A Global Update
Lyme disease research from around the world

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The Problem

- Significant uncertainties in diagnosis, treatment and the scale of the problem
- Current serology tests have limitations
- No gold standard test
- No reliable biomarker of disease activity or cure
- Need better tests and treatments
- Need increased awareness - raising the profile of Lyme and Tick-Borne Diseases through reliably sourced information
- Urgent need for UK expertise and UK research
Lyme Disease Top 10

1. How effective are the current UK tests in detecting infections due to the genospecies and strains of B burgdorferi sl in the UK and which single test and what combination of tests performs best in diagnosing or ruling out active Lyme disease. Should stage of the disease and patient age be taken into account when interpreting these tests?

2. What key questions (clinical and epidemiological) should be considered to help make a diagnosis of Lyme disease in children and adults in the UK and would a weighting table be useful?

3. What is the best treatment for children and adults presenting with a) early Lyme disease without neurological involvement and not including erythema migrans and b) late Lyme disease of any manifestation? To include consideration of drug(s), dose, duration.

4. What is the optimal course of action if symptoms relapse after a treatment course is finished?
Results: 78 studies evaluating an ELISA or immunoblot against a reference standard of clinical criteria were included. None of the studies had low risk of bias.

Sensitivity was highly variable:
- Erythema migrans 50% (40 - 61%)
- Neuroborreliosis 77% (67 - 85 %)
- Acrodermatitis chronica atrophicans 97 % (94 - 99%)
- Unspecified Lyme borreliosis 73% (53 - 87%)

Specificity was around 95% in studies with healthy controls, but around 80% in cross-sectional studies.

Two-tiered algorithms or antibody indices did not outperform single test approaches.
Significant Research Challenges

- Resources: funding, human resources
- ‘Red-tape’
- Methodological challenges: sample size, diagnostics
- Technology: frontiers of biomedical research
  ‘Omics revolution’: genomics, proteomics or metabolomics etc.
- Borrelia-related factors
- Human factors: Lyme disease as a ‘Wicked problem’
  - incomplete/contradictory knowledge
  - number of people/opinions involved
  - economic burden
  - interconnected with other problems
Personalised medicine

Individual Host-Pathogen Interaction

Lyme disease
What are we treating?

Green: Infection
Blue: Autoimmunity
Purple: Tissue Damage

Patient 1

Patient 2

Patient 3

Green: Infection
Blue: Autoimmunity
Purple: Tissue Damage
Heat maps of disease and functional categories predicted to be involved in Lyme disease

Jerome Bouquet et al. mBio 2016; doi:10.1128/mBio.00100-16
Novel Next Generation Tests

- **T cell tests (I = Indirect test):**
  - Inatoss: Netherlands
  - Oxford Immunotec: NCT03201042 - ‘LyTIC study’ - USA

- Advanced serology (I)
- Metabolomics (I)
- Advanced PCR techniques (D = Direct)
- Urine antigen detection (D)
- Xenodiagnosis (D)
- Advanced culture techniques (D)
- T2MRI assay (D)
Advanced serology

• **A Five-Antigen Fluorescent Bead-based Assay**

• **Multiantigen panel for improved detection early Lyme disease**
  Lahey et al. *J Clin Microbiol* 2015

• **Global Lyme Diagnostics**
  - Novel chimeritope (chimeric proteins) technology. IgG and IgM
  - Recombinant proteins
  - Screens for multiple US strains and species of Borrelia
  - Designed for use as a vaccine or as diagnostic antigens
  - Derived from multiple diverse OspC variants, strains and species
  - Diversity of targets allows for reduced false negatives

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What on earth are recombinant chimeric proteins?!
Advanced serology

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- 2-tier serology has low sensitivities (29%-40%) for early infection
- Investigation of metabolic bio-signature for detection of early LD
- Liquid chromatography-mass spectrometry (LC-MS)

- 44 metabolite molecules distinguish early Lyme disease patients from healthy controls
- Sugars, peptides, lipids, amino acids, fatty acids, nucleotides

- Improved sensitivity of 88% (84%-95%), and a specificity of 95% (90%-100%)
- Correctly classified 77%-95% of serology negative cases

Molins et al. *Clin Infect Dis* 2015
Advanced PCR Techniques

- Quantification of Borrelia burgdorferi Membrane Proteins in Human Serum: A New Concept for Detection of Bacterial Infection

- Collaboration between Johns Hopkins, NIST, Institute for Bioscience and Biotechnology Research/USA

- Aims to detect membrane proteins from vesicles released by Bb in human serum as a result of innate immune response

- Detects specific Bb proteins eg OspA in very low concentration in early infection

- Proof of concept study

Advanced PCR Techniques

• TGen = Translation Lyme Genomics Institute  www.tgen.org

• Working in partnership with ‘Focus on Lyme’  www.focusonlyme.org

• Currently crowd-funding: https://www.tgen.org/home/news/2017-media-releases/funding-campaign-launched-for-tgen-lyme-disease-test.aspx#.WVjAOc7rvIV

• ‘LymeSeq’ test

• Targeted DNA amplification and sequencing of specific regions Borrelia genome

• Compared to known data-bases: ‘BorreliaBase’  http://borreliabase.org/

• Awaiting Human trials

TGen media release 2017
Urine Antigen Detection

- Ceres Nanosciences: Nanotrap Lyme Antigen test
- ‘Highly sensitive and specific direct test’
- Non-invasive
- Can be used any time in the infection cycle: before and after treatment

Image: Ceres Nanosciences
• ClinicalTrials.gov Identifier: NCT02741609

• Advanced Laboratory Services [www.advanced-lab.com](http://www.advanced-lab.com)

• Multi-centre study to evaluate a direct Borrelia diagnostic test in subjects with early-stage or late-stage Lyme disease (ALSIBDT)/USA

• Culture of Borrelia spirochetes from human serum in subjects with early or late Lyme disease

Persistence: Xenodiagnosis

- ClinicalTrials.gov Identifier: NCT02446626

- Previous small pilot study of xenodiagnosis. Bb was positive in 2 participants and indeterminate in 2 participants

- National Institute of Allergy and Infectious Diseases (NIAID)

- Lead Investigator Dr Adriana Marques

- Currently recruiting n=240

- Aim: To see if ticks can be used to detect B. burgdorferi in people who have had Lyme disease and received antibiotic therapy and if it correlates with persistent symptoms

- Estimated primary completion date 01/12/2020
- Estimated study completion date 01/12/2030
The Study of Lyme disease Immunology and Clinical Events (SLICE)

- Johns Hopkins University Lyme Disease Research Centre
- Principal Investigator: Professor John Aucott
- Aim: To examine risk factors, symptom severity, and immunologic bio-markers in patients diagnosed with Lyme disease over time
- To develop an extensive biorepository of samples and data
- Similar studies: NIAID, USA: NCT00001539
- Slovenia: NCT02147249
Trials of treatment

- NCT02687165: New York State Psychiatric Institute and Columbia University Medical Centre
  Recruiting. Due to complete Feb 2018.
  Neural and Immune Mechanisms of Chronic Pain in Post Treatment Lyme Syndrome
  Brain imaging, sensory, and immune markers/control group
  Response to a combination of SNRI and glutamatergic treatment for chronic pain in PTLS (Milnacipran and D-cycloserine)

- NCT02344537: Meditation and Stretching for Post Treatment Lyme Disease Syndrome
  Principal Investigator: Professor Brian Fallon
Borrelia persister cells

- Borrelia persister cells: *In vitro* research only


- Funding for animal studies is required, followed by human studies
Prophylaxis

• An effective vaccine?

- NCT01504347
  Phase 1/2 Lyme Vaccine Study, Baxter: Austria and Germany
  Completed 2014. Multivalent recombinant OspA

- NCT03010228
  Valneva: USA and Belgium
  Study Assessing the Safety, Immunogenicity and Dose Response of VLA15, A New Multivalent Recombinant OspA Vaccine Candidate Against Lyme Borreliosis, In Healthy Adults Aged Below 40 Years

• Monoclonal antibodies

- MassBiologics: University Massachusetts Medical School
  Pre-exposure, 6 month seasonal prevention, OspA
Lyme disease: 21st Century Dilemmas
Striving for the prevention and treatment of Lyme disease and associated tick-borne diseases

www.lymediseaseaction.org.uk
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