Managing infection risk and vaccinations in CLL and WM

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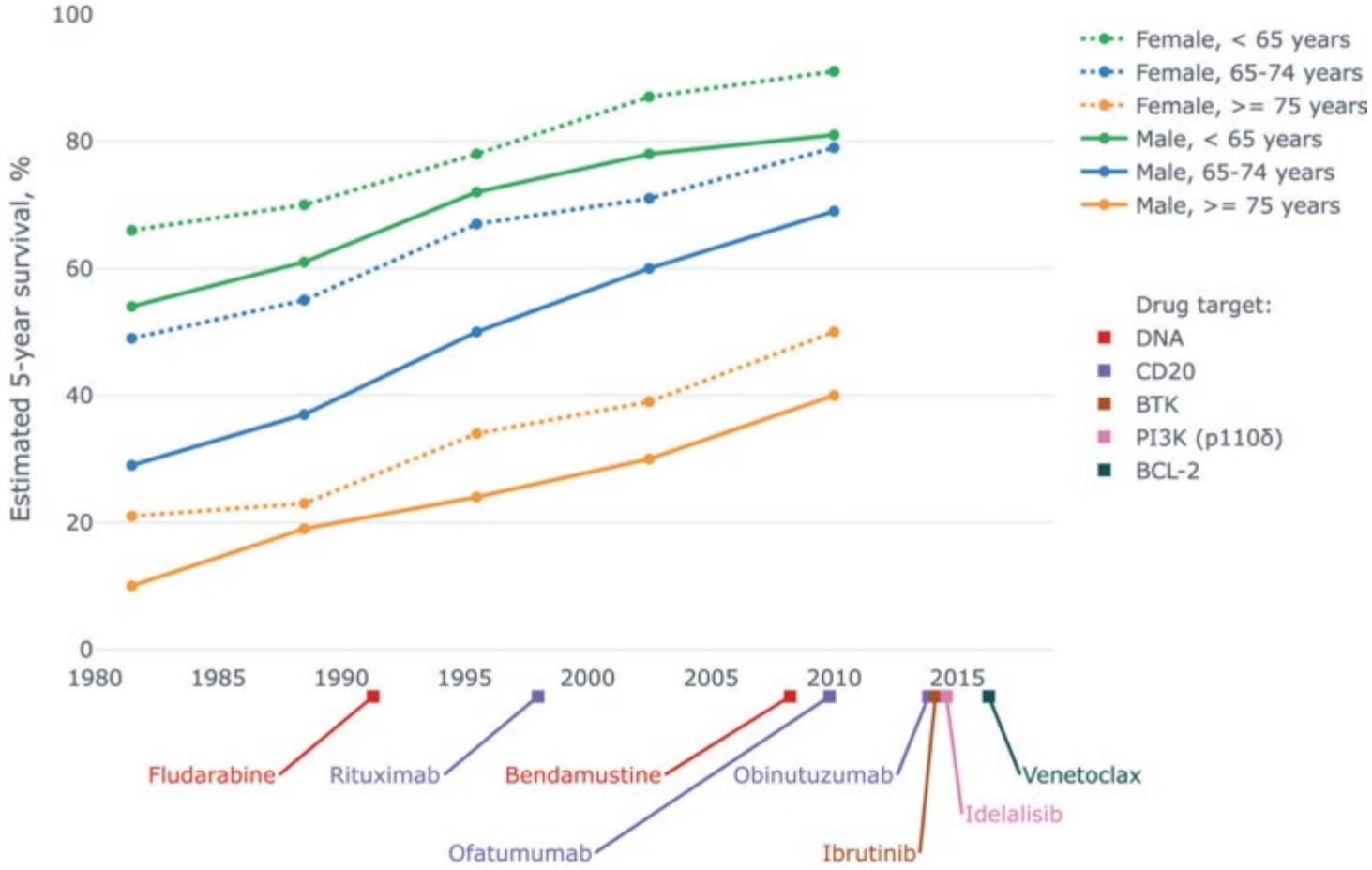
CLL, chronic lymphocytic leukemia; FILO, French Innovative Leukemia Organization; WM, Waldenstrom's macroglobulinemia.

Evolution of survival in CLL

Timeline of regulatory approval of major drugs for the treatment of CLL paralleled by improving survival of CLL patients



BCL-2, B-cell lymphoma 2; BTK, Bruton's tyrosine kinase; CD20, cluster of differentiation 20; CLL, chronic lymphocytic leukemia; DNA, deoxyribonucleic acid; PI3K, phosphoinositide 3-kinase.
Yosifov DY *et al*. *Hemasphere* 2019; 3 (2): e175.

Complications in CLL and WM

Infections
- Hypogammaglobulinemia
- Neutropenia*
- T-cell immune deficiency

→
- **Bacterial**
- **Viral**
- **Opportunists**

Bone marrow failure →
- Anemia – thrombocytopenia
- Differentiating between bone marrow failure and autoimmune mechanism

Autoimmune cytopenias
- AIHA
- ITP
- Autoimmune erythroblastopenia

Richter transformation (DLBCL) →
- Lymphadenopathy – fever – hypercalcemia
- PDL size increase

Increased incidence of other cancers? →
- Skin cancer – surveillance +++

Infections = Risk with long-standing CLL

↑

Cause of up to 50% of deaths[1]

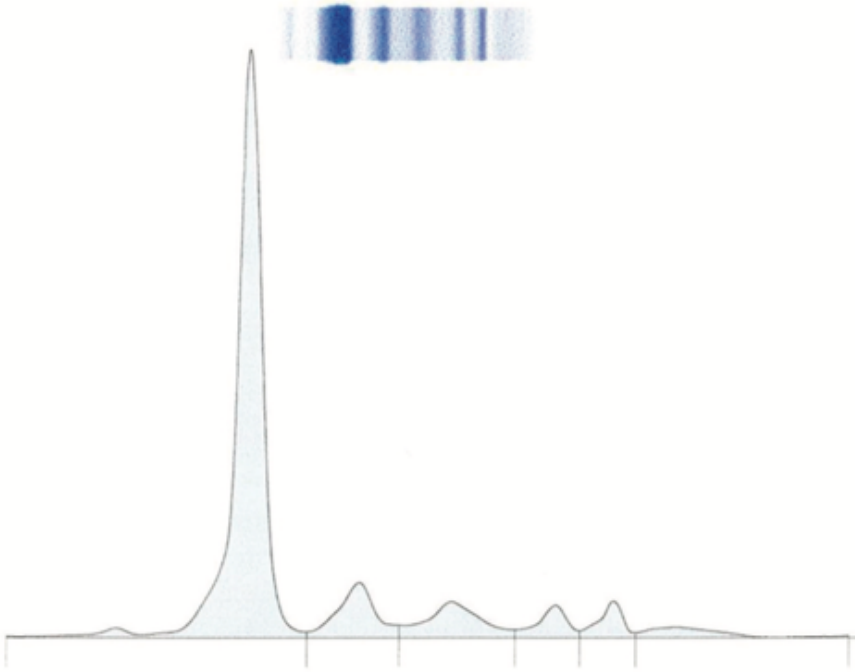
*Induced/enhanced by treatments. AIHA, autoimmune hemolytic anemia; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; ITP, immune thrombocytopenia; PDL, primary diffuse lymphadenopathies; WM, Waldenstrom's macroglobulinemia.

1. Murru R *et al. Ann Hematol* 2024; 103 (5): 1655–1664.

Slide courtesy of Anne-Sophie Michallet.

Hypogammaglobulinemia

- **Diagnosis**[1]
  - Approximately 20%
  - Advanced association
  - Associated with shorter survival?
- **During follow-up**[2]
  - + 11% more patients at 5 years
  - + 23% over 10 years
- **Not an indication for specific treatment**[2]
- **Physiological mechanisms not clearly understood**[2]



Total protein = 40 g L^{-1} Albumin globulin ratio

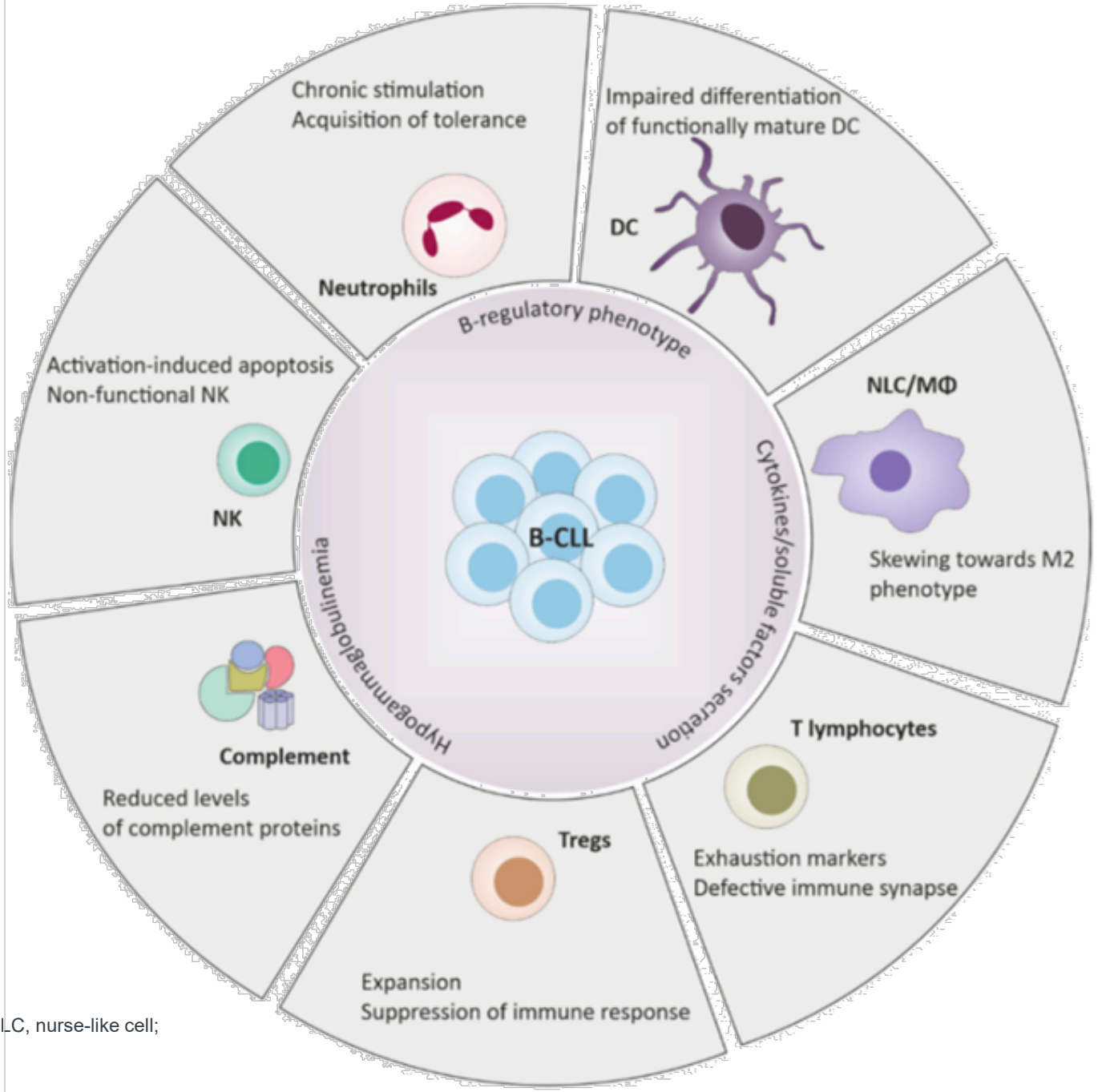
Protein	%	Normal range %	g L^{-1}	Normal range g L^{-1}
Serum albumin	70,6	55,8 - 66,1	28,2 <	40,2 - 47,6
Alpha 1 globulins	9,4	2,9 - 4,9	3,8 >	2,1 - 3,5
Alpha 2 globulins	8,6	7,1 - 11,8	3,4 <	5,1 - 8,5
Beta 1 globulins	4,2	4,7 - 7,2	1,7 <	3,4 - 5,2
Beta 2 globulins	3,9	3,2 - 6,5	1,6 <	2,3 - 4,7
Gamma globulins	3,3	11,1 - 18,8	1,3 <	8,0 - 13,5

Serum electropherogram from a patient with hypogammaglobulinemia[3]

1. Mauro FR *et al*. *Leuk Res* 2017; 57: 65–71. 2. Parikh SA *et al*. *Cancer* 2015; 121 (17): 2883–2891. 3. Frenzel LP. *Hématologie* 2017; 334: 5–11.
Slide courtesy of Anne-Sophie Michallet.

Immune deficiency in CLL and WM

- **Multiple mechanisms**
- **Immune system damage**
  - Adaptive
    - Humoral
    - Cellular
  - Innate

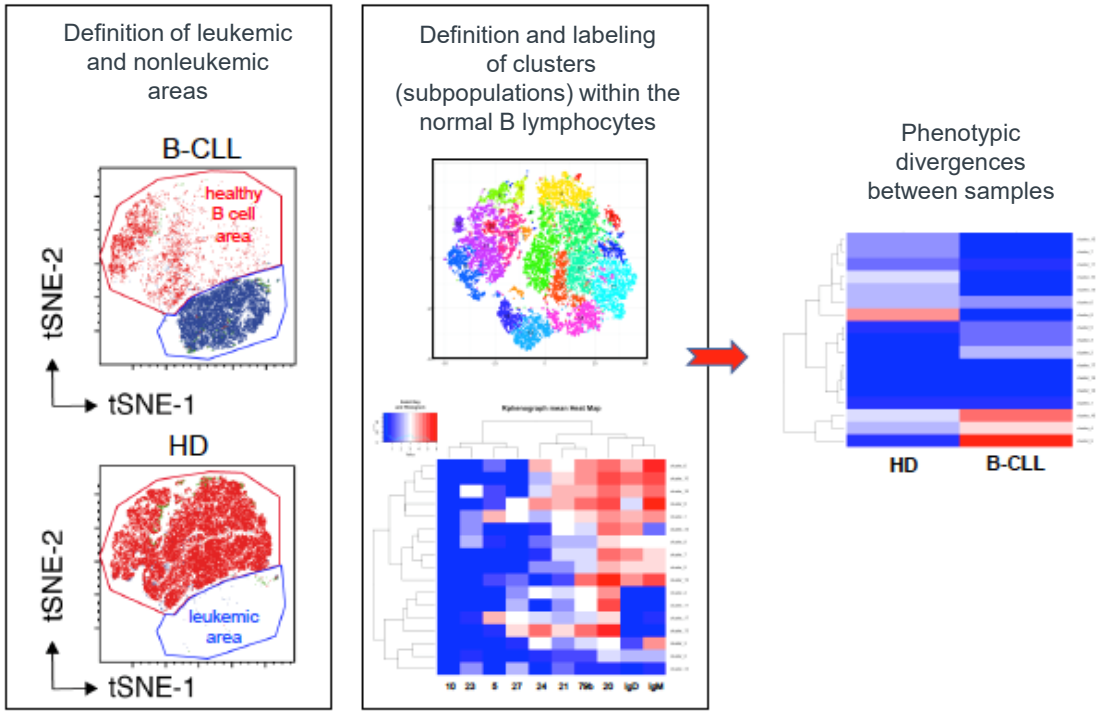


(B-)CLL, (B-cell) chronic lymphocytic leukemia; DC, dendritic cell; NK, natural killer; NLC, nurse-like cell; Treg, regulatory T cell; WM, Waldenstrom's macroglobulinemia.
Arruga F *et al*. *Int J Mol Sci* 2020; 21 (5): 1825.

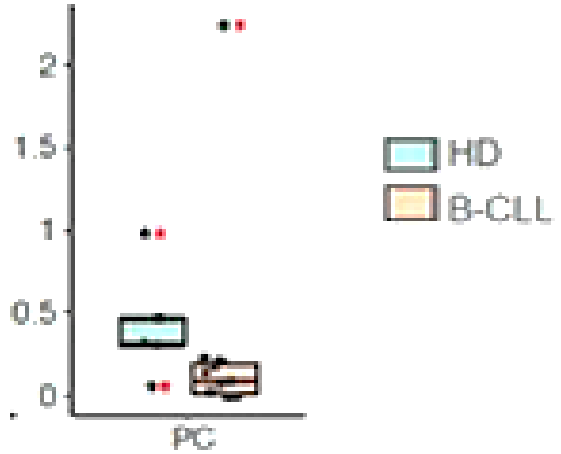
Immune system corruption caused by CLL

Experimental approach: Mass cytometry nonsupervised analysis of lymphocytic B normal residual compartment and of the peripheral hematopoietic environment (DCs, subpopulation T, macrophages, NK, etc.)

Results analyzed with viSNE algorithms, PhenoGraph, and SPADE



Precise separation of nontumor B lymphocytes and CLL lymphocytes by high-throughput flow cytometry



- Attrition of B lymphopoiesis
- Tolerance breakdown responsible for a predisposition to autoimmunity and hypogammaglobulinemia

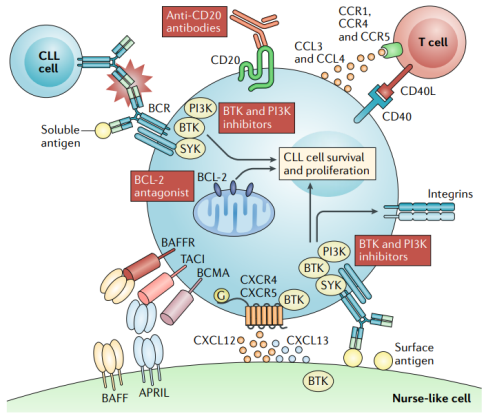
CLL tumor cells leave an imprint on the immune system, leading to developmental or functional abnormalities in normal B lymphocytes

(B-)CLL, (B-cell) chronic lymphocytic leukemia; DC, dendritic cell; NK, natural killer.
Slide courtesy of Anne-Sophie Michallet.
Collaborations: CRCL T Andrieu platform. Project leader: Dr Y Guillermin; Phenotypic study of the B lymphocyte microenvironment in CLL.

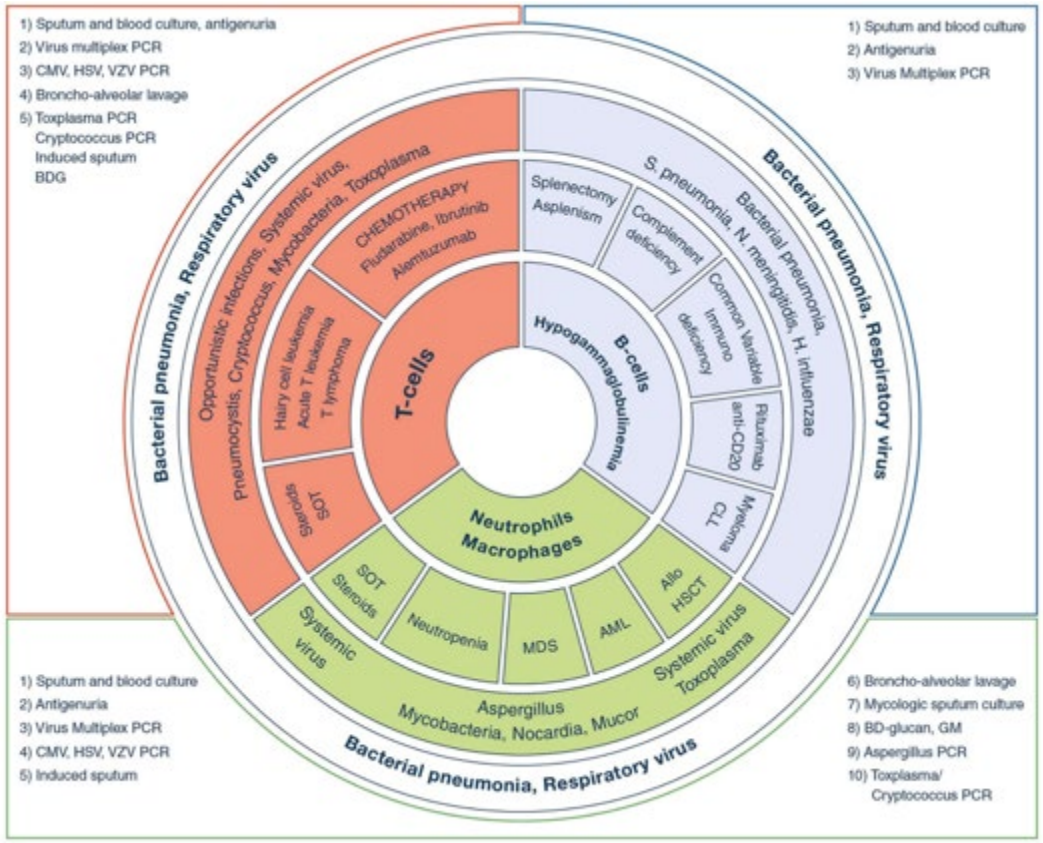
Double penalty: CLL treatments (1/3)[1,2]

- Bruton tyrosine kinase inhibitors (ibrutinib, zanubrutinib, acalabrutinib)
- BCL-2 inhibitors (venetoclax)
- CD20 inhibitors (rituximab, obinutuzumab, etc.)
- Phosphoinositide 3-kinase inhibitors (-lisib)

Burger JA *et al.* 2018[4]



Pulmonary infections according to immunosuppression[3]



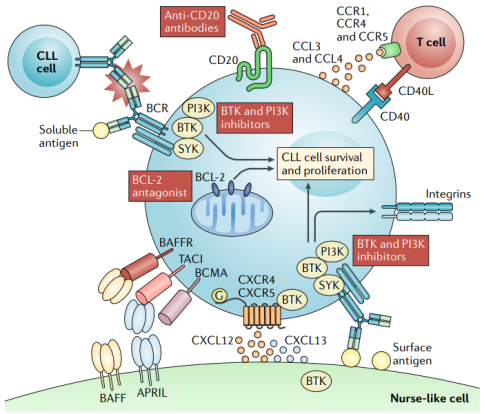
All these treatments target B cells +/− T cells = Humoral and cellular deficiency

BCL2, B-cell lymphoma 2; CD20, cluster of differentiation 20; CLL, chronic lymphocytic leukemia.

1. Shah M *et al*. *Transpl Infect Dis* 2024; 26 (3): e14283. 2. Huang IJ *et al*. *Expert Opin Pharmacother* 2024; 25 (13): 1759–1783. 3. Azoulay E *et al*. *Intensive Care Med* 2020; 46 (2): 298–314;
4. Burger JA, et al. *Nat Rev Clin Oncol* 2018; 15 (8): 510–527.

Double penalty: CLL treatments (2/3)

Burger JA *et al.* 2018[1]



In the course of treatment, new qualitative and/or quantitative alterations are added and are generally associated with:

- **Innate immunity (alkylating agents...)** → Nonspecific bacterial risk
- **B lymphocytes (anti-CD20)** → Increased hypogammaglobulinemia: risk of encapsulated bacterial and viral infections (respiratory and enteric viruses)
- **T lymphocytes** → Risk of viral (herpes virus) and fungal (*Pneumocystis jirovecii* > filamentous and mucorales spp) reactivation

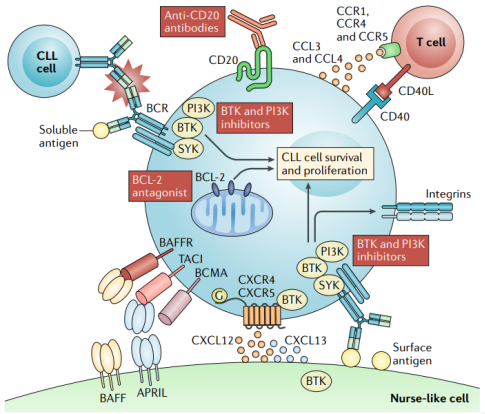
CD20, cluster of differentiation 20; CLL, chronic lymphocytic leukemia; spp, several species.

1. Burger JA *et al. Nat Rev Clin Oncol* 2018; 15 (8): 510–527.

Slide courtesy of Anne-Sophie Michallet.

Double penalty: CLL treatments (3/3)

Burger JA *et al.* 2018[1]



- BTKi: Hypo IgG and hyper IgA, combined inhibition of numerous tyrosine kinases (macrophages, neutrophils, etc.): filamentous risk (*Aspergillus*) > PJP
- BCL2i: Classic neutropenia (Grade 3–4 in >50% of cases) – CD4 T lymphocytopenia?
- Idelalisib: Combined inhibition of LT activation: Increased PJP and CMV risks

BCL2i, B-cell lymphoma 2 inhibitor; BTKi, Bruton's tyrosine kinase inhibitor; CD4, cluster of differentiation 4; CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; Ig, immunoglobulin; LT, lymphotoxin; PJP, *Pneumocystis jirovecii* pneumonia.

1. Burger JA *et al. Nat Rev Clin Oncol* 2018; 15 (8): 510–527.

Slide courtesy of Anne-Sophie Michallet.

CLL treatments: Risk of infections

Ibrutinib (Resonate 2)[1]

Table 2. Adverse Events and Duration of Treatment.

Variable	Ibrutinib (N=135)	Chlorambucil (N=132)
Duration of treatment — mo		
Median	17.4	7.1
Range	0.7–24.7	0.5–11.7
Adverse event of grade ≥3 — no. of patients (%)†		
Upper respiratory tract infection	3 (2)	2 (2)

2%

Ibrutinib + venetoclax (Glow)[2]

Table 2. Grade 3 or 4 Adverse Events Occurring in 5% or More of Either Arm and Grade 5 Adverse Events Occurring in Any Patient (Safety Population).*

	Ibrutinib-Venetoclax (n=106)		Chlorambucil-Obinutuzumab (n=105)	
Treatment exposure — mo, median (range)	13.8 (0.7–19.5)		5.1 (1.8–7.9)	
Adverse events — n (%)	**Grade 3/4**	**Grade 5**	**Grade 3/4**	**Grade 5**
Patients with ≥1 adverse events	73 (68.9)	7 (6.6)	71 (67.6)	2 (1.9)
Neutropenia†	37 (34.9)	0	52 (49.5)	0
Infections and infestations‡	16 (15.1)	2 (1.9)§	11 (10.5)	1 (1.0)

17%

Ibrutinib + venetoclax +/− obinutuzumab (GAIA)[3]

Event	Chemoimmunotherapy (N=216)			Venetoclax–Rituximab (N=237)			Venetoclax–Obinutuzumab (N=228)			Venetoclax–Obinutuzumab–Ibrutinib (N=231)		
	Grade 1 or 2	Grade 3	Grade 4	Grade 1 or 2	Grade 3	Grade 4	Grade 1 or 2	Grade 3	Grade 4	Grade 1 or 2	Grade 3	Grade 4
	number of patients (percent)											
Infections	89 (41.2)	38 (17.6)	2 (0.9)	113 (47.7)	24 (10.1)	1 (0.4)	121 (53.1)	30 (13.2)	0	123 (53.2)	48 (20.8)	1 (0.4)
Upper respiratory tract	42 (19.4)	2 (0.9)	0	73 (30.8)	5 (2.1)	0	82 (36.0)	5 (2.2)	0	78 (33.8)	2 (0.9)	0
Urinary tract	9 (4.2)	2 (0.9)	0	13 (5.5)	5 (2.1)	0	14 (6.1)	3 (1.3)	0	24 (10.4)	9 (3.9)	0
Pneumonia	6 (2.8)	12 (5.6)	0	4 (1.7)	4 (1.7)	0	9 (3.9)	12 (5.3)	0	14 (6.1)	14 (6.1)	1 (0.4)
Infection, NOS	11 (5.1)	5 (2.3)	0	5 (2.1)	1 (0.4)	0	7 (3.1)	4 (1.8)	0	5 (2.2)	4 (1.7)	0
Influenza	2 (0.9)	5 (2.3)	0	8 (3.4)	3 (1.3)	0	9 (3.9)	0	0	5 (2.2)	3 (1.3)	0

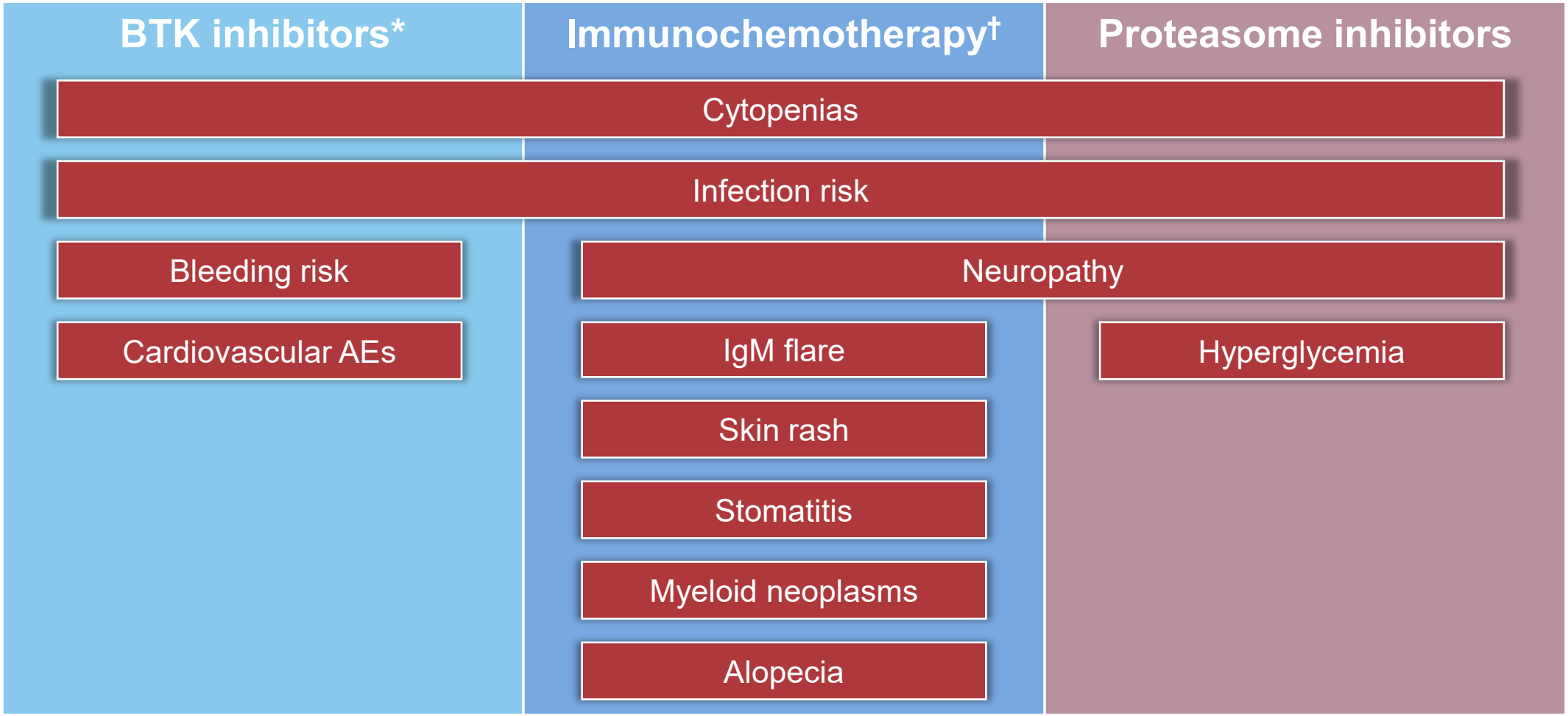
21%

Please note that the comparators used on this slide are not equivalent: e.g. Grade ≥3 upper respiratory tract infections[1] vs. Grade 3/4–5 infections and infestations[2] vs. Grade 3–4 infections.[3]

CD20, cluster of differentiation 20; CLL, chronic lymphocytic leukemia; NOS, not otherwise specified.

1. Burger JA *et al*. *N Engl J Med* 2015; 373 (25): 2425–2437. 2. Kater AP *et al*. *NEJM Evid* 2022; 1 (7): EVIDoa2200006. 3. Eichhorst B *et al*. *N Engl J Med* 2023; 388 (19): 1739–1754.

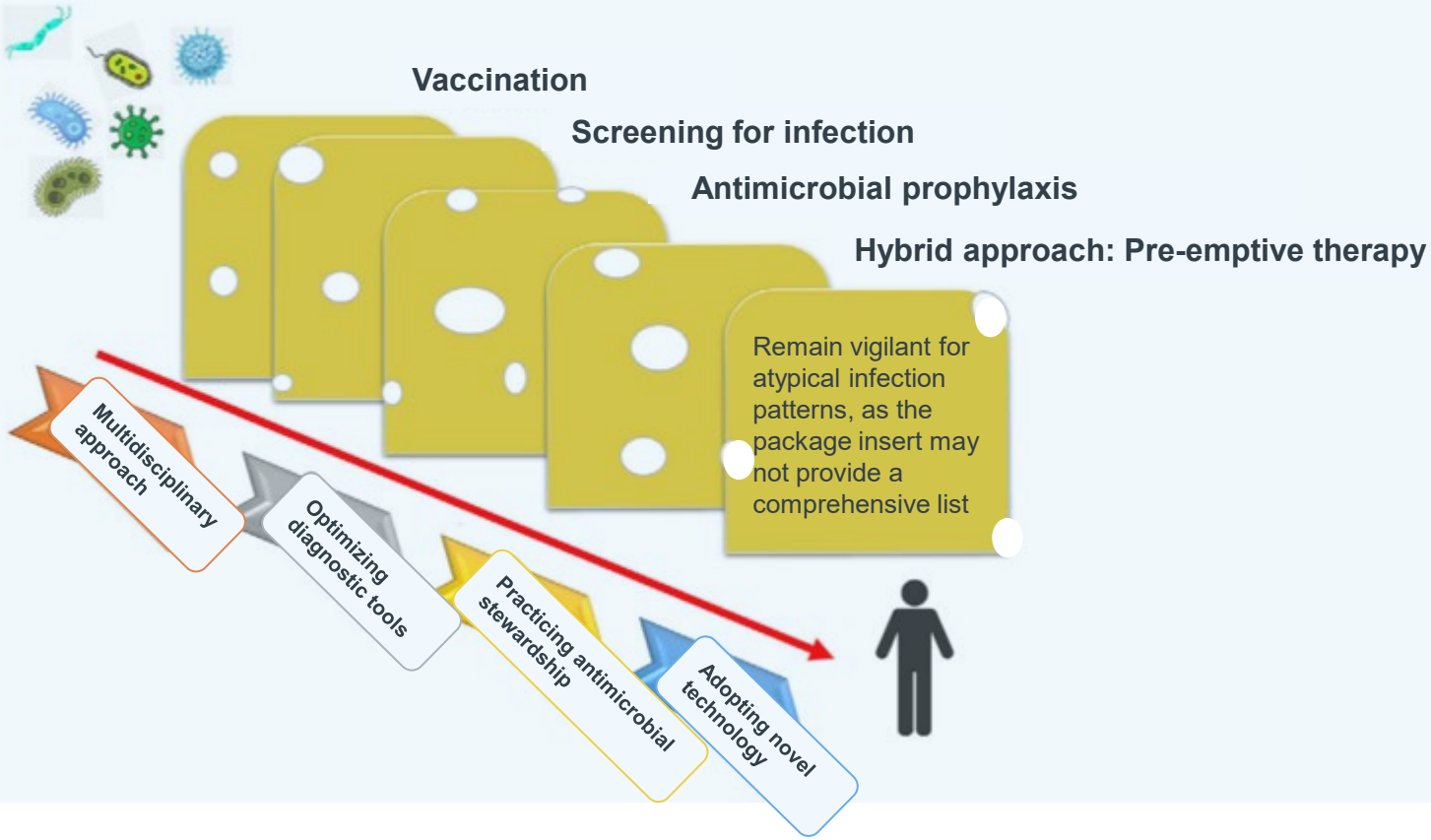
Treatment-related complications in WM



*Side effects noted for each category in Castillo *et al*. 2020. †Includes risks associated with rituximab plus nucleoside analogs; cyclophosphamide, doxorubicin, vincristine, and prednisone; and bendamustine.
AE, adverse event; BTK, Bruton's tyrosine kinase; IgM, immunoglobulin M; WM, Waldenstrom's macroglobulinemia.
Castillo JJ *et al. Lancet Haematol* 2020; 7 (11): e827–e837.

Preventive measures (1/4)

Prevention of infections in hematologic malignancy patients receiving novel agents: The Swiss cheese model



Shah M *et al*. *Transpl Infect Dis* 2024; 26 (3): e14283.

Preventive measures (2/4)

Nonspecific preventive measures

- Daily hygiene
- **Hand washing, hand sanitizer, wound disinfection, oral hygiene**
- **Wearing a mask in a confined environment**
- Information for relatives (vaccinations, sick children, etc.)
- Protection against infections from pets (pet vaccinations, excreta...)
- Travel to high-risk areas: Remember to have a certificate of contraindication to yellow fever vaccination (Guyana...) if not previously vaccinated (single dose valid for life)

Prophylactic anti-infectives*

- **Cotrimoxazole:** Systematic from the start of treatment[1]
  - Anti-pneumocystis **and** antibiotic activity (covers >90% of *pneumococci* and >80% of *haemophilus*)
  - Efficacy demonstrated but not absolute:
    - Duration not conditioned by CD4 count: Excluding HIV, more than 50% of PJP cases have CD4 >200/mm^3 [2]
- **Valaciclovir:** Systematic from start of treatment (aciclovir absorption 20% vs. 60%)
  - Anti-HSV and anti-VZV activity, but not anti-CMV
- **Prophylactic antibiotic therapy: Controversial**
  - As secondary prophylaxis in cases of bronchiectasis (anti-inflammatory and immunomodulatory action):
    - Azithromycin (25% pneumococcal resistance) 250 mg × 3/week

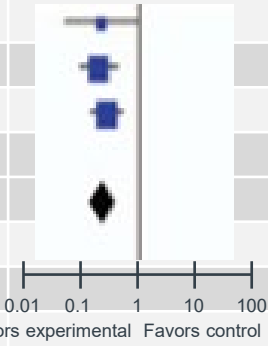
*Based on the speaker's own experience.
CD4, cluster of differentiation 4; CMV, cytomegalovirus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; *Pneumocystis jirovecii* pneumonia; VZV, varicella zoster virus.
1. Maertens J *et al*. *J Antimicrob Chemother* 2016; 71 (9): 2397–2404. 2. Huang L *et al. BMC Pulm Med* 2023; 23 (1): 72.
Slide courtesy of Anne-Sophie Michallet.

Preventive measures (3/4): Passive immunotherapy

Polyvalent immunoglobulin: Useful or futile?

- Meta-analysis of documented infections: ↓51%
- Mortality: No change

	Polyvalent IVIG		Control			Risk ratio	Risk ratio
Study or study group	Events	Total	Events	Total	Weight	M-H, fixed, 95% CI	M-H, fixed, 95% CI
Boughton 1995	7	24	11	18	14.0%	0.48 (0.23, 0.98)	
Chapel 1994	17	41	38	41	42.2%	0.45 (0.31, 0.65)	
Cooperative CLL 1988	21	41	39	40	43.8%	0.53 (0.39, 0.71)	
Total (95% CI)		106		99	100.0%	0.49 (0.39, 0.61)	
Total events	45		88				
Heterogeneity: Chi² = 0.45, df = 2 (*P*=0.80); I² = 0%							
Test for overall effect Z = 6.21 (*P*<0.00001)							



Polyvalent immunoglobulins:

- EMA recommendations for substitution

Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF)* or serum IgG level of <4 g/L.

Major supply shortage since 2021:

- Indications restricted by ANSM in agreement with many learned societies

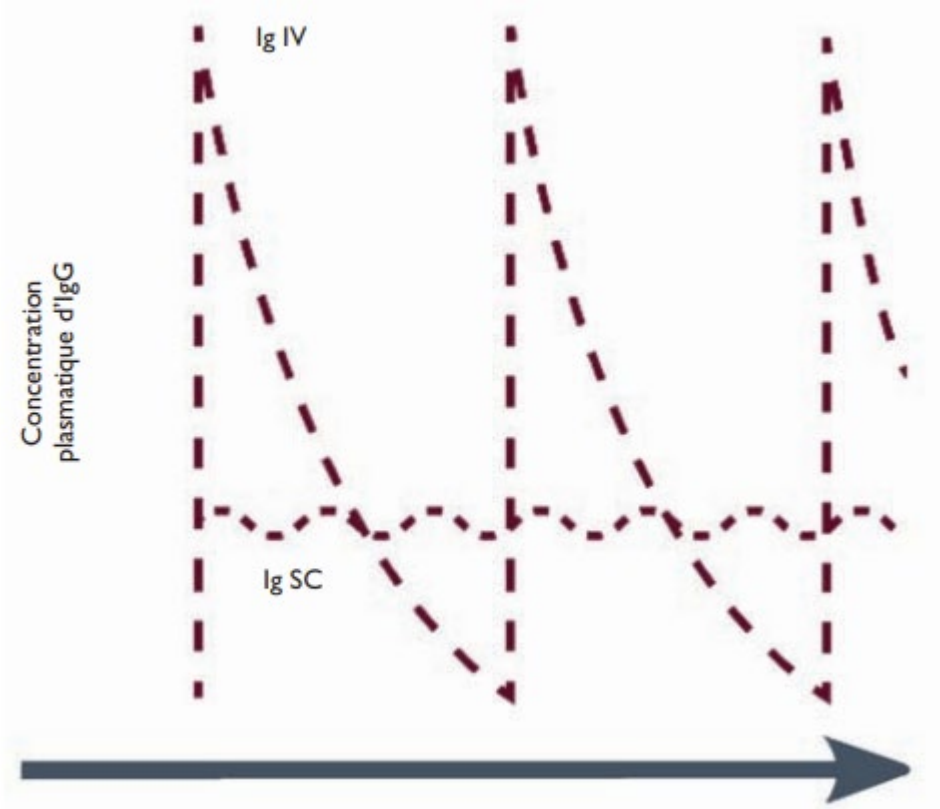
Secondary immunodeficiencies:

Déficits immunitaires secondaires : ▪LLC*, LNH et autres avec défaut de production d'Ac **(dosage pondéral des IgG <4g/L), associées à des infections à répétition survenus malgré une antibioprophylaxie bien conduite et entraînant une hospitalisation**	[UV]	**Passage en RCP**	Reserved for vital emergencies and/or functional and/or in case of lack of alternative therapies

ANSM, French National Agency for Medicines and Health Products Safety; CI, confidence interval; CLL, chronic lymphocytic leukemia; df, degrees of freedom; EMA, European Medicines Agency; IgG, immunoglobulin G; IVIg, intravenous immunoglobulin; M-H, Mantel–Haenszel. Raanani P *et al*. *Leuk Lymphoma* 2009; 50 (5): 764–772.
Slide courtesy of Anne-Sophie Michallet.

Preventive measures (4/4): Passive immunotherapy

- There are two different routes of administration for immunoglobulin treatment:[1,2]
  - Intravenous (IV Ig – monthly administration in a medical setting)
  - Subcutaneous (SC Ig – weekly self-administration at home)
- Efficacy and safety are similar[2]
  - SC: May improve quality of life and satisfaction
  - IV: Monthly administration leads to variations in serum IgG levels, resulting in low levels in the days prior to the next infusion and increased susceptibility to infection
- Common (≥1/100 to <1/10) to very common (≥1/10) adverse events are systemic, such as headache, fever, fatigue, and/or nausea[2]



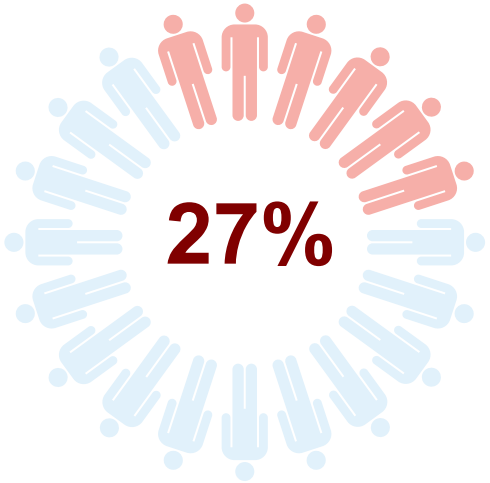
Schematic illustrating plasma concentration of IgG during IV and SC administration[2]

Ig, immunoglobulin; IV, intravenous; SC, subcutaneous.

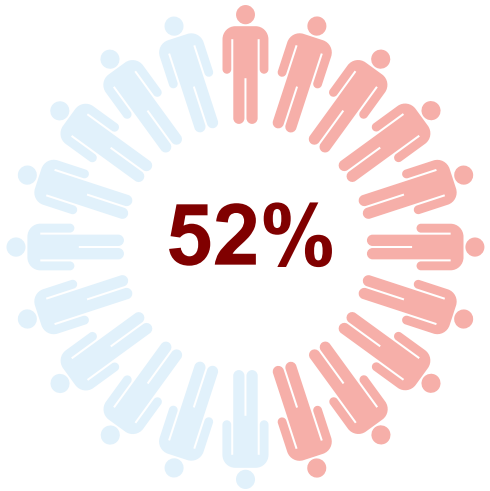
1. Jolles S *et al*. *Clin Exp Immunol* 2005; 142 (1): 1–11. 2. Bourdin A *et al*. *Rev Med Suisse* 2015; 11 (469): 831–835.

Vaccinations and CLL

National multicentric retrospective study of COVID-19 vaccine response in CLL (N=530 patients)[1]

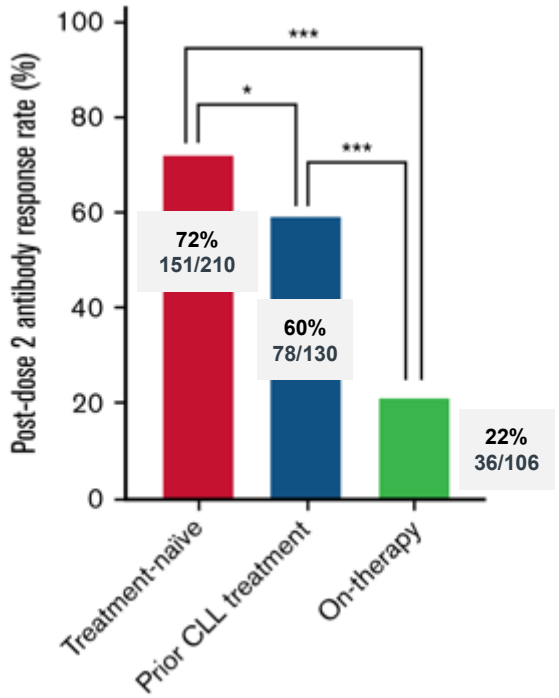


Antibody response rate after dose 1
(43/158)



Antibody response rate after dose 2
(265/506)

Antibody response rates in patients with CLL after two doses of COVID-19 vaccine[2]



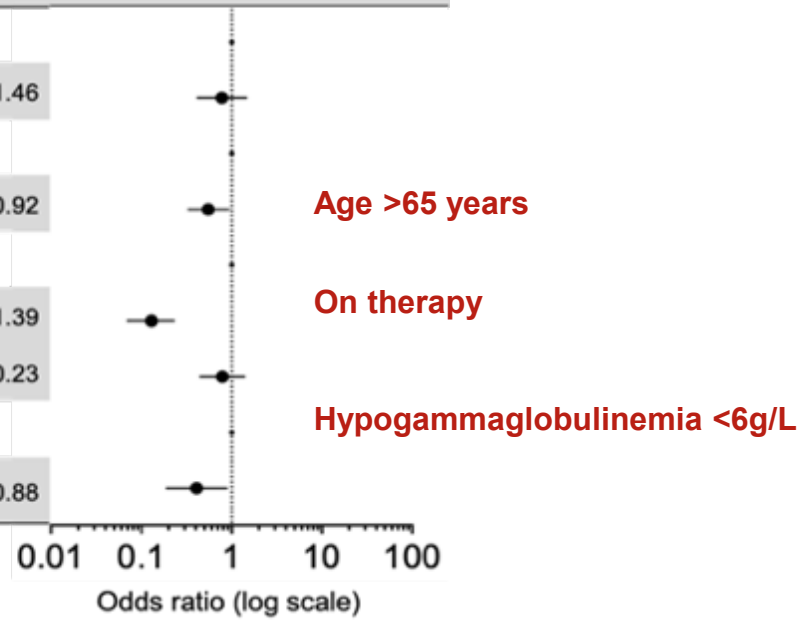
*P<0.01. **P<0.001. ***P<0.0001.
CLL, chronic lymphocytic leukemia; COVID-19, coronavirus disease 2019.
1. Gerard V *et al*. Poster 09 presented at 43rd Congress of SFH 2023; Paris, France, March 29–31, 2023. 2. Bagacean C *et al*. *Blood Adv* 2022; 6 (1): 207–211.
Slide courtesy of Anne-Sophie Michallet.

Vaccinations and CLL

National multicentric retrospective study of COVID-19 vaccine response in CLL (N=530 patients)

Predictors of humoral responses

Variable		Serological response Positive n (%)	Negative n (%)	Total	*P*-value	Odds ratio	95% CI
Vaccine type	mRNA-1273 - Moderna (%)	47 (68%)	22 (32%)	69			
	BNT162b2 – Pfizer BioNTech (%)	187 (51%)	180 (49%)	367	0.44	0.78	0.42-1.46
Age	Age ≤ 65 years	70 (49%)	73 (51%)	143			
	Age >65 years	170 (48%)	187 (52%)	357	0.02	0.55	0.33-0.92
CLL treatment	Treatment-naïve	151 (72%)	59 (28%)	210			
	Prior CLL treatment	78 (60%)	52 (40%)	130	0.42	0.79	0.45-1.39
	On therapy	36 (22%)	130 (78%)	166	< 0.001	0.13	0.07-0.23
Gamma-globulins	Gamma-globulins > 6g/L	48 (71%)	20 (29%)	68			
	Gamma-globulins ≤ 6g/L	24 (41%)	35 (59%)	59	0.03	0.41	0.19-0.88



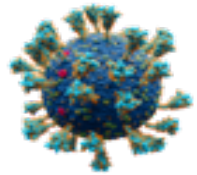
CLL, chronic lymphocytic leukemia; COVID-19, coronavirus disease 2019; mRNA, messenger ribonucleic acid.
Bagacean C *et al*. *Blood Adv* 2022; 6 (1): 207–211.

2024 UPDATE

Flu and COVID-19 vaccines

2024 vaccination schedule in France

- Autumn vaccination
- Quadrivalent (H1N1, H3N2, two B strains)
- Three vaccines on the market
- No immunological correlate of protection
- VE: 20%–80%
- Marketing authorization: >6 months of age
- Vaccination schedule: ≥65 years of age (and at risk)
- 100% reimbursement (if vaccinated)



- Autumn vaccination
- Monovalent JN.1 (95%)
- One vaccine on the market
- No need for serology
- VE: 95%
- Marketing authorization: >12 years of age
- Vaccination schedule: ≥65 years of age (and at risk)
- 100% reimbursement

COVID-19, coronavirus disease 2019; VE, vaccine efficacy.
Slide courtesy of Anne-Sophie Michallet.

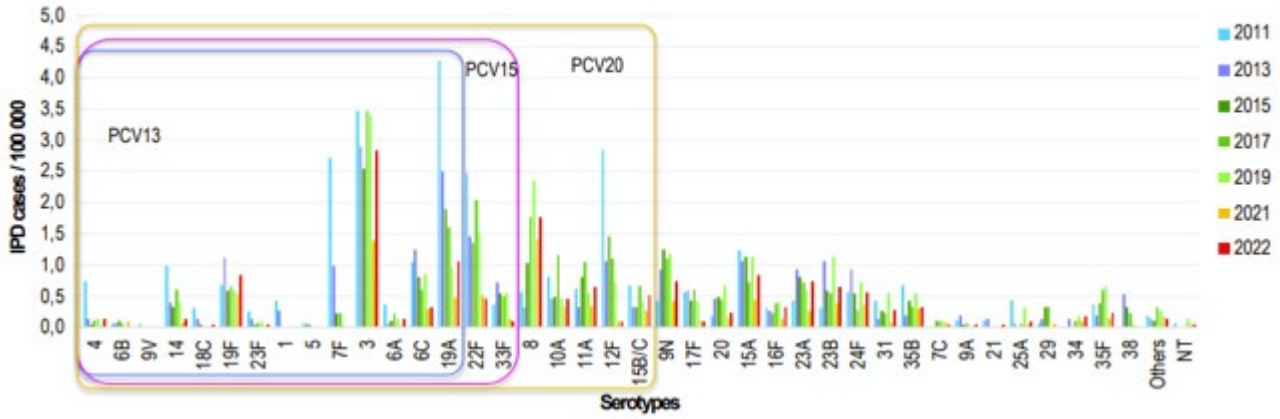
2024 UPDATE

Pneumococcal vaccine

In France, recommended for general population aged over 65 years

- Inactivated 20-valent polysaccharide conjugate vaccine (60% of circulating serotypes)[1]
- Protective immunological correlate for children only: ≥0.35 µg/mL
- VE: Unknown (VE=85% with PCV13 in children)
- Duration of efficacy: Unknown (5 years?)
- Vaccination schedule: Adults at risk of pneumococcal infection
- History of PCV23 or PCV13: PCV20 if >1 year of age
- Previous PCV13 then PCV23 at S+8: PCV20 if >5 years of age
- 65% reimbursement (≈60€)

Evolution of the incidence of *pneumococcus* infections according to serotype in adults >64 years, between 2011–2022[2]



IPD, individual patient data; PCV, pneumococcal conjugate vaccine; VE, vaccine efficacy.

1. Essink B *et al*. *Clin Infect Dis* 2022; 75 (3): 390–398. 2. Centre National de Référence Pneumococques. Rapport Annuel D'Activité 2024.

Slide courtesy of Anne-Sophie Michallet.

2024 UPDATE

Shingles vaccine

- Inactivated adjuvanted recombinant glycoprotein E[1]
- No immunological correlate of protection[1]
- **Clinical efficacy in hematological malignancies (30% CLL/NLH): 87% (65% in real-life ID)[1,2]**
  - → Incidence of shingles within 1 year: 2/259 (0.8%) vs. 14/256 (5.5%)[1]
  - → **Significant reduction in post-herpetic pain**
- HAS: ASMR III (moderate)
- Efficacy data preserved for 10 years in the general population
- Vaccination schedule: Adults ≥65 years and immunocompromised adults ≥18 years (ideally 2nd doses 14 days before chemotherapy, interval between two doses reduced to 1 month, respect a delay of 1 year if shingles or Zostavax® vaccination) but vaccination may be started as soon as clinical recovery is complete if the risk of recurrence is considered significant
- Reimbursement: 65% (based on 188€)

ASMR, Amélioration du service médical rendu *(improvement of medical service received);* CLL, chronic lymphocytic leukemia; HAS, Haute Autorité de Santé (*French Health Authority*); ID, infectious diseases; NHL, non-Hodgkin lymphoma.

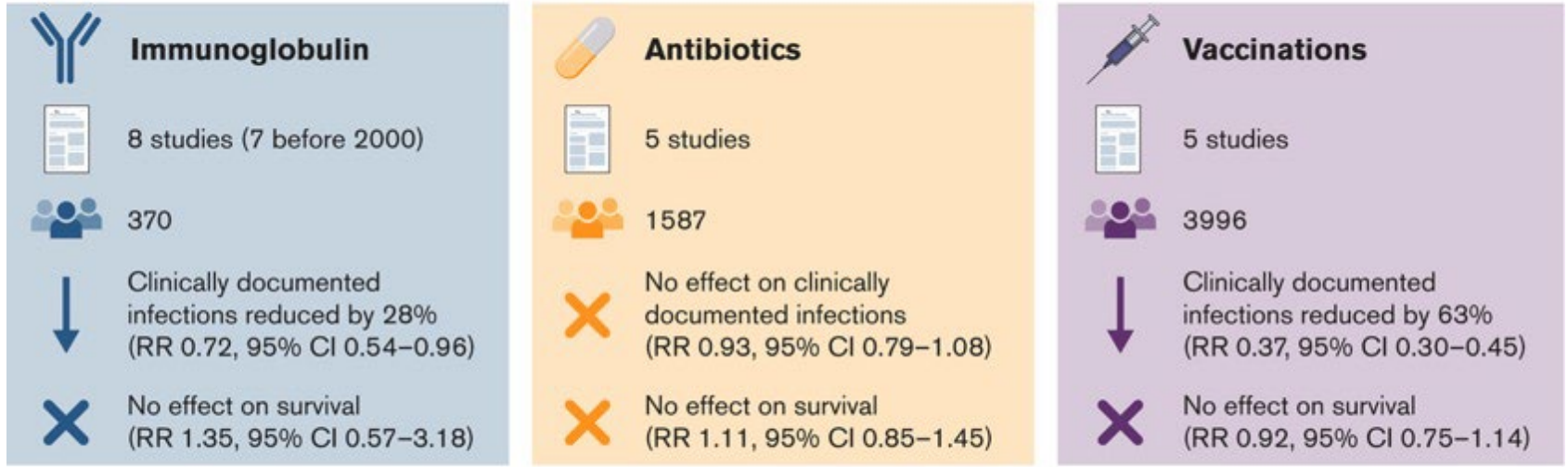
1. Dagnew AF *et* al. *Lancet Infect Dis* 2019; 19 (9): 988–1000. 2. Zerbo O *et al*. *Ann Intern Med* 2024; 177 (2): 189–195.

Slide courtesy of Anne-Sophie Michallet.

Take-home messages

Interventions to reduce infections in patients with hematological malignancies: A systematic review and meta-analysis

Population: Adult patients with chronic lymphocytic leukemia, myeloma or non-Hodgkin lymphoma
Intervention: Prophylactic immunoglobulin, antibiotics, vaccinations
Comparator: No intervention, placebo or standard care
Main outcomes: All-cause mortality or clinically documented infections



Summary

- Prophylactic immunoglobulin and vaccinations appear to reduce this risk of clinically documented infections, but findings should be interpreted with caution due to high risk of bias, heterogeneity and limited generalizability.
- Only one feasibility trial directly compared between interventions.

Future research

Future studies should compare different interventions, use standardised definitions of infection outcomes and incorporate cost-effectiveness analyses.

CI, confidence interval; RR, relative risk.
Chai KL *et al. Blood Adv* 2023; 7 (1): 20–31.

Merci!

Complications in WM

Symptom/complaint	Implications	Action
Fatigue, lack of energy	Anemia	Evaluate for anemia, including iron, folate, or cobalamin deficiency, hemolytic anemia (warm and cold antibodies), etc. Patients with iron deficiency may benefit from parenteral iron.
Constitutional symptoms	Disease progression	Obtain serum IgM levels and SPEP. Evaluate other causes of fever, night sweats, and unintentional weight loss.
Recurrent sinus and bronchial infections	Hypogammaglobulinemia	Antibiotic support. If patient refractory to antibiotics, required hospitalization, or infections were life threatening, consider IVIg replacement.
Headaches, blurry vision or visual loss, confusion, epistaxis	Hyperviscosity	Funduscopic examination, obtain serum IgM and serum viscosity levels. Consider emergent plasmapheresis for symptomatic hyperviscosity.
Easy bruising, bleeding diathesis	Thrombocytopenia; acquired vWD; acquired coagulation factor deficiency	Complete blood count, evaluate for immune thrombocytopenia or hypersplenism if indicated; consider evaluation for vWD; consider amyloidosis. Evaluate other bleeding diathesis with INR, PTT, and coagulation factor levels, as clinically indicated.
Progressive symmetrical numbness, tingling, burning, pain in feet and hands	IgM-related neuropathy; amyloidosis	Obtain EMG studies and neurology consultation. Obtain anti-MAG, and if negative anti-GM1 and anti-sulfatide IgM antibody studies. Consider fat pad biopsy and Congo red stain for amyloidosis. Evaluate other causes of neuropathy: diabetes, thyroid dysfunction, HIV infection, cobalamin deficiency, etc.
Raynaud-like symptoms, acrocyanosis, ulcers on extremities	Cryoglobulinemia; cold agglutinemia	Obtain cryoglobulins and cold agglutinins. In patients suspected of having cryoglobulins, IgM should be obtained in a warm bath to avoid cryoprecipitation. Consider emergent plasmapheresis.
Diarrhea, gastrointestinal cramping	Malabsorption	Endoscopy to evaluate small bowel, biopsy to evaluate for amyloidosis, IgM deposition, tumor involvement. Evaluate other causes of diarrhea.
Foamy urine, bipedal oedema	Kidney dysfunction	Obtain serum free light chains, 24-h urine protein, and consider kidney biopsy. Evaluate other causes of kidney dysfunction.
Urticaria, papules, dermatitis	Schnitzler syndrome, IgM / tumor cell infiltration, amyloid deposits	Skin biopsy, histological examination for tumor cell infiltration, stain for IgM, Congo red staining for amyloid. Evaluate other causes of rash.

EMG, electromyography; HIV, human immunodeficiency virus; IgM, immunoglobulin M; INR, International normalized ratio; IVIg, intravenous immunoglobulin; MAG, myelin-associated glycoprotein; PTT, partial thromboplastin time; SPEP, serum protein electrophoresis; vWD, von Willebrand disease; WM, Waldenstrom's macroglobulinemia.

Castillo JJ *et al. Br J Haematol* 2016; 17: 77–86.