FONDAZIONE ITALIANA LINFOMI

I "LINFOMI INDOLENTI"

Milano, Best Western Hotel Madison
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LINFOMI DELLA ZONA MARGINALE E AGENTI INFETTIVI

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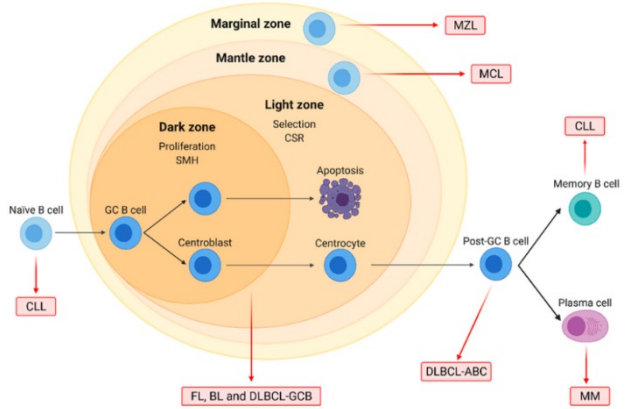
Disclosures of Elena Flospergher

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
none							

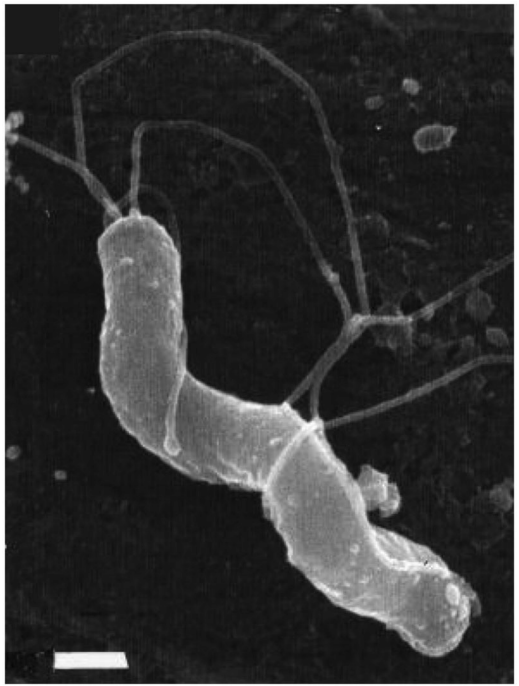
Marginal Zone Lymphoma



WHO 5th
Marginal zone lymphoma
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue
Primary cutaneous marginal zone lymphoma
Nodal marginal zone lymphoma
Paediatric marginal zone lymphoma
Splenic marginal zone lymphoma

ICC
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Primary cutaneous marginal zone lymphoproliferative disorder*
Nodal marginal zone lymphoma
Pediatric nodal marginal zone lymphoma
Splenic marginal zone lymphoma

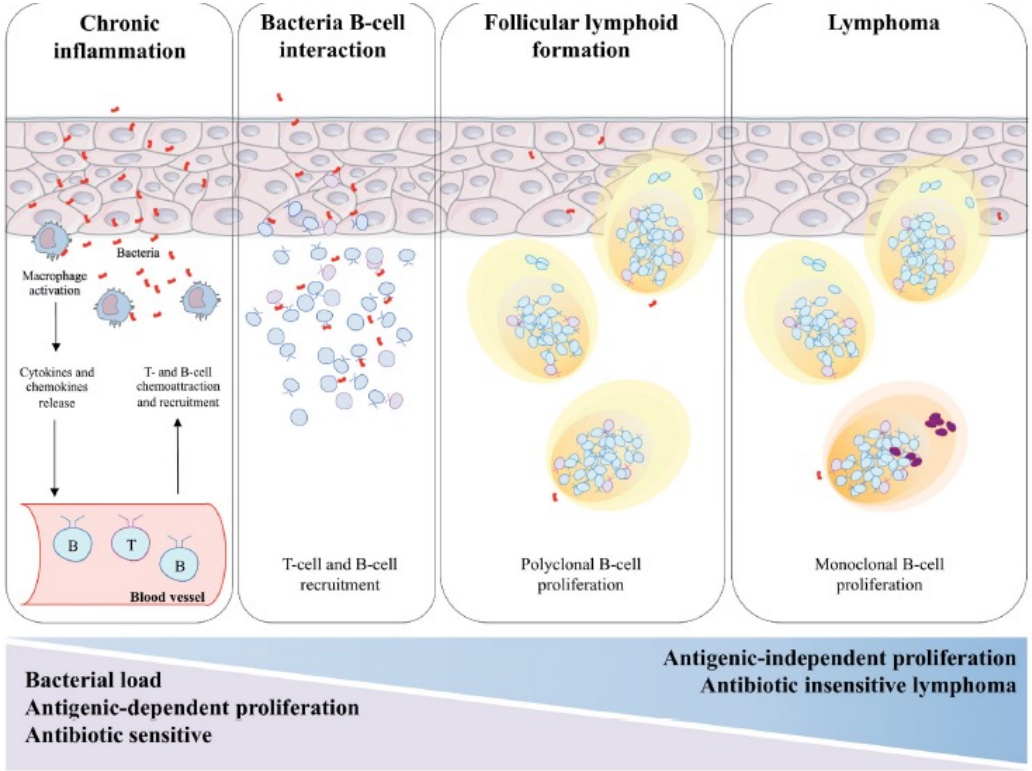
Helicobacter pylori (Hp) and Gastric MALT

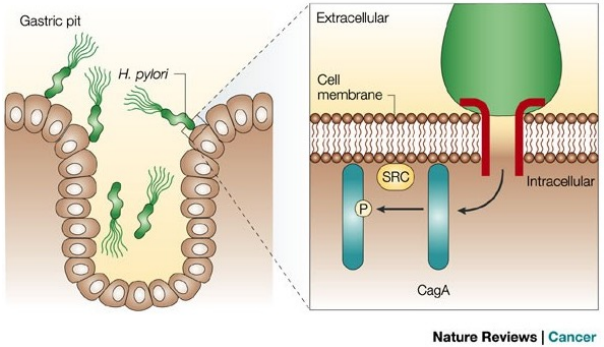


- Scoperto da Robin Warren e Barry Marshall nel 1982
- Batterio gram negativo, spiraliforme, fragellato, microaerofilo
- Colonizza la mucosa gastrica >50% della popolazione mondiale
- Causa gastrite cronica e ulcere gastriche/duodenali

- **Infezione da *Hp* associata ad aumentato rischio di carcinoma e linfoma gastrici**
  → dal 1994 *Hp* è considerato un patogeno cancerogeno per l'uomo

Helicobacter pylori (Hp) and Gastric MALT: Multistep Lymphomagenesis+CagA





Melenotte 2020

Helicobacter pylori (Hp) and Gastric MALT: Causality Criteria Revised

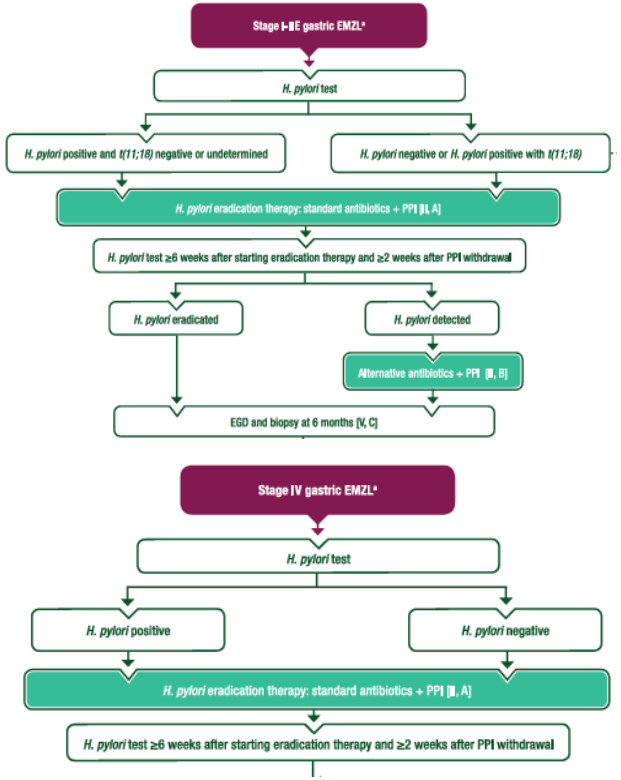
Koch's postulate, 1880
(Evans 1993)

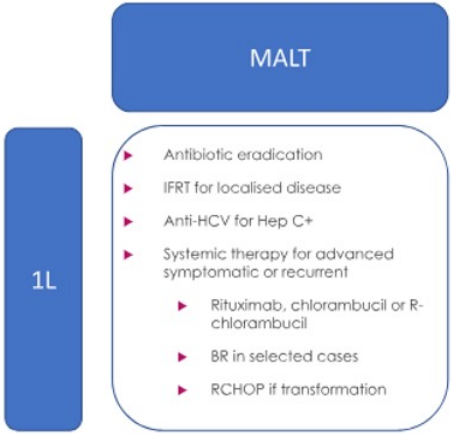
1. The parasite occurs in every case of the disease in question and under circumstances which can account for the pathological changes and clinical course of the disease.
2. It occurs in no other disease as a fortuitous and non-pathogenic parasite.
3. After being fully isolated from the body and repeatedly grown in pure culture, it can induce the disease anew.

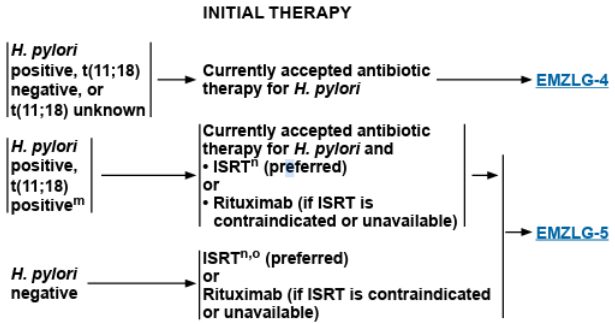
Melenotte et al., 2018

1. Strength of the association: the infectious disease induces an increased risk of NHL compared to the general population
2. Consistency: the relationship is observed Repeatedly
3. Temporality, the infectious disease precedes the NHL
4. Spatial proximity (anatomical) on physical examination or imagine (CT or PET-scan imaging): the infectious focus is located next to the NHL focus
5. The infectious agent is identified in the tumoural microenvironment.
6. *In vitro*: the bacteria should be able to transform human cells into malignant cells
7. *In vivo*: The bacteria should be able to induce the tumour in a susceptible experimental animal model
8. Remission after antibiotherapy

Helicobacter pylori (Hp) and Gastric MALT: Therapeutic Guidelines







ESMO guidelines 2025 BSH guidelines 2023 NCCN guidelines v.1.2026

Table 1
Level of evidence supporting MZL-bacteria association according to the Koch's postulates.

Koch's postulate	*Hp* and GMZL	*Cp* and OAMZL	*Bb* and CMZL	*Cj* and IPSID
The microorganism is found in the lesion of the disease	Yes	Yes	A few cases	Anecdotal cases
The organism can be isolated and grown *in vitro*	Yes	Yes	No	No
Inoculation of the organism causes lesions in healthy susceptible animals	Yes	Unknown	Unknown	Unknown
The organism can be recovered from the experimental animal	Yes	Unknown	Unknown	Unknown

GMZL = gastric marginal zone lymphoma; OAMZL = ocular adnexal marginal zone lymphoma; CMZL = cutaneous marginal zone lymphoma; IPSID = immunoproliferative small intestine disorder.

Ferreri 2013

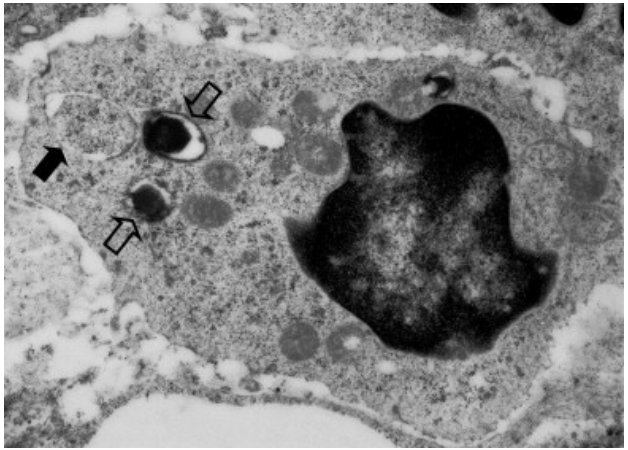
Table 1. Causality criteria related to bacteria and parasites associated with NHL

Melenotte Causality Criteria	Infectious Agents					
	H. pylori	*C. psittaci*	*B. burgdorferi*	*C. jejuni*	*C. burnetii*	*A. xylosoxidans*
Epidemiological link	X	X	X		X	
Consistency	X	X	X	X		
Temporality	X		X		X	X
Anatomical Proximity	X	X	X		X	X
Bacteria detection within lymphoma microenvironment	X	X	X	X	X	X
In-vitro B cell transformation	X				X	
In-vivo transformation in animal models	X					
Lymphoma regression after bacteria eradication	X	X	X	X		

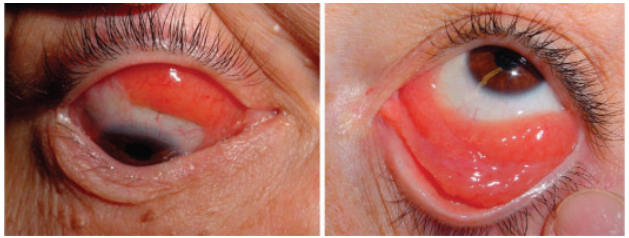
Evidence of a pathogenetic relationship according to the criteria recommended by Melenotte *et al.* [42••], who have recently proposed a revision of the principle used by the WHO International Agency for Research on Cancer (IARC) to establish a causal link between infection and cancer [22].

Vannata 2022

Chlamydophila psittaci (Cp) and OAMZL



Ferreri 2013



Ferreri 2008

- Batterio gram negativo intracellulare obbligato
- Agente eziologico della Psittacosi negli uomini
- Serbatoio: uccelli
- Trasmissione all’uomo per via aerea
- Ciclo vitale bifasico: corpo elementare vs corpo reticolato
- →**corpo persistente: infezioni croniche**

- Prevalenza OAMZL *Cp+* molto variabile tra paesi/regioni
- Rischio aumentato da esposizione cronica a uccelli/animali domestici, provenienza da aree rurali
- Talvolta storia di congiuntivite cronica

- Presente nei monociti/macrofagi del microambiente tumorale
- Presente nella congiuntiva e nelle PBMC dei pazienti

Chlamydophila psittaci (Cp) and OAMZL: Doxycycline

IELSG27

Cp+ su biopsia 39/44 (89%) → swab 97%, PMBC 69%

ORR 65% (poche CR), 2y PFS 60%→ migliori ORR e PFS nei pazienti che eradicano *Cp*

Eradicazione Cp 48%

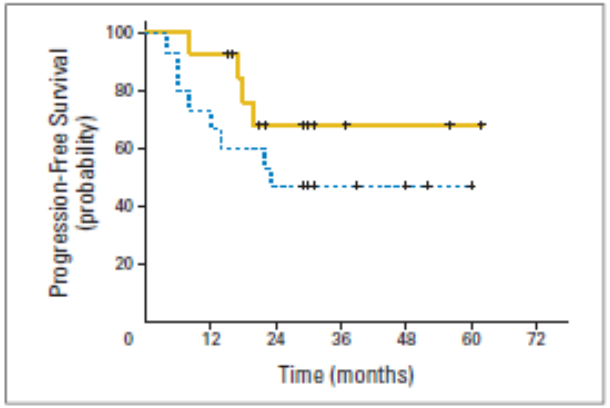


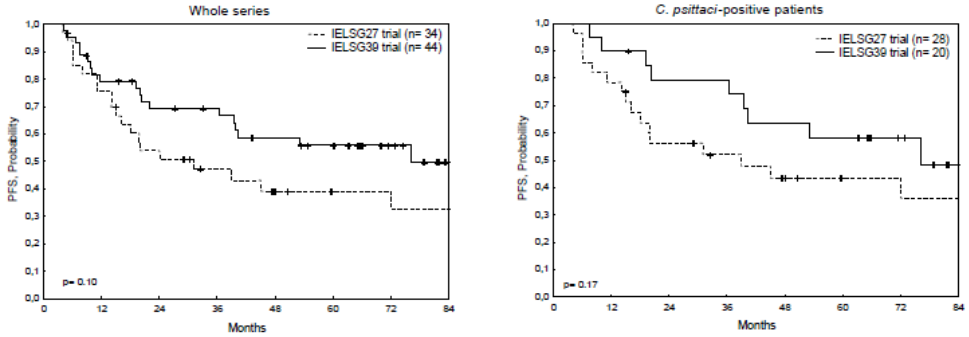
Fig 3. Progression-free survival (PFS) curves of patients registered in part A and divided according to *Chlamydophila psittaci* (Cp) eradication. Successful *Cp* eradication (solid line) was associated with better PFS.

IELSG39

Doxiciclina 100 mg bid per 4 settimane seguite da 4 settimane di stop per 3 cicli

Cp+ 64% 21/33 (11 pt con analisi in corso)

ORR 64% (metà CR), 2y PFS 75%→2y PFS *Cp*+ 90%



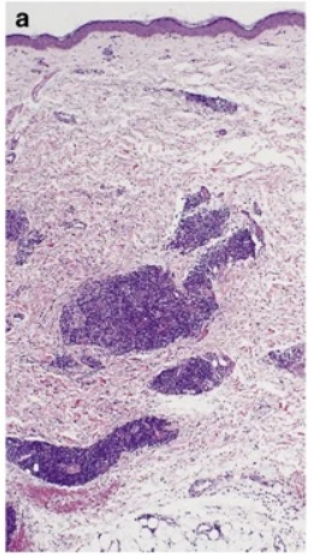
The six-month doxycycline treatment was associated with a trend towards better PFS in comparison with the shorter regimen used in the IELSG27 trial (median follow-up 75 months; range 5-155), both when whole populations (left figure) and Cp-positive subgroups (right figure) were analysed

Campylobacter jejuni (Cj) and IPSID

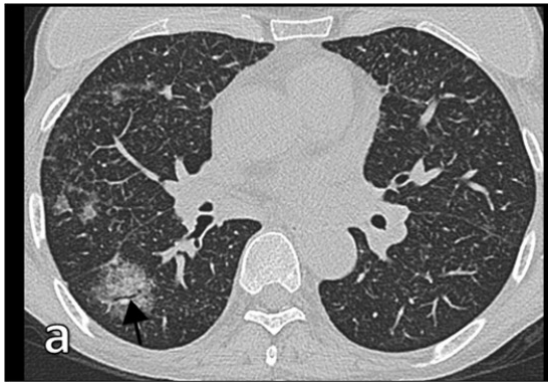
- *Cj* bastoncello gram negativo →causa enterite acuta (infezioni croniche/persistenti?)
- IPSD: infiltrato intestinale linfoplasmocitico con espressione monotipica di catene pesanti alfa (MALT piccolo intestino)
- Antibiotici efficaci negli stadi iniziali (tetracicline, metronidazolo)

Borrelia burgdorferi (Bb) and Primary Cutaneous MZL

- *Bb* spirocheta gram negativa→malattia di Lyme
- Associazione a diverse forme di linfoma primitivo cutaneo con ampia variabilità geografica→ricerca giustificata in aree endemiche
- Aneddotici casi di eradicazione del linfoma dopo terapia antibiotica (cefalosporine, tetracicline)



Altri batteri associati a MZL



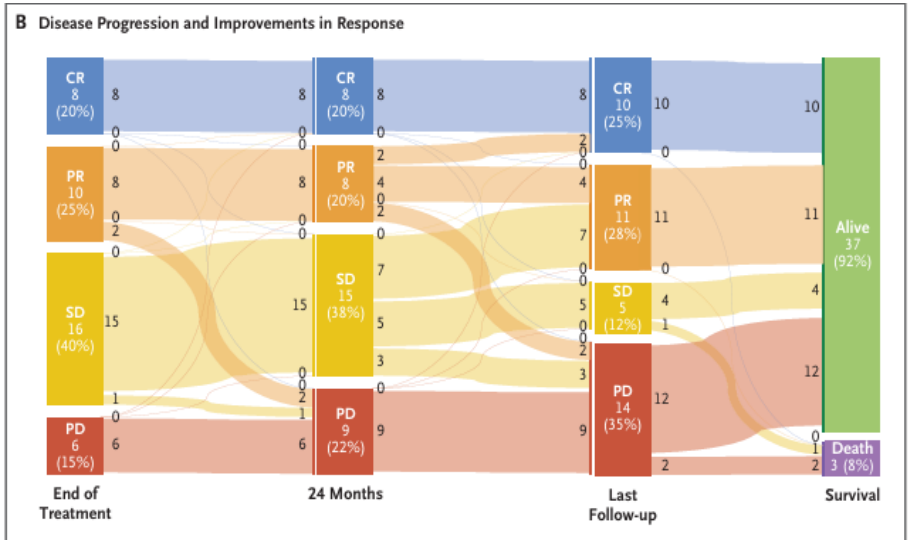
- *Achromobacter xylosoxidans* and BALT lymphoma
- *Coxiella Burnetii* and NHL
- *E.coli* and primary bladder MALT lymphoma
- *Haemophilus influenzae* and pediatric NMZL

HCV and MZL: FIL_BArT

TABLE 2. Lymphoma Responses After Direct-Acting Antivirals in 40 Patients With Hepatitis C Virus–Positive Indolent Lymphomas

	Response, No. (%)				
Histology	**CR**	**PR**	**SD**	**PD**	**ORR**
All (n = 40)	8 (20)	10 (25)	16 (40)	6 (15)	18 (45)
MZL (n = 27)	7 (26)	6 (22)	10 (37)	4 (15)	13 (48)
Splenic (n = 6)	0	0	4	2	0 (0)
Nodal (n = 7)	3	0	3	1	3 (43)
MALT (n = 14)	4	6	3	1	10 (71)
Non-MZL (n = 13)	1 (8)	4 (30)	6 (46)	2 (16)	5 (38)
CD5-NOS (n = 4)	1	1	1	1	2 (50)
SLL (n = 2)	—	1	—	1	1 (50)
LPL (n = 6)	—	1	5	—	1 (17)
FL (n = 1)	—	1	—	—	1 (100)

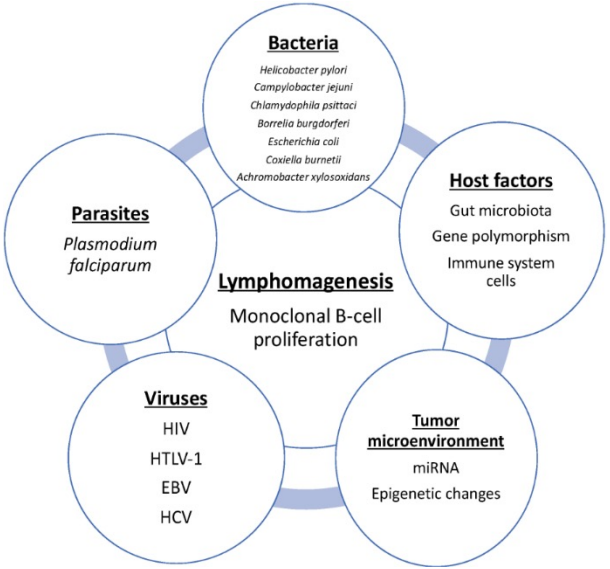
Merli 2022



Merli 2026

Conclusioni

- La linfomagenesi è un processo complesso e multifattoriale
- Alcuni batteri/virus risultano coinvolti (con vari livelli di evidenza) nella patogenesi dei linfomi marginali
- Rilevanza clinica:
  - possibilità di trattare linfomi a decorso indolente con terapie antibiotiche/antivirali (evitando/procrastinando terapie convenzionali)
  - prevenire i linfomi?
- **HP va eradicato in tutti i casi di linfoma MALT gastrico indipendentemente dallo stadio e dalla positività per Hp**
- **Cp va cercata e eradicata nei pazienti con OAMZL nelle aree geografiche in cui l’associazione è risultata più forte**
- **HCV va eradicato in tutti i casi di B-NHL indolente che non necessitino di terapia (convenzionale) urgente**



Biernat 2021