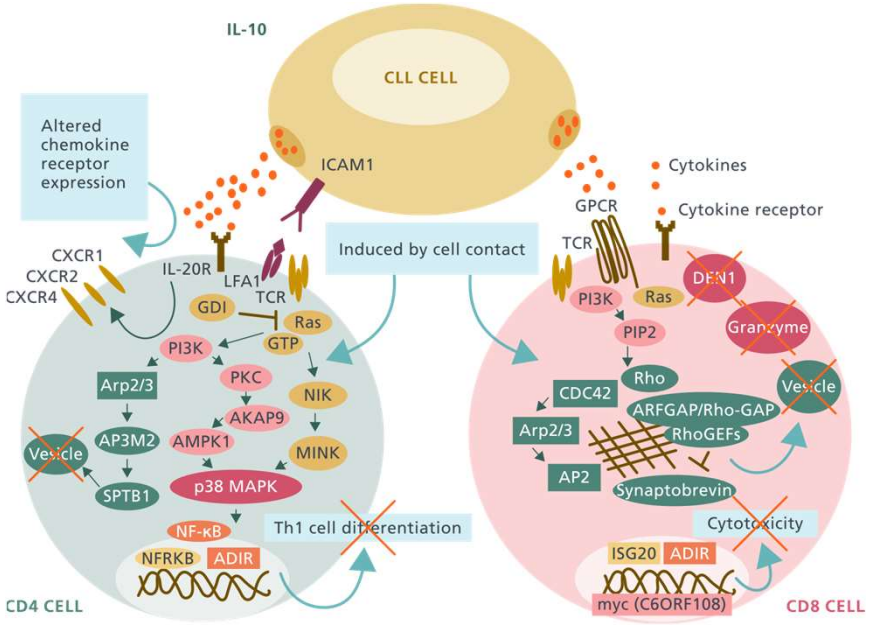
Possible link between T-cell defects and malignant CLL cells[1]



- CD4 cell (left): Differentially expressed genes involved in cell differentiation, particularly JNK (pink) and p38 MAPK (yellow) pathways and cytoskeleton formation and vesicle transportation (blue), in CD4 T cells from CLL patients compared with healthy donors are represented by selected genes that were increased (rectangles) or decreased (ovals).

- CD8 cell (right): Differentially expressed genes involved in cytoskeleton formation, vesicle trafficking (blue), and cytotoxicity (red) in CD8 T cells from CLL patients compared with healthy donors are represented by selected increased genes (rectangles) and decreased genes (ovals).

JNK: Jun N-terminal kinase; MAPK: mitogen-activated protein kinase; CLL: chronic lymphocytic leukaemia.
Adapted from Gorgun G et al. J Clin Invest 2005; 115: 1797- 805.

NK-cells immune defects in CLL

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- **While NK-cells are considered important for mediating antitumor activity of CD-20 specific monoclonal antibodies,[1] they are also suggested to have a functional defect in CLL, showing reduced ability to lyse leukemia cell lines possibly due to a lack of cytoplasmic granules.[2,3]**
- The mechanism by which CLL B-cells downregulate NK-cell function is not known, although there is some evidence that it may involve soluble factors.[4]
- The NK-cell defect appears to be of clinical significance, as higher NK-cell:CLL B-cell ratio were observed in patients with early stage disease and in those with mutated IgV_H genes.
- Among Rai stage 0, I and II, a higher NK:CLL B-cell ratio was predictive of a longer time to treatment, implying a protective effect of NK-cells.[5]

CLL: chronic lymphocytic leukaemia; NK-cells: natural killer cells; IgV_H: immunoglobulin heavy chain variable region.

1. Forconi F. et al., Blood 2015; 126: 573-581. ; 2. Ziegler HW et al. . Int J Cancer 1981; 27: 321-7. ; 3. Kay NE et al. . Blood. 1984; 63: 305-9. ; 4. Burton JD et al.. Am J Hematol 1989; 30: 61-7. ; 5.Palmer S et al. Br J Haematol 2008; 141: 607-14.

Monocytes and neutrophils have immune defects in CLL

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- There is also evidence suggesting that monocytes and neutrophils are defective in CLL. Neutrophils have been shown to be deficient in lysozyme and myeloperoxidase, and to modulate CLL B-cell survival through altered secretion of TNF-superfamily proteins.[1,2]

CLL: chronic lymphocytic leukaemia; TNF: tumor necrosis factor.

1. Zeya HI, et al. Am J Pathol 1979; 95: 43-54. ; 2. Sawicka-Powierza J, et al. Neoplasma 2011; 58: 45-50.

Hypogammaglobulinaemia in CLL patients

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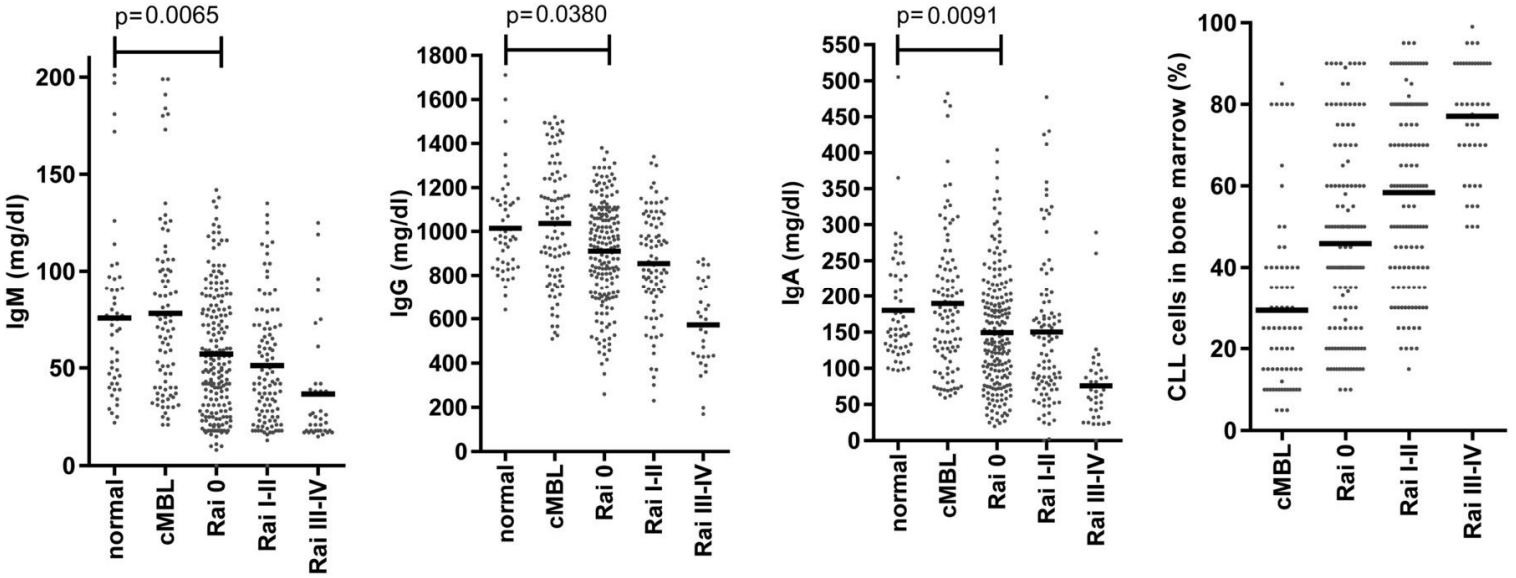
Early reduction of serum immunoglobulin levels in patients with CLL*



The severity of hypogammaglobulinaemia and the infiltration rate of the bone marrow increases with the duration and progression of disease, and progresses to involve all Ig classes (IgG, IgA, and IgM)

CLL: chronic lymphocytic leukaemia; Ig: immunoglobulin.

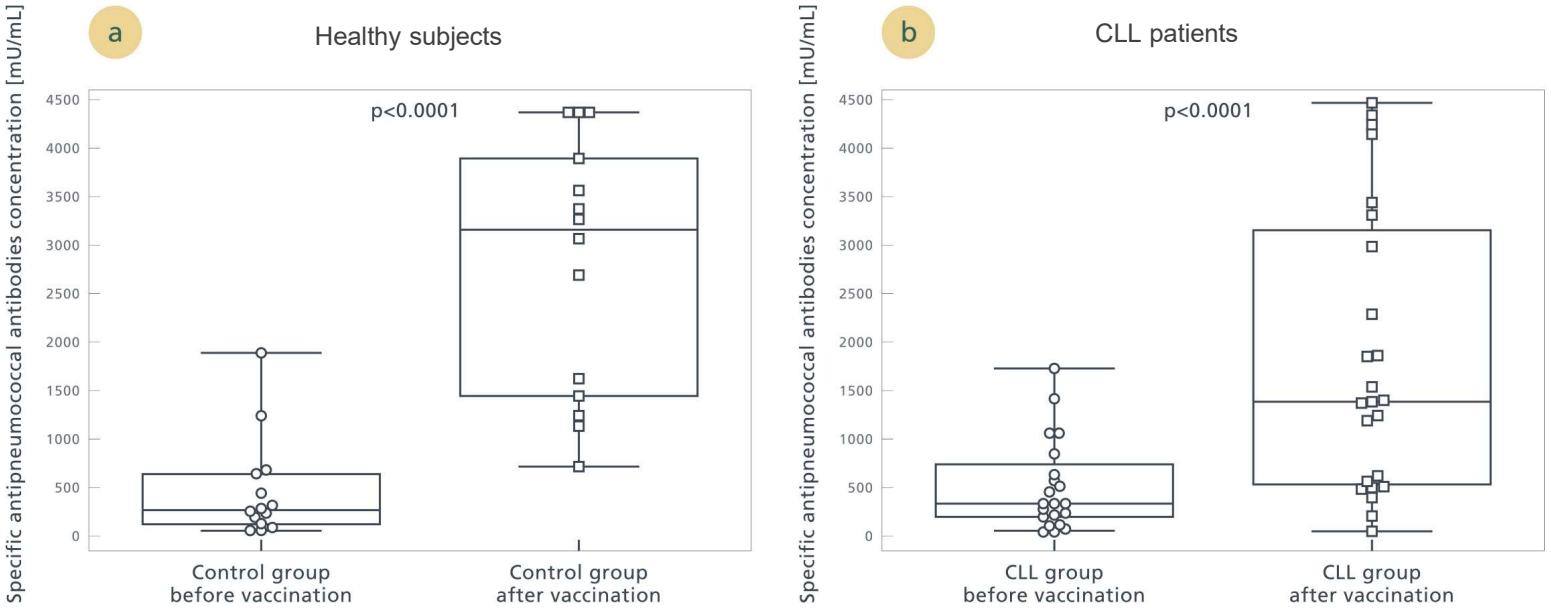
**Serum IgM, IgG, and IgA levels in cMBL (clinical monoclonal B-cell lymphocytosis) and Rai stage 0, I-II, III-IV CLL at diagnosis are represented as dot plots. The normal aged-matched donor cohort was used as internal reference values and for statistical comparison. The bone marrow infiltration by CLL cells at the early and late stage of disease according to Rai classification is also represented.*

Forconi F. et al., Blood 2015; 126: 573-581.

Impaired specific antibody response in CLL patients

SECONDARY IMMUNE DEFICIENCY

Response to 13-Valent Pneumococcal Conjugate Vaccine in CLL Patients



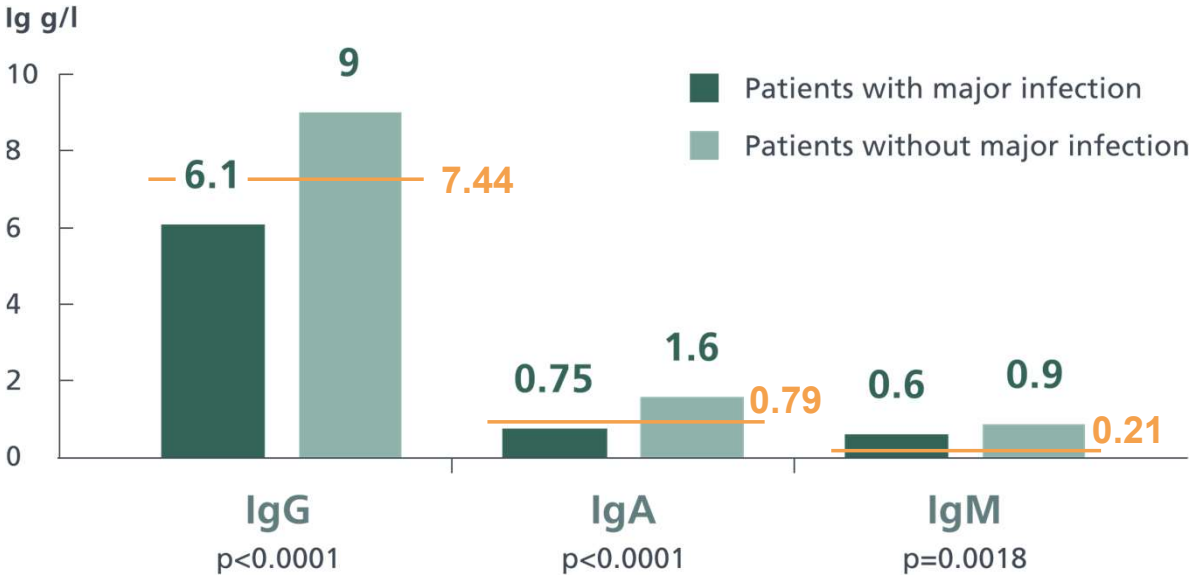
Adequate response to vaccination, defined as an at least two-fold increase in specific pneumococcal antibody titers versus pre-vaccination baseline titers, was found in only 58.3% of CLL patients (graph b) and 100% of healthy subjects (graph a).

CLL: chronic lymphocytic leukaemia.
Adapted from: Pasiarski M et al. PLoS One. 2014 15;9(12):e114966. doi: 10.1371/journal.pone.0114966. eCollection 2014.

Infection in CLL is associated with low Ig levels

SECONDARY IMMUNE DEFICIENCY

Ig levels in CLL Patients with or without major infections (n=706)



65% of patients with major infections and 20% of patients without infections had

- **IgG levels below 7.44 g/L**
- **IgA below 0.79 g/L**
- **and/or IgM below 0.21 g/L**

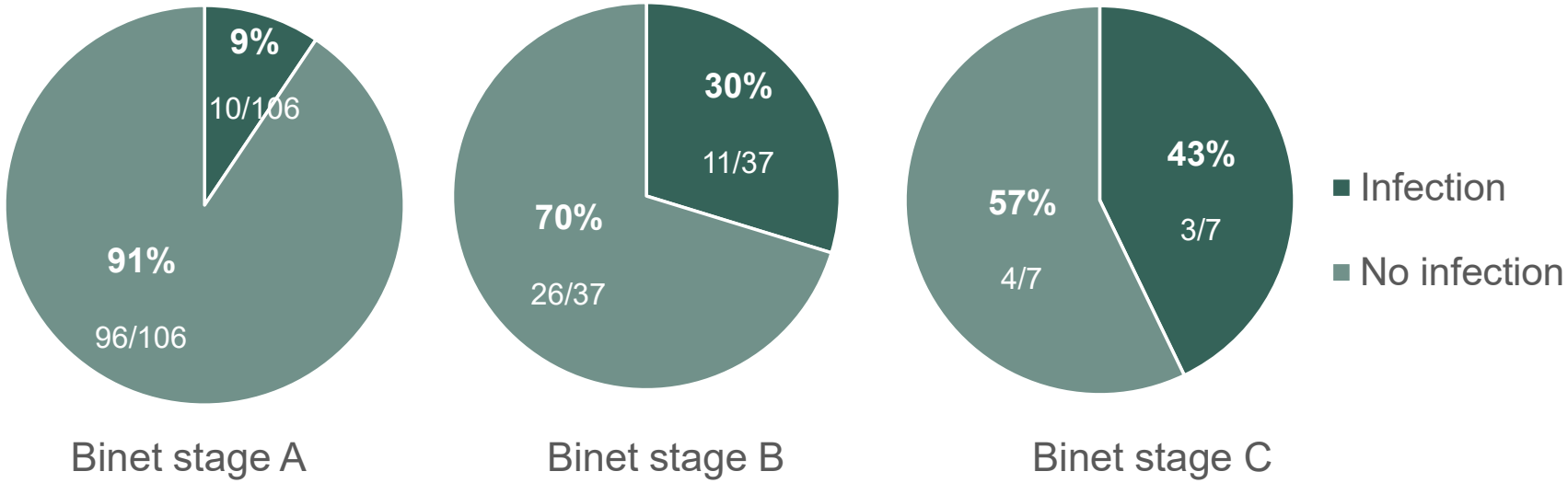
CLL: chronic lymphocytic leukemia; Ig: immunoglobulin.
Major infections: infective events that required inpatient management or intravenous antibiotics. Major infections associated with a concomitant neutropenia (white cell count <1.0x10^9/L) were excluded.
Data from 706 patients with CLL was retrospectively reviewed; 63% of patients were in stage 0–I, 16% in stage II and 21% in stages III–IV, and 40% of patients received treatment. Receiver operating characteristic curve analysis.
Adapted from: Visentin, A. et al., Haematologica 2015;100:e515.

Infections in CLL are more frequent as disease progresses

SECONDARY IMMUNE DEFICIENCY

Significant and recurrent infections in CLL patients according to the disease stage (n=150)

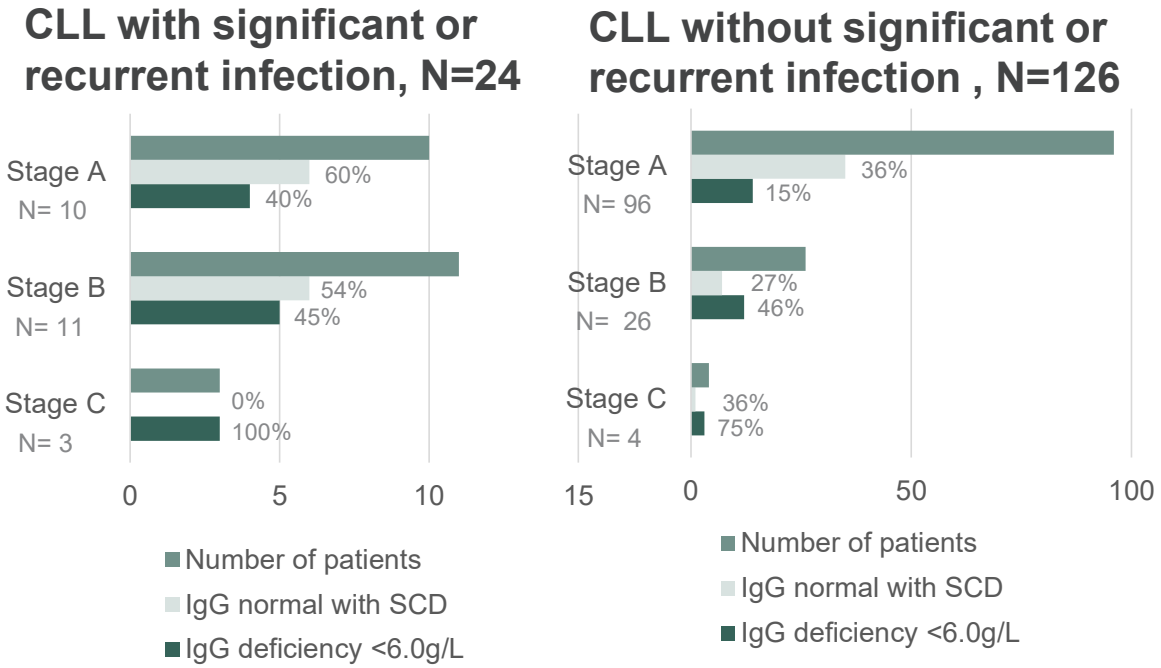
CLL progression is associated with higher infection rates



CLL: chronic lymphocytic leukaemia.
All patients had an existing diagnosis of CLL, with the date of diagnosis ranging from 1 month to 23 years previously. Disease stage was assessed clinically by the treating physician. Median age: 67.5 years. Only «significant» and «recurrent» infections were assessed. See next slide for the definition of «significant» and «recurrent» infections. 107/150 patients were untreated, 43 patients having received chemotherapy for CLL. 21/43 had received fludarabine-based chemotherapy, 10/43 had received regimens containing rituximab (six with fludarabine, cyclophosphamide and rituximab). Patients who had received intravenous immunoglobulin, or any other form of immunoglobulin therapy, at any time were excluded from the analysis. Patients receiving chemotherapy currently or in the preceding 3 months, and all patients with absolute neutrophil counts of 1.0 10 9 /L from any cause, were also excluded from analysis. While these three exclusion factors eliminated several potential confounding influences, it also significantly reduced the number of patients with more advanced stage disease, those on active therapy, and more heavily pretreated patients from the cohort analyzed, as many were already receiving immunoglobulin replacement therapy. Adapted from: Freeman, J.A. et al., Leuk Lymphoma 2013;54:99.

Low IgG subclass levels is associated with infection in CLL regardless of total IgG level

SECONDARY IMMUNE DEFICIENCY



- In the study population, **24/150 patients had a CLL with significant or recurrent infections.** Among them, **50% had IgG deficiency.**
- **All patients with significant or recurrent infections had at least one IgG subclass deficiency regardless of the total immunoglobulin (IgG) level.***
- Less patients without infections have a IgG deficiency, however a substantial amount has a subclass deficiency with a normal total IgG.

CLL: chronic lymphocytic leukemia; Ig: immunoglobulin, SCD: subclass deficiency. Only «significant» and «recurrent» infections were assessed. Infections deemed significant included: any episode of septicemia, lower respiratory tract infections (including pneumonia, recurrent bronchitis and bronchiectasis), persistent or recurrent sinobronchial disease, urosepsis (not including uncomplicated cystitis in women), bacterial cellulitis requiring hospital admission for intravenous antibiotic therapy, and varicella zoster infections. One patient with fungal pneumonia was included. Bacterial and viral infections were defined as " recurrent " if there were three or more episodes over the preceding 3 years. Minor viral infections such as upper respiratory tract infections without a bacterial component, and influenza without lower respiratory tract complications, were not deemed to be " significant " or " recurrent " infections for the purposes of this study.

**Data from 150 unselected patients with CLL was retrospectively reviewed; 71% of patients were in stage A, 25% in stage B and 4% in stages C. 71% of patients received no treatment. 21 patients had received fludarabine based chemotherapy and 10 patients had received regimens containing rituximab.*

Adapted from: Freeman J., A. et al Leukemia & Lymphoma January 2013;54(1): 99-104.

Low IgG subclass levels is associated with infection in Chronic Lymphocytic Leukaemia

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IgG subclass deficiencies in CLL patients

			IgG1 deficiency		IgG2 deficiency		IgG3 deficiency		IgG4 deficiency	
Stage A		106	21	(19.81%)	15	(14.15%)	45	(42.45%)	17	(16.04%)
	Infection present	10	2	(20%)	3	(30%)	7	(70%)	5	(50%)
	Infection absent	96	19	(19.79%)	12	(12.5%)	38	(39.58%)	12	(12.5%)
Stage B		37	16	(43.24%)	10	(27.03%)	26	(70.27%)	14	(37.84%)
	Infection present	11	6	(54.55%)	3	(27.27%)	10	(90.91%)	7	(63.64%)
	Infection absent	26	10	(38.46%)	7	(26.92%)	16	(61.54)	7	(26.92%)
Stage C		7	5	(71.43%)	4	(57.14%)	7	(100%)	3	(42.86%)
	Infection present	3	3	(100%)	1	(33.33%)	3	(100%)	2	(66.67%)
	Infection absent	4	2	(50%)	3	(75%)	4	(100%)	1	(25%)
Cohort		150	42	(28%)	29	(19.33%)	78	(52%)	34	(22.67%)
	Infection present	24	11	(45.83%)	7	(29.17%)	20	(83.33%)	14	(58.33%)
	Infection absent	126	31	(24.6%)	22	(17.46%)	58	(46.03%)	20	(15.87%)

***IgG subclass levels by stage and presence or absence of infection. Percentages are calculated across rows.**

- **IgG subclass deficiency was observed in 96 of the 150 patients analysed.**
- **The prevalence of IgG subclass deficiency increased with disease stage**: 59 stage A patients (55.7%) were deficient in at least one IgG subclass, with 30 stage B (81.1%) and seven stage C patients (100%)
- **prevalence of multiple IgG subclass deficiencies also increased with disease stage**

CLL: chronic lymphocytic leukaemia; Ig: immunoglobulin.
**IgG subclass deficiencies are defined by IgG1 <4 g/L, IgG2 <1.3 g/L, IgG3 <0.4 g/L, and IgG4 <0.05 g/L. †24 of 150 patients had infections.*
Adapted from: Freeman, J.A. et al., Leuk Lymphoma, 2013;54:99.

Low IgG subclass levels is associated with infection in CLL

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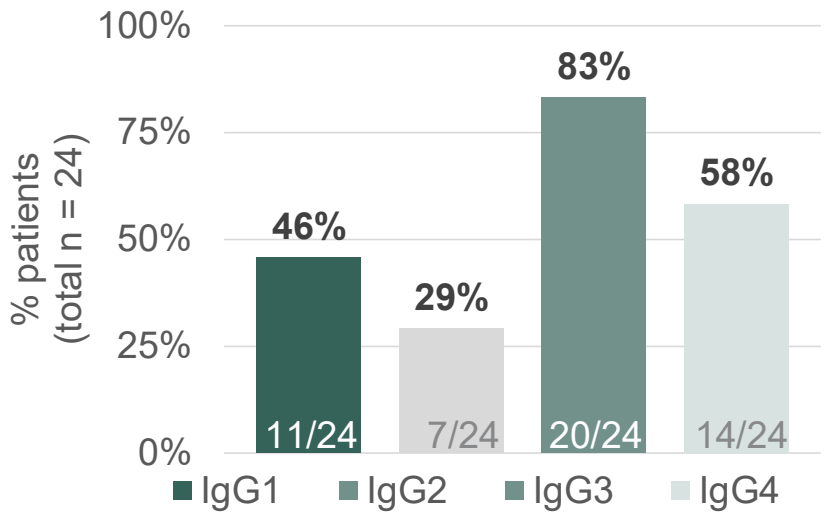
- In the study population, **ALL the 24/150 patients who had a CLL with significant or recurrent infections had ≥1 IgG subclass deficiency***
- **IgG3 and IgG4 are the most common subclass deficiencies**
- The most common deficiency occurring alone was a deficiency in IgG3 in CLL patients with infections
- The relationship between any IgG subclass deficiency and infection was significant (p 0.0001), as was the relationship between IgG1, IgG3 and IgG4 subclass deficiencies and infection (p=0.0465, p=0.0008 and p=0.0001), and the combination of IgG3 and IgG4 deficiency and infection (p=0.0001).

IgG subclass deficiencies in CLL patients with infections†



CLL: chronic lymphocytic leukaemia; Ig: immunoglobulin.
**IgG subclass deficiencies are defined by IgG1 <4 g/L, IgG2 <1.3 g/L, IgG3 <0.4 g/L, and IgG4 <0.05 g/L. †24 of 150 patients had infections.*
Adapted from: Freeman, J.A. et al., Leuk Lymphoma 2013;54:99.

Additional Independent Risk factors for infections in CLL Retrospective Analysis in 706 Patients

SECONDARY IMMUNE DEFICIENCY

Parameter	Specifics	Population (n=706)	*P*
Gender	Female Male	286 (41%) 420 (59%)	0.1807
Age	<65 years ≥65 years	360 (51%) 346 (49%)	0.5516
Treatment	Treated Not treated	280 (40%) 426 (60%)	<0.0001
Stage	0-I II III-IV	448 (63%) 110 (16%) 148 (21%)	<0.0001
IGHV	Mutated Unmutated	285 (60%) 188 (40%)	0.0012

Parameter	Specifics	Population (n=706)	*P*
FISH findings	Del 13q Normal +12 Del 11q Del 17p	200 (45%) 124 (28%) 54 (12%) 38 (8%) 32 (7%)	<0.0001
CD38	<30% ≥30%	410 (77%) 119 (23%)	0.0046
ZAP70	<20% ≥20%	285 (57%) 217 (43%)	0.3549
TP53/NOTCH1/ BIRC3/SF3B1	Mutated Wild-type	20 (11%) 156 (89%)	0.9998

- **Treatment, advanced stage (III-IV), unmutated CLL cells, Del 11q, Del 17p and expression of ≥30% of CD38 are identified risk factors for infection in CLL**
- **The combination of previous treatment and CAD increases the risk of infections and shortens the time to first infection**

CLL: chronic lymphocytic leukaemia; Ig: immunoglobulin; IGHV: immunoglobulin heavy chain variable region; FISH: fluorescence in situ hybridization; ZAP: zeta-chain-associated protein kinase; TP53: tumor protein kinase 53 CAD: combined antibody deficiency.
**Data from 706 patients with CLL was retrospectively reviewed; 63% of patients were in stage 0–I, 16% in stage II and 21% in stages III–IV, and 40% of patients received treatment.*
Adapted from: Visentin, A. et al., Haematologica 2015;100:e515.

Potential risk factors for infections (for all haematological malignancies)

SECONDARY IMMUNE DEFICIENCY

Low infection risk

High infection risk

- Normal Ig levels
- No history of severe or recurring infections
- Neutropenia <7 days
- Few co-morbidities

- Hypogammaglobulinaemia
- Severe or recurring infections
- Neutropenia (<0.1 x 10^9/L) >7 days
- Co-morbidities

Ig: immunoglobulin.

1. Freifeld, A. G., et al., Clin Infect Dis. 2001; 52:427. ; 2. Tomblyn, M. et al., Biol Blood Marrow Transplant. 2009; 15:1143. ; 3. Lachance, S. et al., Current Oncology 2016; 23:42. ; 4. Visentin, A. et al., Haematologica 2015;100:e515.

Iatrogenic causes of immune deficiency in CLL

SECONDARY IMMUNE DEFICIENCY

Class of Therapy, Corresponding Immune Dysfunction, and Potential Infections

Chemotherapy	Immune dysfunction	Infections
Alkylating agents (e.g chlorambucil, bendamustine, and cyclophosphamide)	Neutropenia Lymphopenia (T cell dysfunction)	Bacterial
Purine analogues (e.g. fludarabine, pentostatin, bendamustine and cladribine	Lymphopenia (T cell dysfunction +++) Neutropenia	Bacterial, viral, Fungal, if prolonged PJP Cryptococcus

Immunotherapy	Immune dysfunction	Infections
Anti-CD20 antibodies (e.g. rituximab, ofatumumab, obinutuzumab)	Lymphopenia B	Bacterial , Hepatitis B reactivation, Viruses (e.g. enterovirus, JC virus)
Anti-CD22 antibodies (moxetumomab pasudotox)*	Platelet, white blood cells, neutrophil and lymphocyte count decreased	Pneumonia, upper respiratory infection, febrile neutropenia
Anti-CD52 antibody (alemtuzumab)	Lymphopenia (B and T cell dysfunction)	Viruses (e.g. CMV, HSV, VZV), Fungal, PJP

PJP: pmeumocystis jirovecii pneumonia; CMV: cytomegalovirus; HSV: herpes simplex virus; VZV: varicella-zoster virus
Hilal T et al., Blood Reviews 2018; 32:387-399.
**Kreitmann et al. Leukemia 2018; 32:1768–1777.*

Iatrogenic causes of immune deficiency in CLL

SECONDARY IMMUNE DEFICIENCY

Class of Therapy, Corresponding Immune Dysfunction, and Potential Infections

Small molecules inhibitors	Immune dysfunction	Infections
BTK inhibitors (e.g. ibrutinib, acalabrutinib)	Lymphopenia (B cell dysfunction, possible T cell dysfunction)	Hepatitis B reactivation, Fungal (Aspergillus, Cryptococcus) PJP
PI3K inhibitors (e.g. idelalisib, duvelisib)	Neutropenia Lymphopenia (B and T cell dysfunction)	Bacterial, Fungal, if prolonged Viruses (e.g. CMV, HSV) Aspergillus PJP
BCL-2 inhibitors (e.g. venetoclax)	Neutropenia Lymphopenia (B cell dysfunction)	Bacterial, Viruses (e.g. enterovirus)

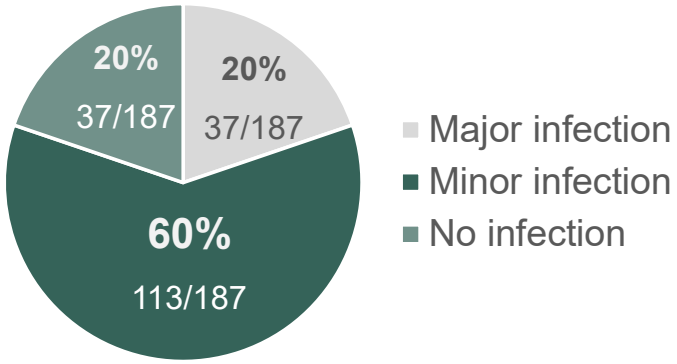
CLL: chronic lymphocytic leukaemia; BTK: Bruton tyrosine kinase; PI3K: phosphatidylinositol 3-kinase; BCL-2: B-cell lymphoma 2; PJP: pmeumocystis jirovecii pneumonia; CMV: cytomegalovirus; HSV: herpes simplex virus.

Hilal T et al., Blood Reviews 2018; 32:387-399.

Infections are frequent in CLL

SECONDARY IMMUNE DEFICIENCY

Incidence of infection by severity in CLL*



Patients Characteristics (n=187)	
Median Age	65.3yrs (range 21.4-96.2)
Disease stage (Rai)	0 : 50 (27%) I: 43 (23%) II: 43 (23%) III: 22 (12%) IV: 29 (15%)
Median number of pre-treatments	0 regimens: 95 (51%) 1 regimen: 22 (12%) 2 regimens: 21 (11%) ≥3 regimens: 49 (26%)

In this study, 80% of CLL patient developed infection. Among them, 24% of CLL patients developed major infections.

Patients treated for CLL had a higher risk of major infections and minor infections compared to those never treated.

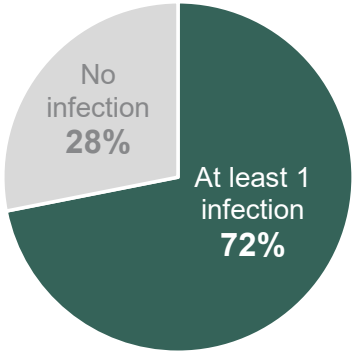
CLL: chronic lymphocytic leukaemia.
Records with the clinical data of all patients (n - 187) were retrospectively reviewed to determine the clinicopathological features of CLL and infections that had been documented in patient charts. Furthermore, in order to get data about infections that were treated at home by their general practitioner, patients and their physicians were asked to answer a questionnaire.
**Maior infections were identified as those requiring inpatient and intravenous (i.v.) antibiotic treatment. Infections treated with oral antibiotics alone / antiviral treatment and on an outpatient basis were considered to be minor infections.*
Adapted from: Hensel, M. et al., Br J Haematol. 2003;122:600.

Infections are frequent in CLL

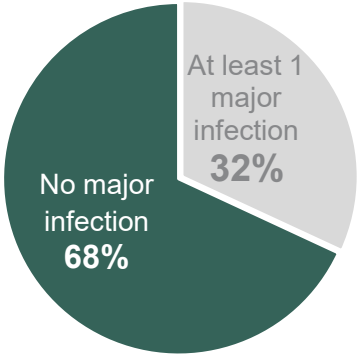
SECONDARY IMMUNE DEFICIENCY

Incidence rate of infection

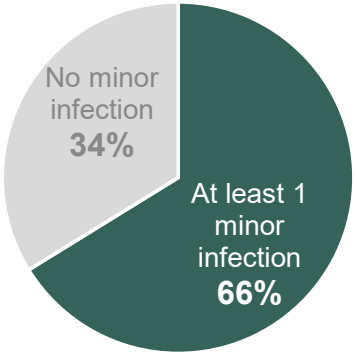
Patients with any infections



Patients with **major** infections



Patients with **minor** infections



Patients Characteristics (n=263)	
Median Age at diagnosis	62.19 yrs
Disease stage (Rai) (n=199)	0 : 111 (55.8%); I or II: 70 (35.2%); III or IV: 18 (9%)
Number of pre-treatments	Never treated: 106 (40.3%) Progressed to treatment: 157 (59.7%) (2 or more regimens: 102 (38.8%))

In this study, 32% of patients experienced at least one major infection and 66% experienced at least one minor infection

CLL: chronic lymphocytic leukaemia.
**Infections were categorized as major if requiring an inpatient admission or IV antimicrobial treatment and minor if not meeting these criteria (only outpatient care and no IV antimicrobial therapy). Antimicrobial prophylaxis for Pneumocystis pneumonia and herpes virus infections were standard of care for treatment regimens with purine analog containing chemoimmunotherapy (n=54) or alemtuzumab (n=10).*
Adapted from: Williams A.M. et al., Leukemia & Lymphoma 2017;1029-2403.

Respiratory tract and skin infections are the most common infections that occur in CLL

SECONDARY IMMUNE DEFICIENCY

Incidence rate of infection by site per 100 person-years

Infections	Major*	Minor*
Upper Respiratory, including sinusitis	1.92	**26.79**
Skin	**2.56**	**10.99**
Lower respiratory, including pneumonia, influenza, and tuberculosis	**7.79**	4.91
Bronchitis	0.85	**9.29**
Urogenital	**2.03**	8.32
Other/unknown	1.07	2.99
Oral	0.53	3.84
Gastroenteritis	1.17	2.1
Blood	1.92	0.32
CNS	0.43	0.11

Patients Characteristics (n=263)	
Median Age at diagnosis	62.19 yrs
Disease stage (Rai) (n=199)	0 : 111 (55.8%); I or II: 70 (35.2%); III or IV: 18 (9%)
Number of pre-treatments	Never treated: 106 (40.3%) Progressed to treatment: 157 (59.7%) (2 or more regimens: 102 (38.8%))

- **Most common sites of major infections were the lower respiratory tract, skin, and urogenital tract**
- **Most common minor infections were upper respiratory tract, skin including shingles, and bronchitis**

CLL: chronic lymphocytic leukaemia; CNS: central nervous system.
**Infections were categorized as major if requiring an inpatient admission or IV antimicrobial treatment and minor if not meeting these criteria (only outpatient care and no IV antimicrobial therapy). Antimicrobial prophylaxis for Pneumocystis pneumonia and herpes virus infections were standard of care for treatment regimens with purine analog containing chemoimmunotherapy (n=54) or alemtuzumab (n=10).*
Williams A.M. et al., Leukemia & Lymphoma 2017;1029-2403.

Treated patients have a higher risk of infection in CLL

SECONDARY IMMUNE DEFICIENCY

Incidence rate of infection in treatment and treatment-naive patients

Infections	Major*		Minor*	
	Incidence rate per 100 person-years	Incidence rate ratio (range) (95%CI)	Incidence rate per 100 person-years	Incidence rate ratio (range) (95%CI)
Patients with “high risk” immunosuppressive potential therapy: any purine analog (fludarabine, pentostatin, or cladribine) or alemtuzumab containing therapy,	28.11	3.31 (1.98, 5.54)	81.21	1.81 (1.40, 2.35)
Patients with “intermediate risk” immunosuppressive potential therapy: any therapy containing other DNA damaging or cell cycle inhibiting chemotherapies,	30.01	3.16 (1.76, 5.69)	71.46	1.59 (1.16, 2.18)
Patients with “lower risk immunosuppressive potential therapy”: other treatments (including anti-CD20 monoclonal antibodies, BCR pathway inhibitors, and immune modulating drugs).	26.99	2.56 (1.07, 6.18)	103.05	2.04 (1.28, 3.26)
Treatment naive	8.47	1.0 (ref.)	50.09	1.0 (ref.)

Patients Characteristics (n=263)	
Median Age at diagnosis	62.19 yrs
Disease stage (Rai) (n=199)	0 : 111 (55.8%); I or II: 70 (35.2%); III or IV: 18 (9%)
Number of pre-treatments	Never treated: 106 (40.3%) Progressed to treatment: 157 (59.7%) (2 or more regimens: 102 (38.8%))

The risk of major and minor infections is high in treatment-naive patients with CLL and is increased by therapy for progressive CLL, even among those treated with ibrutinib. Patients treated with regimens containing purine analogs or alemtuzumab had the highest risk of major infections.

CLL: chronic lymphocytic leukaemia.

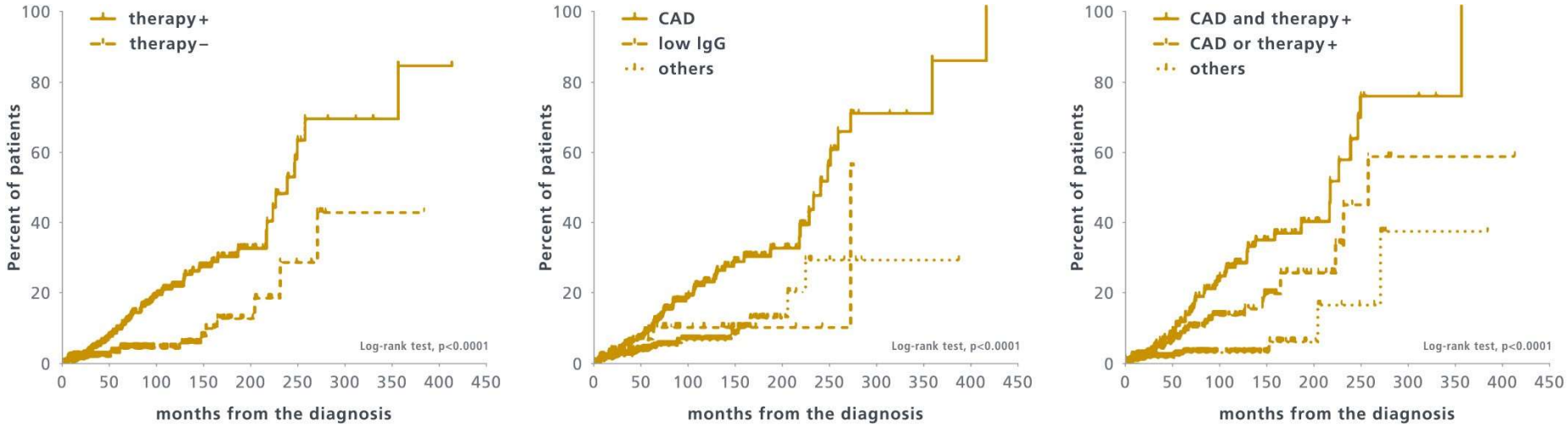
**Infections were categorized as major if requiring an inpatient admission or IV antimicrobial treatment and minor if not meeting these criteria (only outpatient care and no IV antimicrobial therapy). Antimicrobial prophylaxis for Pneumocystis pneumonia and herpes virus infections were standard of care for treatment regimens with purine analog containing chemoimmunotherapy (n=54) or alemtuzumab (n=10). CLL treatment was first classified dichotomously as treatment-naive versus treated. CLL treatment was then categorized using a hierarchical method into four discrete periods based on the immunosuppressive potential.*

Williams A.M. et al., Leukemia & Lymphoma 2017;1029-2403.

Therapy and combined antibody deficiency as risk factors for infections in patients with CLL

SECONDARY IMMUNE DEFICIENCY

Time to major infection in the CLL population with history of infection (n=79)



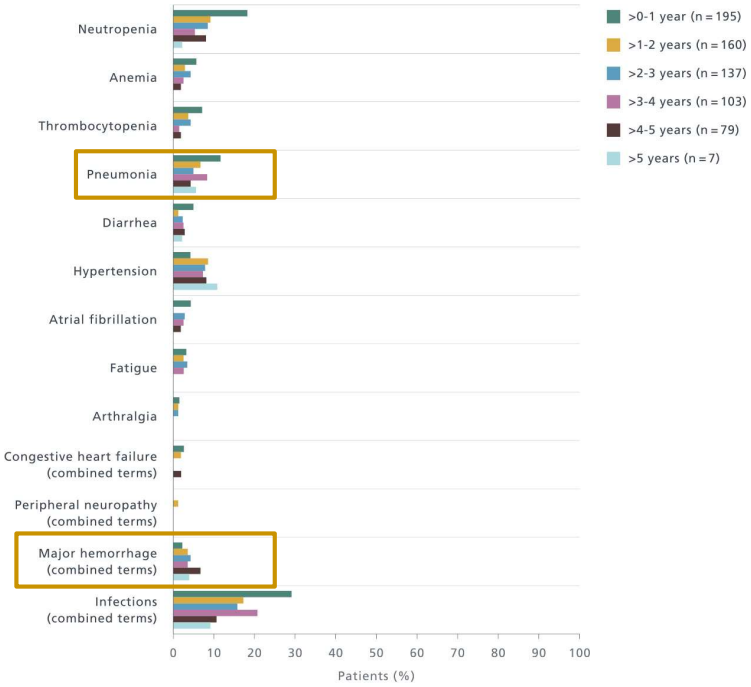
- **Previously treated patients developed major infections in a significantly shorter time than patients who were not treated with CLL-specific therapy.**
- **The median time to major infections was significantly shorter in patients who had both a history of CLL treatment and CAD than in subjects with only one or none of these markers.**

CAD: combined antibody deficiency.
Best protective cut-off value were identified for each Ig isotype: 744mg/dL for IgG, 79mg/dL for IgA and 21mg/dL for IgM. CAD was defined as low level of IgG (<744mg/dL) associated with low levels of either IgA (<79mg/dl) or IgM (21mg/dL). Major infections were defined as infective events that required inpatient management or intravenous antibiotics. No neutropenia. Total number of patients in the study=706; 79 patients had major infections: 61/79 received treatment for CLL. 51/79 had CAD. Treatment regimens were not described in the publication. Adapted from: Visentin A et al., Haematologica 2015;100:e515.

Infections are frequent following Bruton's tyrosine kinase inhibitor therapy

SECONDARY IMMUNE DEFICIENCY

Prevalence of grade ≥3 AEs in CLL/SLL patients treated with ibrutinib (N=195) *[1]



Prevalence of opportunistic infections in CLL patients (grade ≥3) treated with ibrutinib*[1]

Opportunistic infections

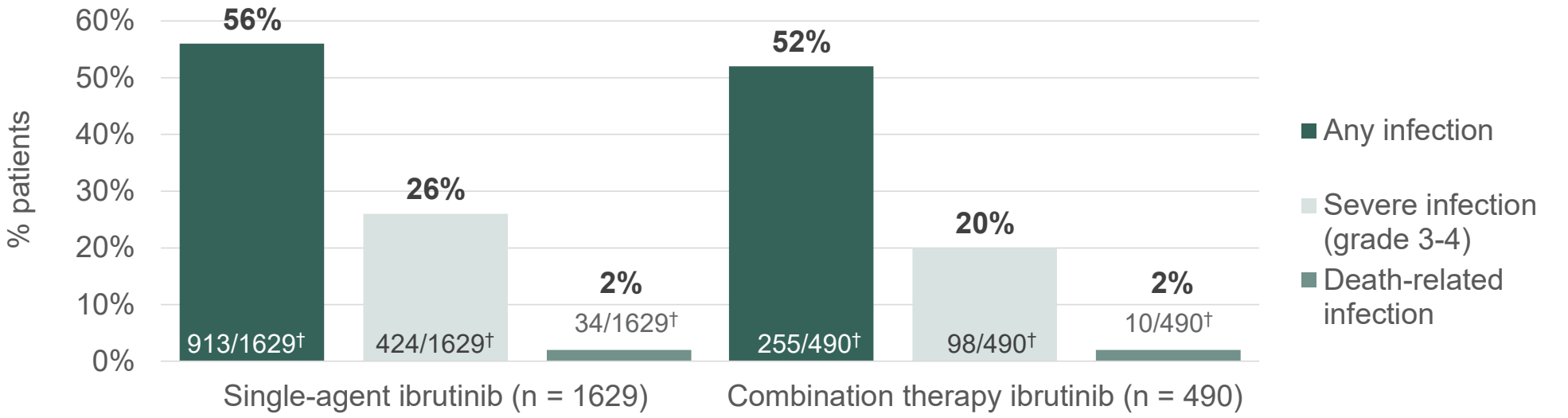
Organism	Cases
Aspergillosis (pulmonary and/or CNS)	14
Cryptococcus	1
Cytomegalovirus	1
Histoplasmosis	1
Listeria	1
Mycrobacterium avium intracellulare pulmonary	1
Mycrobacterium tuberculosis, CNS	1
Nocardiosis	1
Pneumocystis jirovecii pneumonia	6
Varicella zoster	15

CLL: chronic lymphocytic leukaemia; SLL: small lymphocytic lymphoma; AEs: adverse events; CNS: central nervous system.
**Prevalence was determined by the proportion of patients with a given AE (existing event or new onset of an event) during each yearly interval. Multiple onsets of the same AE term within a specific yearly interval were counted once, and the same AE term continuing across several yearly intervals was counted in each of the intervals.*
1. Adapted from Munir, Am J Hematol 2019;94:1353–1363. ; 2. Tillmann et al., Eur. J. Haematol. 2018;100:325–334.

Infections are frequent following Bruton's tyrosine kinase inhibitor therapy and result in mortality

SECONDARY IMMUNE DEFICIENCY

Prevalence of infections in patients treated with ibrutinib*



CLL=1'067, MCL=266, WM=98, MZL=63, FL=54, HCL=28, PCNSL/SCNSL=20, PCNSL/PVRL=18, NHL=15

CLL, MCL, MM, NHL, DLBCL, PCNSL, FL, SCNSL

Bendamustine, rituximab, fludarabine, cyclophosphamide, doxorubicin, vincristine, prednisone, dexamethasone, cytarabine, cisplatin, oxaliplatin, obinutuzumab, lenalidomide, etoposide, temozolomide, doxil

** Systematic review of 48 trial cohorts with 2,119 patients. Severe infections correspond to a 3–4 common terminology criteria for adverse events (CTCAE) grade.*
†The indicated patient number are derived from the percentages given (the actual patient numbers are not specified in the original reference).
Adapted from Tillman, B. F., et al., Eur J Haematol., 2018;100:325.

Infections remain a major cause of mortality in CLL

SECONDARY IMMUNE DEFICIENCY

Cause-specific mortality for patients diagnosed with CLL (solid color) vs. matched background population (dashed bars)

- Significant morbidity and mortality due to infections caused by CLL itself and by treatment-related adverse events are reported in clinical trials and seen in daily clinical practice
- Approximately 50% increased risk of death with infections as contributory or underlying cause was demonstrated compared with the matched controls
- Infection-related deaths did not improve over the time

10'455 CLL patients and 508'995 CLL-free control persons.
Adapted from: Cunha-Bang, C. et al., Blood Cancer J. 2016; 6 (11).

Conclusions of this module

SECONDARY IMMUNE DEFICIENCY

- Patients with CLL are at risk of immunodeficiency
- This secondary immunodeficiency can relate to the underlying disease, or its treatment
- The incidence of infection in CLL patients is substantial
- Infection contributes to death in people with CLL

SECONDARY IMMUNE DEFICIENCY

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