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Chronic Lyme and Co-Infections including Anaplasma : the Irish Experience

Studies of Lyme in Ireland

- Smith, H. V, J. S. Gray, and G. Mckenzie. 1991. "A Lyme Borreliosis Human Serosurvey of Asymptomatic Adults in Ireland." *International journal of medical microbiology* 275(3)
- This paper indicates that 9.75% of samples were seropositive (Borrelia infection).

Studies of Lyme Ireland (2)

- Robertson, J. N., J. S. Gray, S. MacDonald, and H. Johnson. 1998. “Seroprevalence of Borrelia Burgdorferi Sensu Lato Infection in Blood Donors and Park Rangers in Relation to Local Habitat.” *International journal of medical microbiology* 288(2):293–301.
- This shows a lower overall seropositive level 3.4%. *Serum samples were obtained from blood donors in eleven selected locations in Ireland and tested for antibodies to Borrelia The highest seroprevalence (8.7%) was found in Portumna, an area rated as high risk because of the presence of public access woodland harbouring both ticks and spirochaete reservoir hosts*

So does Lyme exist in Ireland?

- Currently we only capture ‘Lyme neuro-borreliosis’ so you need to come to the hospital and get a lumbar puncture to be counted as having Lyme in Ireland.
- We do not keep track of all those infected, or those who present with Lyme manifestation (tick bite and symptoms or ECM) where the antibody test is negative or it is too early to detect the infection by antibody
- There are ticks in Ireland, and some of them are carrying Lyme but no studies done to support. HPSC reports for Ireland 2011-0 cases, 2015-13

So where to Irish get bitten by ticks?

- South County Dublin, Wicklow, Galway, Sligo, Donegal, Limerick, ‘down country’
- Do Irish people travel? USA on J1 Visa, Boston area, NY and LI, Eastern Europe, France, Lanzarote, Canada
- When you travel you can bitten by a mosquito, a sand fly, and/or a tick, and bring back more than you think and its diagnosed as ‘flu’.

High throughput sequencing reveals multiple bacteria in French ticks from Alsace (culture of saliva)

Vayssier-Taussat et al. PLOS One 2013, 8

- *Anaplasma phagocytophilum*
- *Bartonella henselae, B. grahamii*
- *Borrelia afzelii, B. burgdorferi, B. miyamotoi*
- *Neoehrlichia mikurensis*
- *Ehrlichia canis*
- *Rickettsia canadensis, R. felis, R. helvetica*

Symptoms in LD/Co-infections

- **Every organ & organ system can be affected This is a list of some of the LD symptoms by body system and is not an exhaustive compilation of possible symptoms**
- **Neuro:** headaches, facial paralysis, seizures, meningitis, stiff neck, burning, tingling or prickly sensations (parathesia), loss of reflexes, or possible increased or normal reflexes with slow return, loss of coordination and equilibrium.
- **Neuropsych:** mood swings, irritability, anxiety, rage ("Lyme Rage"), poor concentration, cognitive loss, memory loss, loss of appetite, mental deterioration, depression, disorientation, insomnia and numerous mood and psychiatric disorders that were not present prior to lyme disease or are extremely exacerbated by lyme disease.
- **Head:** Headache, neck pain, facial pain and paralysis, difficulty chewing, pain in teeth, dry mouth, decreased sense of taste and smell, numb tongue/mouth, peculiar metallic, salty and other tastes in mouth are also common
- **Eyes:** Pain due to inflammation (scleritis, uveitis, optic neuritis), dry eyes, sensitivity to light, ptosis of eyelids, conjunctivitis, blurry or double vision, floaters, difficulty with eye teaming and convergence, swelling around eyes/bags below eyes.

Chronic Lyme?

- Lyme disease commonly causes additional disease 1 week to 2 years after the initial illness'. In 75% of untreated patients there are additional later manifestations of disease, seen from one week to >2 years after the onset of illness. These include neurologic (meningitis, encephalitis, peripheral neuropathy), cardiogenic (heart block, myocarditis), and arthritis/arthralgias, which may persist for months or years. Immune complexes are found in affected joints. These late manifestations are immunologic in origin and are probably due to antigenic cross-reactivity between Borrelia and host tissues. The Borrelia themselves are rarely detectable at this stage.

Chronic Rickettsiae/Anaplasma?

- Descriptions of Rickettsiae are as follows: ‘Rickettsia is small bacteria and infections tend to persistent or become latent. Rickettsia multiply in vascular endothelium to cause vasculitis of skin, CNS, and liver. Despite immune response there is a tendency for Rickettsia infections to persist in the body for long periods or become latent. There is a persistent asthenia in a small percentage of patients despite response to anti-Rickettsial treatment. The possibility of chronic illness with SGF Rickettsial infections has also been suggested from patients from Australia

Chronic Chlamydia and Mycoplasma?

- The description of chronic Chlamydophilia infections are as follows: The Chlamydia are very small bacteria that are obligate intracellular parasites.
- The clinical effects of C trachomatis and pneumonia infection appear to result from cell destruction and the host's inflammatory response. One of the distinguishing characteristics of Chlamydiae is the ability to cause persistent, often subclinical infections for years. Chronic persistent infection has been implicated in the pathogenesis of several chronic diseases, including asthma, arthritis, and atherosclerosis. However, studies have been hampered with difficulty in a definitive diagnosis of chronic persistent infection, which makes determination of the efficacy of interventions difficult to prove. Descriptions of Mycoplasma pneumonia include the following: in addition to pulmonary infections, Mycoplasma cause a number of extra-pulmonary complications from blood to joint to neurological manifestations

Lyme is not the only cause! Other borrelioses exist

- **Numerous borrelioses**

  (in addition to *Borreliae* responsible for relapsing fever)

  - ***Borrelia burgdorferi sensu lato :***

    B. burgdorferi sensu stricto, B. afzelii, B. garinii

  - **More than 10 other species** of *Borrelia*

- Two species, recently discovered:
  - ***Borrelia miyamotoi*** (Lyme or relapsing fever)
  - ***Borrelia mayonii*** (Mayo Clinic, *Pritt 2016)*

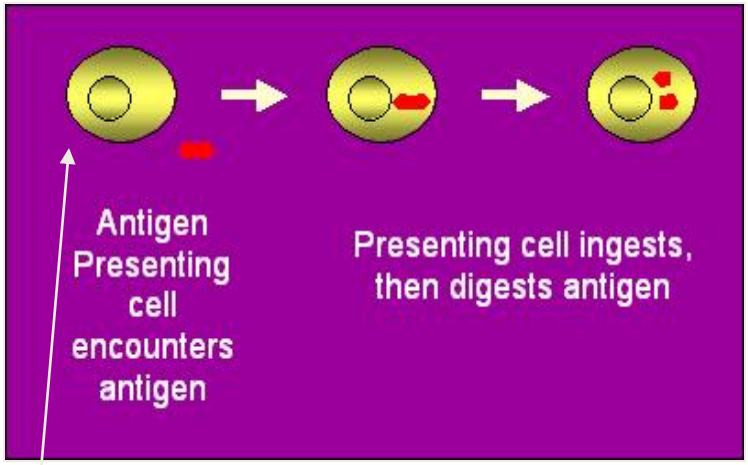
- **For most of them: no diagnostic test available, no cross reactivity**

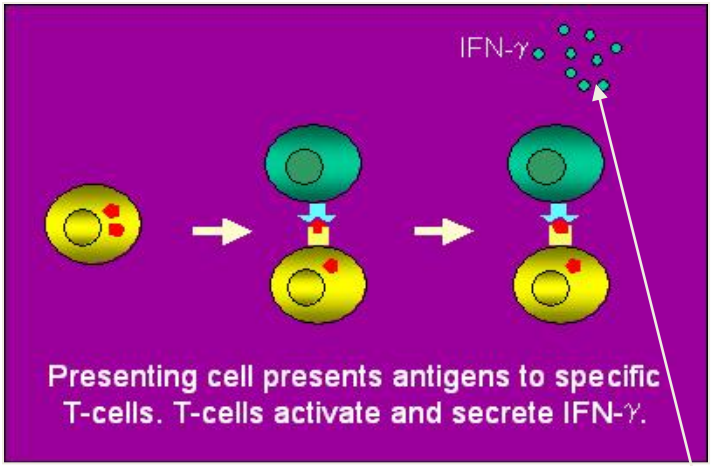
Prevalence and distribution of Borrelia and Babesia species in ticks feeding on dogs in the U.K

- B. burgdorferi s.l. was detected in 94 (2.0%). Four Borrelia genospecies were identified: Borrelia garinii (41.5%); Borrelia afzelli (31.9%); Borrelia burgdorferi sensu stricto (25.5%), and Borrelia spielmanii (1.1%). One Rhipicephalus sanguineus Latreille (Ixodida: Ixodidae), collected from a dog with a history of travel outside the U.K., was positive for B. garinii. Seventy ticks (1.5%) were positive for Babesia spp. Of these, 84.3% were positive for Babesia venatorum, 10.0% for Babesia vulpes sp. nov., 2.9% for Babesia divergens/Babesia capreoli and 1.4% for Babesia microti.

- Med Vet Entomol. 2017 Aug 28. doi: 10.1111/mve.12257

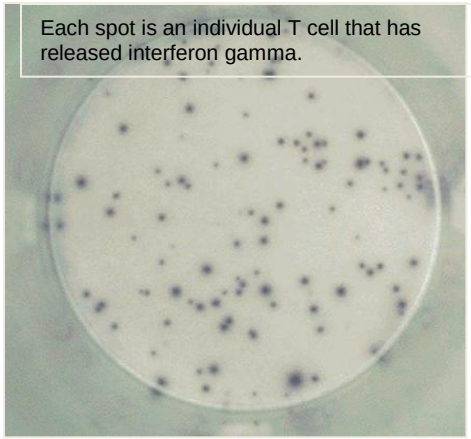
Principal of T cell / IFN-γ based assays for the diagnosis of tuberculosis (Lyme!)





Whole blood or PBMC

Assay with ELISA or ELISPOT



Comparison of Elispot and "Standard" Lyme Testing

Method:

- 35 consecutive patients attending the clinic were enrolled in a pilot study carried out with the UCD National Virus Laboratory.
- Samples were subjected to a panel of tests for a range of diseases.
- Lyme Borreliosis testing was carried out at two locations using "Standard" testing with C6 ELISA and Western Blot test kits and duplicate sample using an Elispot test.
- Databases were merged and a comparison made of test results.

Results

EliSpot and C6 ELISA Tests

Sample size (n=31)	**Lyme Positive**	**%**
EliSpot	26	84%
C6 ELISA	10	32%
C6 Capture rate	38%	
Missed cases	62%	

EliSpot and Western Blot

Sample size (n=13)	**Lyme Positive**	**%**
EliSpot	11	85%
WB	2	15%
WB Capture rate	18%	
Missed cases	82%	

Elispot and two-tier test

Sample size (n=12)	**Lyme Positive**	**%**
Elispot	12	100%
Two-tier	2	17%
Two-tier Capture rate	17%	
Missed cases	83%	

Summary:

- "Standard" tests miss between 62% and 83% of LD cases detected by EliSpot.
- EliSpot test accuracy is supported by positive response with LD treatment protocols and known poor sensitivity

An Audit of 100 patients from an Infectious Disease Practice, Dublin, Ireland, with Lyme-like symptoms

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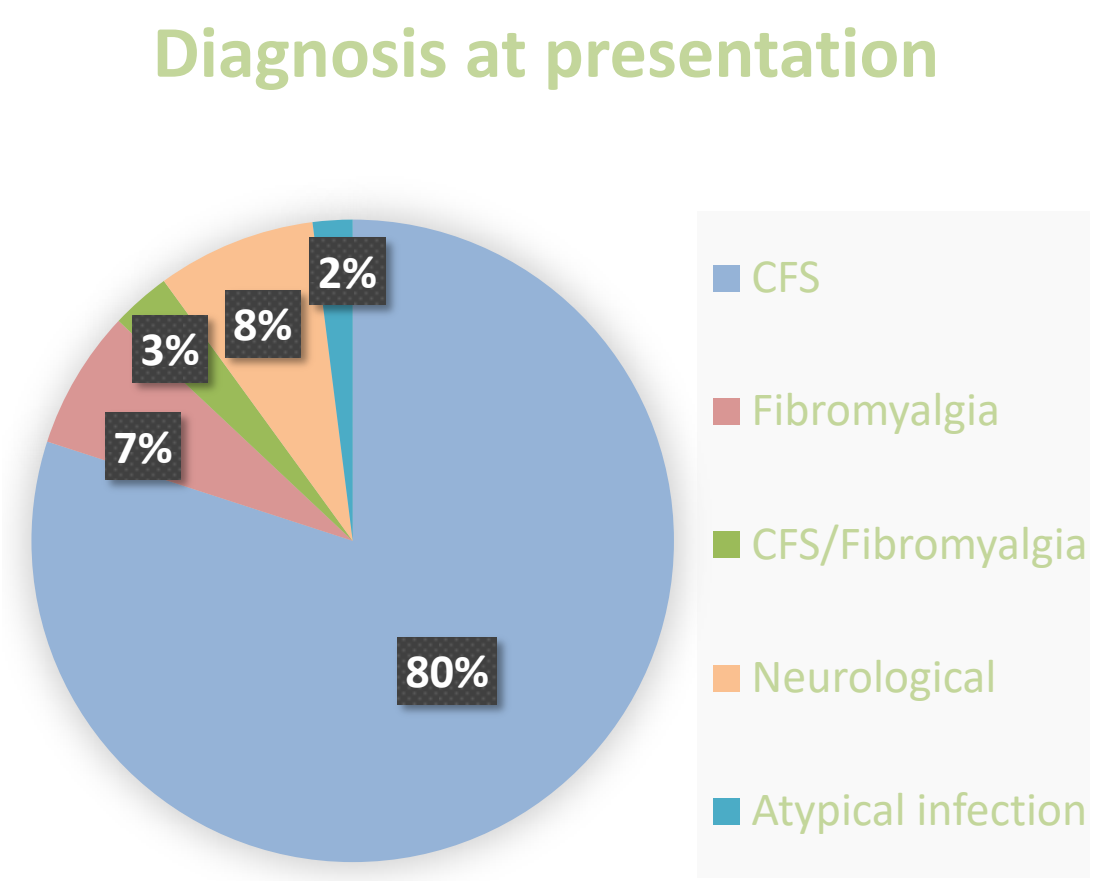
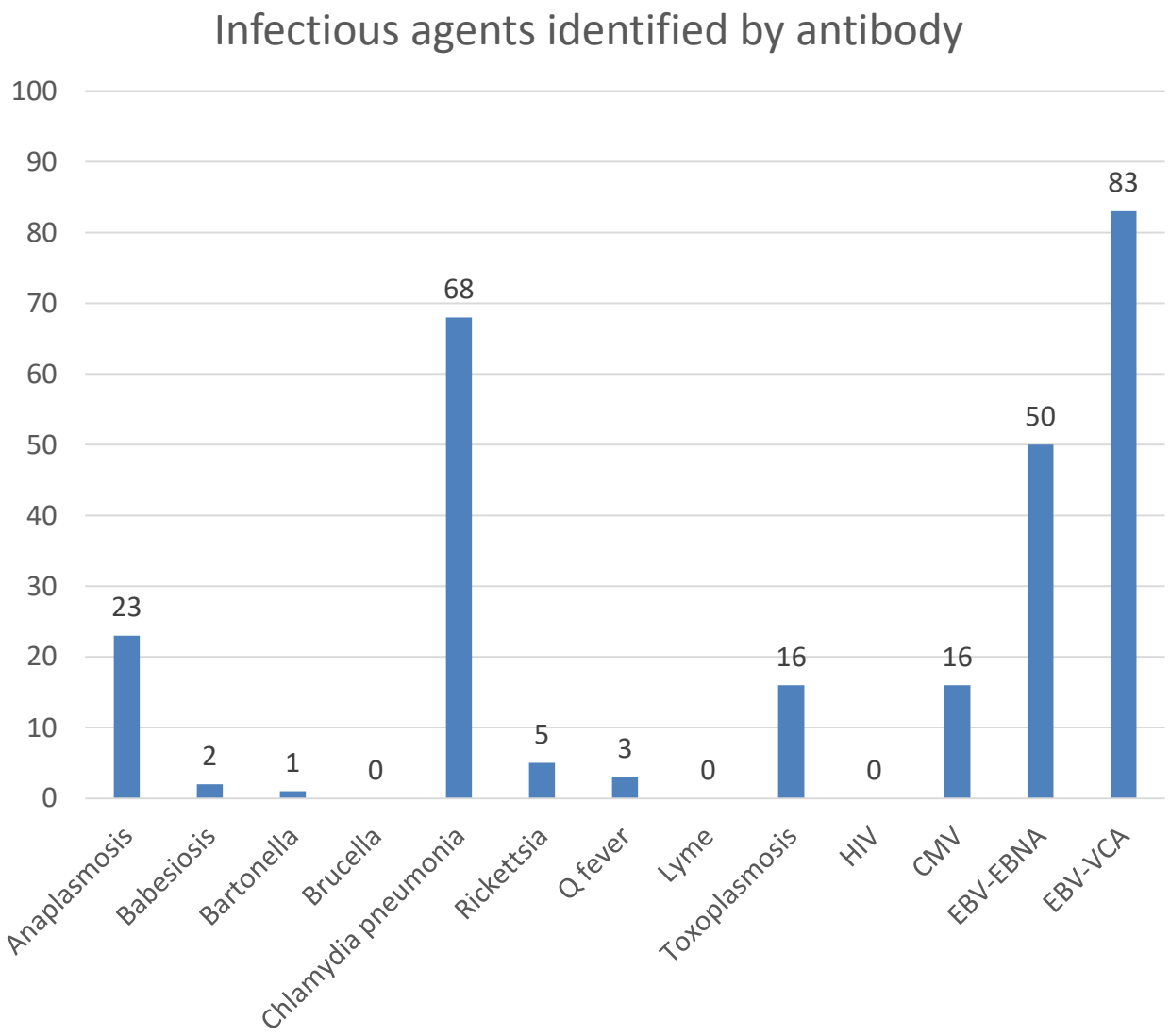
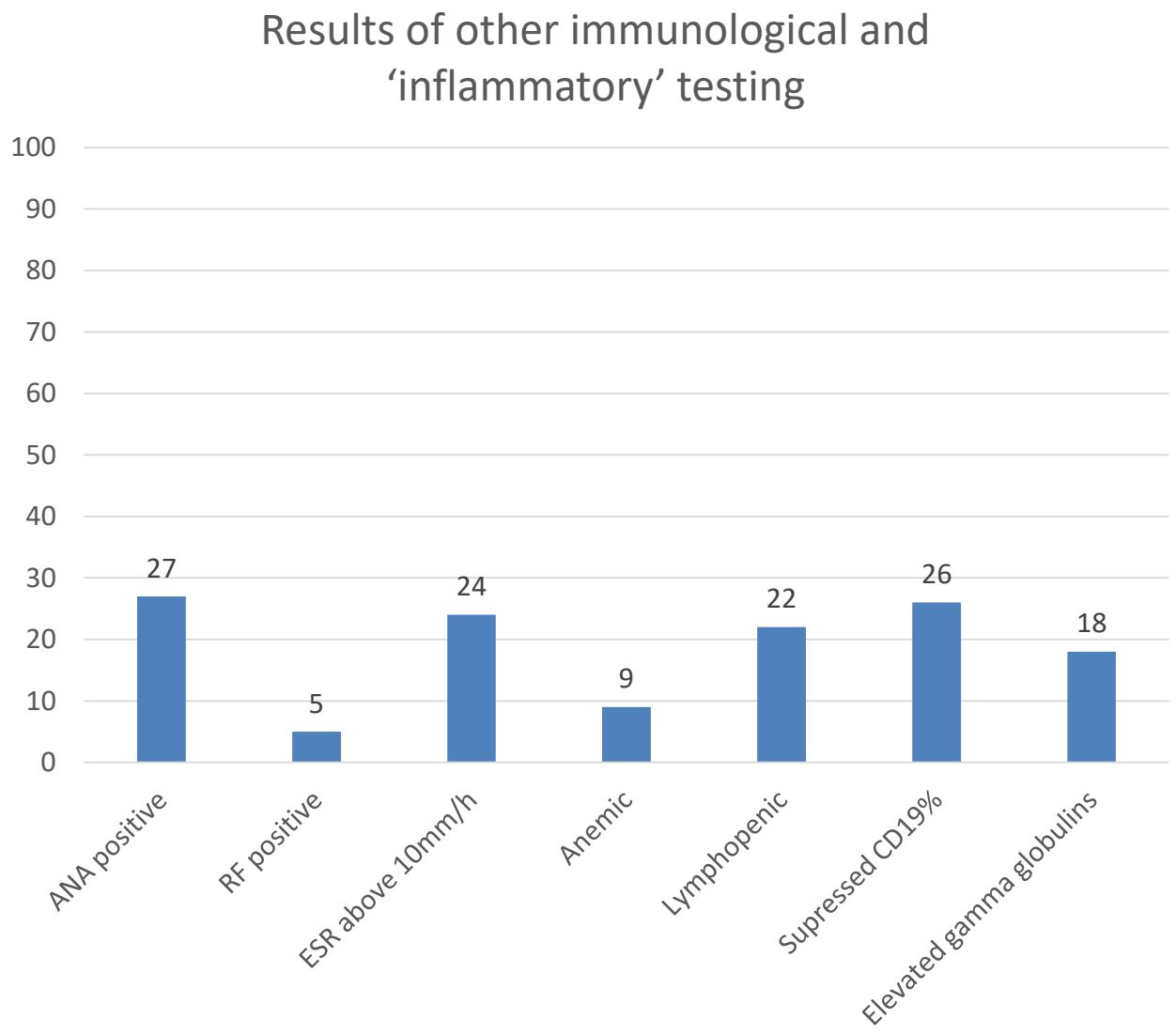
Methods & Results

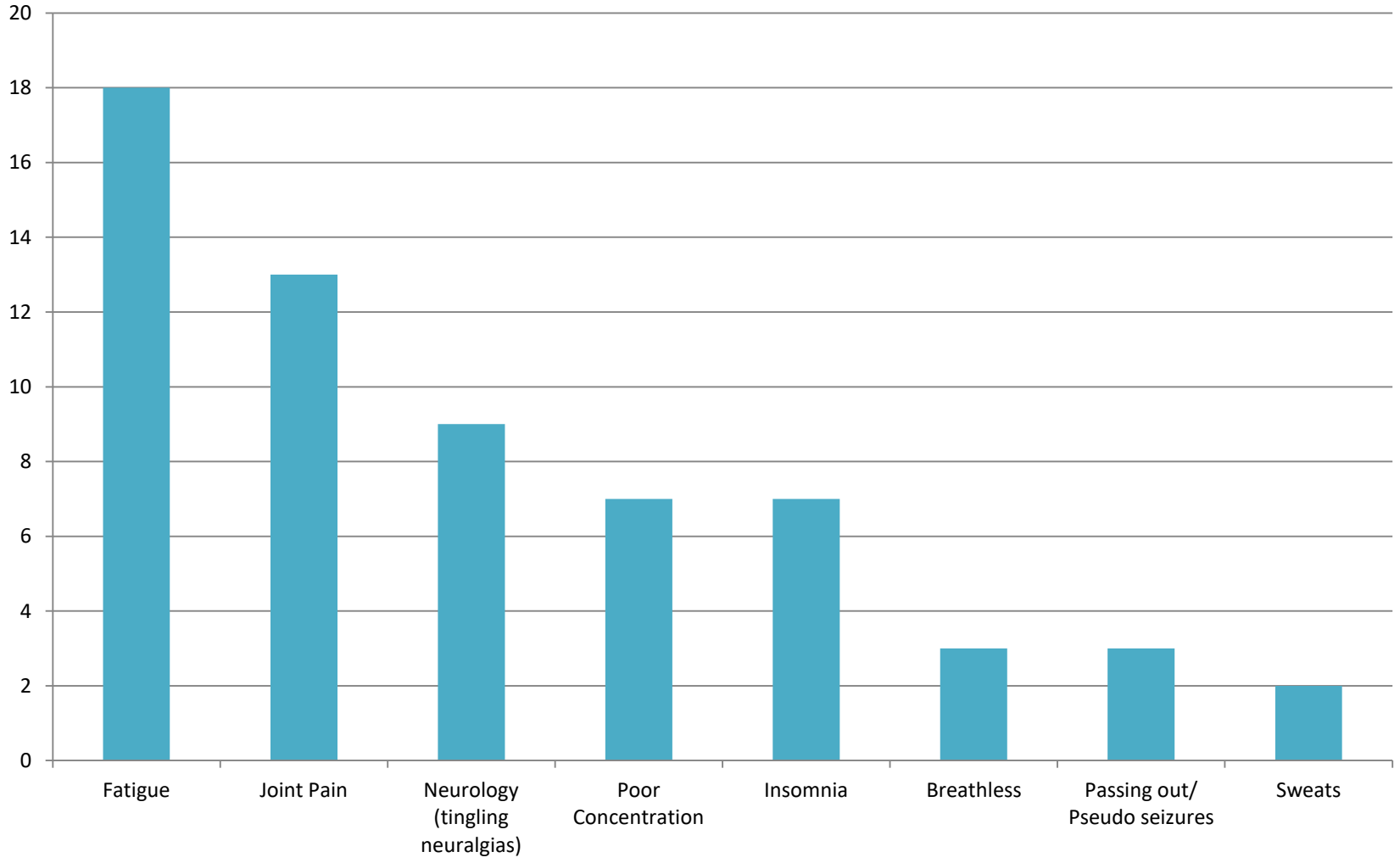



Infectious agents identified by antibody
100
90
80
70
60
50
40
30
20
10
0
23
2
1
0
68
5
3
0
16
0
16
50
83
Anaplasmosis
Babesiosis
Bartonella
Brucella
Chlamydia pneumonia
Rickettsia
Q fever
Lyme
Toxoplasmosis
HIV
CMV
EBV-EBNA
EBV-VCA


Results of other immunological and 'inflammatory' testing
100
90
80
70
60
50
40
30
20
10
0
27
5
24
9
22
26
18
ANA positive
RF positive
ESR above 10mm/h
Anemic
Lymphopenic
Supressed CD19%
Elevated gamma globulins

Anaplasma Symptomatology

(n= 18 evaluable)

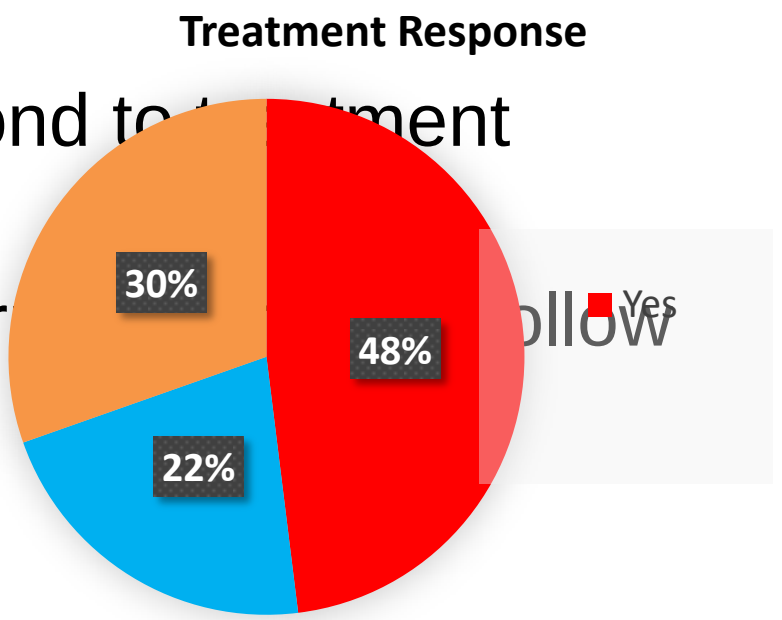


Summary of Irish Diagnostic Tests

- None were positive for Lyme antibody tests though many who went on to get German Elispot tests done were found positive for Lyme
- Other Co-infections: 5-25 positive for Anaplasma, Babesia, Rickettsiae, Q fever, also acquired from tick bites
- Other non-tick borne infections found consistent with patients clinical syndromes: Chlamydia pneumonia

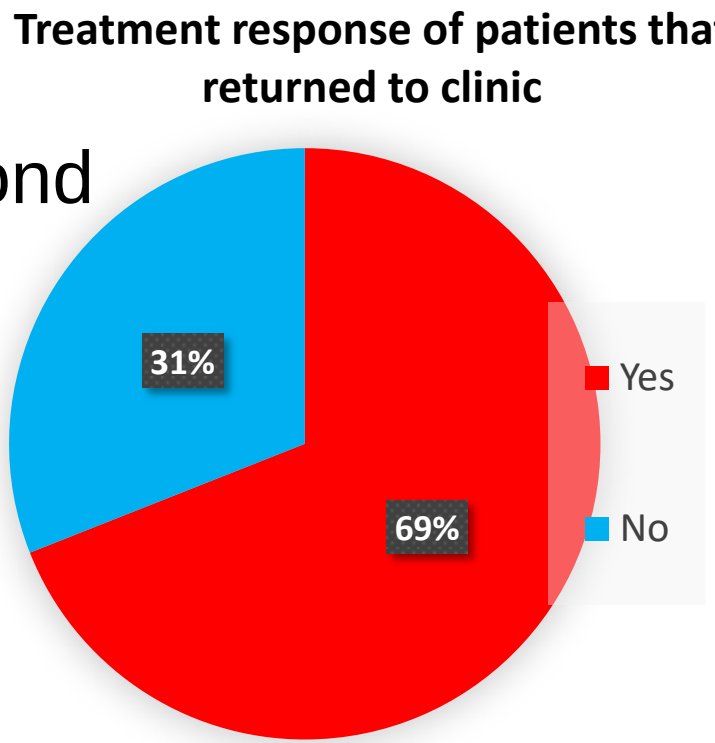
Treatment response

- The patients can be split into three groups after 6 months of treatment:
  - Patients that responded to treatment
    - 49%
  - Patients that did not respond to treatment
    - 22%
  - Patients that did not return for follow up
    - 29%



Treatment response

- Treatment results are available on 71% of patients that returned after 6 months of treatment for review, of whom:
  - 69% responded
  - 31% did not respond



So what got the 69% better?

- Infection-treating with combination antibiotics
- Immunity-boosting immune system with a series of ‘immune supplements’
- Inflammation-agents to decrease the inflammation, including natural products (curcumin/tumeric, LDN)

What gets these patients better?

- A combination of treatments focusing on
- Infection = antibiotics
- Inflammation = natural anti-inflammatories
- Dys-immunity= products to modulate the immune system
- Having an accurate diagnosis: as we cannot culture these organisms we only have indirect measures of infection (immunological assays, which are imperfect in an imperfect host)

What we do not know

- Chronic, persistent manifestations of Lyme and Co-infections have been poorly studied.
- No Infectious Diseases Textbook descriptions of ‘chronic, peristent Lyme, Rickettsiae, Babesia, Bartonella etc in ‘normal’ hosts
- But there is clear medical literature that these infections can stay ‘subclinical’ or ‘dormant’ in your system for many years
- What part of these conditions still represents active infection, what is ‘post-infectious- autoimmunity’ we don’t know, but both infection and auto-immunity is likely both involved

Understanding Lyme and Co-infections

- Often multiple infections, rather than one
- Do some patients have underlying immunological or genetic predisposition that make them more susceptible and less able to clear these infections?
- Do these infections make patients immunocompromised?
- If you have a deranged immune system, is your ‘antibody response’ defective? If you have chronic infection, what is the pattern of antibody decay?
- Are there triggers that reactivate chronic ‘subclinical’ infections?

The paradigm of altered immunity and chronic infection is not new

- HIV: when patients with HIV get a low immune system they get reactivation of all sorts of bacterial and viral infections, and if you treat the HIV with medications, the immune system go back to normal (resolution of CD4 lymphopenia)
- Transplant medicines: if you give too much immunosuppressing medicines to patients with organ transplants, infections flare up (shingles, herpes, Epstein Barr Virus, CMV)
- Lyme and Co-infections are no different

Summary

- The ‘Irish experience’ is not unique, and likely is a ‘snapshot’ of other EU countries.
- Current surveillance and reporting is inadequate
- Current antibody tests, the ‘gold standard’ are missing many patients.
- The finding, in the setting of a negative lyme antibody, of a positive anaplasma, babesia, rickettsial antibody, means previous/current infection by a tick borne infection, probably Borrelia as well
- The ‘German Tests’, much maligned by ID specialists in Ireland, represent an additional tool to identify a Co-infection when other ‘standard testing’ missed the diagnosis.
- Patients are being ‘labeled’ with diagnosis they don’t have, as consultants can figure out what’s wrong with them, Some consultants don’t want to reconsider their diagnosis, even when patients get better with treatment.

ITS COMPLICATED: Where in the world