Empirical antibacterial treatment of infection with *Chlamydophila pneumoniae* in Multiple Sclerosis

David Wheldon MB FRCPath

After much controversy there is now powerful evidence for the respiratory pathogen *Chlamydophila (Chlamydia) pneumoniae* being a causal factor in some variants of the neurological illness multiple sclerosis. A series of remarkable studies finds:

• **the presence of *C. pneumoniae* gene sequences in the cerebrospinal fluid of patients who have the disease, and culture of the organism when sensitive cultural methods are used** [Sriram S, Stratton CW, Yao S, Tharp A, Ding L, Bannan JD, Mitchell WM. *Chlamydia pneumoniae* infection of the central nervous system in multiple sclerosis. Ann Neurol. 1999 Jul;46(1):6-14.]

• **an association of new *C. pneumoniae* respiratory infections with episodes of clinical relapse** [Buljevac D, Verkooyen RP, Jacobs BC, Hop W, van der Zwaan LA, van Doorn PA, Hintzen RQ. *Chlamydia pneumoniae* and the risk for exacerbation in multiple sclerosis patients. *Ann Neurol.* 2003 Dec;54(6):828-31.]

• **a statistically significant elevation of *C. pneumoniae*-specific serum antibody levels when the disease shifts into the progressive form** [Munger KL, Peeling RW, Hernán MA, Chasan-Taber L, Olek MJ, Hankinson SE, Hunter D, Ascherio A. Infection with *Chlamydia pneumoniae* and risk of multiple sclerosis. *Epidemiology* 2003 14:2 141-147]

• **antibodies to *C. pneumoniae* in the cerebrospinal fluid of patients with the disease** [**(1.)** Yao, S., Stratton, C.W., Mitchell, W.M., Sriram, S. (2001). CSF oligoclonal bands in multiple sclerosis represent antibodies against Chlamydophila. *Neurology* 56, 1168-76. **(2.)** Fainardi, E., Castellazzi, M., Casetta, I. et al. (2004). Intrathecal production of *Chlamydia pneumoniae*-specific high-affinity antibodies is significantly associated with a subset of multiple sclerosis patients with progressive forms. *Journal of the Neurological Sciences* 217, 181-8.]

• **evidence of active *C. pneumoniae* protein synthesis in the central nervous system, with production of a bacterial protein evoking an antibody shown to cause death of oligodendrocyte precursor cells** [Cid C, Alvarez-Cermeno JC, Camafeita E, Salinas M, Alcazar A. Antibodies reactive to heat shock protein 90 induce oligodendrocyte precursor cell death in culture. Implications for demyelination in multiple sclerosis. FASEB J. 2004 Feb;18(2):409-11.]

•**a peptide specific to *C. pneumoniae* causes inflammatory CNS disease (with some parallels to MS) in rats** [Lenz DC, Lu L, Conant SB, Wolf NA, Gerard HC, Whittum-Hudson JA, Hudson AP, Swanborg RH. A *Chlamydia pneumoniae*-specific peptide induces experimental autoimmune encephalomyelitis in rats.
J Immunol. 2001 Aug 1;167(3):1803-8.]

•***C. pneumoniae* gene transcription in the CSF of patients with MS** [Dong-Si T, Weber J, Liu YB, Buhmann C, Bauer H, Bendl C, Schnitzler P, Grond-Ginsbach C, Grau AJ. Increased prevalence of and gene transcription by Chlamydia pneumoniae in cerebrospinal fluid of patients with relapsing-remitting multiple sclerosis. *J Neurol.* 2004 May;251(5):542-547.]

• **MRI improvement in antibiotic-treated patients with early disease in a small but fastidious double-blind trial of non-immunomodulatory antibiotics** [Sriram S, Yao SY, Stratton C, Moses H, Narayana PA, Wolinsky JS. Pilot study to examine the effect of antibiotic therapy on MRI outcomes in RRMS. J Neurol Sci. 2005 Jul 15;234(1-2):87-91.]

• **MRI improvement, with reduction of the number of Gd-enhancing lesions, in a second treatment study with minocycline** [Metz LM, Zhang Y, Yeung M, Patry DG, Bell RB, Stoian CA, et al. Minocycline reduces gadolinium-enhancing magnetic resonance imaging lesions in multiple sclerosis. *Ann Neurol.* 2004 May;55(5):756.]

• **An association of *C. pneumoniae* in the CNS with MS is demonstrated by immunohistochemical, molecular and ultrastructural methods.** [Sriram S, Ljunggren-Rose A, Yao SY, Whetsell WO Jr. Detection of chlamydial bodies and antigens in the central nervous system of patients with multiple sclerosis. J Infect Dis. 2005;192(7):1219-28.]

The evidence for a causal association of *C. pneumoniae* with majority subsets of MS has been garnered by a surprisingly diverse array of methods; cultural, molecular (both DNA and RNA based), immunohistological, serological (blood and CSF based), animal model, ultrastructural and therapeutic trial. It is this very diversity of methodology which makes the evidence compelling. The subject has recently been reviewed in some detail by Chuck Stratton and myself [Stratton CW, Wheldon DB. Multiple sclerosis: an infectious syndrome involving *Chlamydophila pneumoniae*. *Trends Microbiol*. 2006 Nov;14(11):474-9.]

The results of antichlamydial treatment have been very promising, particularly in early disease.

It should be stressed at the outset that this bacterium is not sexually transmitted. It causes respiratory infection and is spread by droplet infection — coughing and sneezing.

Evidence that *Chlamydia pneumoniae* has a causal association with Multiple Sclerosis: a brief review.

C pneumoniae is known to patchily parasitize the cells which line small blood-vessels, causing episodes of vasculitis. This is a local inflammatory process characterised by tiny punctures in the vessel walls and leakage of blood-components into the surrounding tissue space. It can be visualized directly in the retinal veins, where the vessels appear to be coated with a thin greyish sheath. This sheath is comprised of T lymphocytes. A very similar pathology takes place in the brain in early MS. The association between sheathing of retinal veins and MS was first made in 1944. The anatomical distribution of lesions within the brain in MS is often centred on small veins; elongated plaques may follow the sinuous curves of the vessels they surround. [Esiri MM, ed. *Oppenheimer's Diagnostic Neuropathology*, 2nd edition, 1996 Blackwell: 256-9.] Vasculitic phemomena were recognised surprisingly early: in 1873 Rindfleisch commented: "If one looks carefully at freshly altered parts of the white matter in the brain, one sees with the naked eye a red point or line in the middle of each individual focus, the transversely or obliquely cut lumen of a small vessel engorged with blood. . . All vessels running inside the foci, but also that traverse the immediately surrounding but still intact parenchyma are in a state of chronic inflammation." Rindfleisch had recognized, over 130 years ago, that inflammation of small vessels — *vasculitis* — precedes neural damage.

Examination of the eye reveals retinal vasculitis in about a third of persons with early MS, but it is probably present in far more. It is especially common following optic neuritis (a common precursor of MS), and is characterised by leakage of dye in a fluorescein dye test, blood cells, and cuffing of the vessel walls by inflammatory cells. Where it is seen, there is a raised likelihood that MS will follow.

MS is currently considered an autoimmune demyelinating disease. Myelin is an insulating lipoprotein; its sudden local loss causes the acute MS relapse. But this myelin loss may well be a secondary phenomenon. The very fact that retinal vasculitis is commonly associated with MS casts considerable doubt on myelinopathy being the root cause of MS; myelin, and the oligodendrocyte cells which produce it, are not found in the retina, and the earliest pathological manifestations of MS are in blood-vessels, not nerves and glial cells. Demyelination has recently been shown to be a secondary phenomenon in the acute, typical lesion of MS: the first visible event in a newly-forming fatal MS lesion is the sudden, orderly, non-inflammatory local mass death of oligodendrocytes, the cells which make and support myelin. [Barnett MH, Prineas JW. Relapsing and remitting multiple sclerosis: pathology of the newly forming lesion. *Ann Neurol*. 2004; 55(4): 458-68.] This casts further doubt on the notion of MS as a primary autoimmune disease. The removal of unsupported myelin by inflammatory cells may well be a secondary 'housekeeping' activity. We may be witnessing the beginning of a sea-change in thought. [Chaudhuri A, Behan PO. Multiple sclerosis: looking beyond autoimmunity. *J Roy Soc Med* 2005; 98: 303-306.] These authors cite ten important considerations about MS which cannot be explained by the concept of a myelin-specific autoimmune process.

The epidemiology of MS has been well studied in the Faroe Islands, where MS was unknown until the Second World War. It suggests a communicable factor acquired in early adolescence, starting at about the age of 11. [Kurtzke JF, Heltberg A. Multiple sclerosis in the Faroe Islands: an epitome. *J Clin Epidemiol.* 2001 Jan;54(1):1-22.] This is the age when seroconversion to *C pneumoniae* often begins. Two other organisms posited to initiate MS - Human Herpes Virus 6 and the Epstein-Barr virus - would seem unlikely candidates when this evidence is considered. HHV-6 is acquired by almost all individuals by the age of three. Seroconversion to the Epstein-Barr virus occurs in two peaks; one in very young children and the second in later adolescence and adulthood. Furthermore, Kurtzke's Faroese data suggest an agent which caused outbreaks at 13 year intervals: EBV, due to its close and personal mode of spread, rarely causes outbreaks. The agent which caused MS in the Faroese seemed to be rather ineffectively spread; this is consistent with infection caused by *C pneumoniae*, which is known to be inefficiently transmitted and thus causes patchy outbreaks. In 2000 there were areas of the Faroes free of MS. [Kurtzke JF. Multiple sclerosis in time and space - geographic clues to cause. *J Neurovirol.* 2000;6 Suppl 2:S134-40.] Niki and Kishimoto, with regard to *C pneumoniae* outbreaks, note that 'transmission occurs only after repeated and close contact. Small outbreaks may occur in households and schools where persons have prolonged close contact. Unlike acute viral infections, it may spread slowly.' [Niki Y, Kishimoto T. Epidemiology of intracellular pathogens. *Clin Microbiol Infect.* 1996 Mar;1 Suppl 1:S11-S13.] In an urban environment the situation is different from that of island populations: *C pneumoniae* is ubiquitous; infection is endemic and outbreaks are correspondingly difficult to delineate.

C pneumoniae has been linked to relapsing-remitting forms of disease elsewhere in the body, including asthma, reactive arthritis and coronary artery disease. Causal associations have been made by isolation of the organism and by detection of diagnostically raised antibody levels which subside on treatment. MS can be considered an analogue of these conditions; it is, for instance, characterized by lipid peroxidation, elevated serum homocysteine and antioxidant depletion — a pathology characteristic of chronic chlamydial disease and one likely to be due to local endotoxin activity — but, because it represents an intracerebral infection, shielded from the general circulation, high circulating antibodies are not to be expected. Actually, *C pneumoniae* serology is notoriously difficult to interpret.

A historic study was published by workers at the Vanderbilt School of Medicine in 1999. CSF samples from 17 patients with relapsing-remitting MS, 20 patients with progressive MS, and 27 patients with other neurological diseases (OND) were examined by culture, by PCR and by antibody detection. *C pneumoniae* was isolated from CSF in 64% of MS patients against 11% of OND controls. Polymerase chain reaction assays demonstrated the presence of C pneumoniae MOMP gene in the CSF of 97% of MS patients versus 18% of OND controls. Finally, 86% of MS patients had increased CSF antibodies to *C pneumoniae* elementary body antigens as shown by enzyme-linked immunosorbent assay absorbance values that were 3 SD greater than those seen in OND controls. The specificity of this antibody response was confirmed by western blot assays of the CSF, using elementary body antigens. Moreover, CSF isoelectric focusing followed by western blot assays revealed cationic antibodies against *C pneumoniae*. [Sriram S, Stratton CW, Yao S, Tharp A, Ding L, Bannan JD, Mitchell WM. *Chlamydia pneumoniae* infection of the central nervous system in multiple sclerosis. *Ann Neurol.* 1999 Jul;46(1):6-14.] It should be noted that the methodology used by the Vanderbilt workers is fastidious. In tissue-culture isolation, for instance, repeated centrifugation and prolonged incubation was carried out; this is very important as in chronic infection the organism may produce few of the spore-like elementary bodies, and those that are produced may be damaged. (It is interesting to note that the discovery of *Helicobacter pylori* was made possible by extending traditional incubation times.)

Episodes of relapse in MS patients are associated with new respiratory infections with *C pneumoniae*; [Buljevac D, Verkooyen RP, Jacobs BC, Hop W, van der Zwaan LA, van Doorn PA, Hintzen RQ. *Chlamydia pneumoniae* and the risk for exacerbation in multiple sclerosis patients. *Ann Neurol.* 2003 Dec;54(6):828-31.] The relapse is evidence of host ‘collateral damage’.

At a population level antibodies to *C pneumoniae* rise as the disease becomes progressive [Munger KL, Peeling RW, Hernán MA, Chasan-Taber L, Olek MJ, Hankinson SE, Hunter D, Ascherio A. Infection with *Chlamydia pneumoniae* and risk of multiple sclerosis. *Epidemiology* 2003 14:2 141-147.]

These three seminal papers triangulate the evidence that *C pneumoniae* plays a pathogenic role in the evolution of Multiple Sclerosis.

A schedule of treatment.

This is one schedule that strikes all stages of the organism's life-cycle. Other equally good schedules are possible. It is important that a committed care-giver (for instance, spouse, partner or parent) should ensure that medication is given, and swallowed, consistently.)

Doxycycline 100mg orally once daily is taken with plenty of water.

When this is well tolerated, **Azithromycin** 250mg orally, three times a week should be added. (**Roxithromycin,** 150mg twice daily, is an alternative.)

When all this is well tolerated, the dose of Doxycycline is increased to 200mg daily.

The reason for this slow, step-wise introduction of antichlamydials is to minimize any reactions caused by bacterial die-off. These can be unpleasant. NOTE: in rapidly progressive MS it may be prudent to offset the benefits of stopping progression against the risk of reactions, giving full doses of azithromycin and doxicycline from the beginning.

This combination is taken continuously.

Two or three months into the treatment regimen three-weekly cycles of intermittent oral **Metronidazole** are added. During the first cycle metronidazole is given only for the first day. When metronidazole is well tolerated the period of administration in each cycle is increased to five days. There is no reason for the intermittent use of metronidazole other than acceptability: if someone undergoing treatment is able to take longer cycles of metronidazole then it seems reasonable that they should do so.

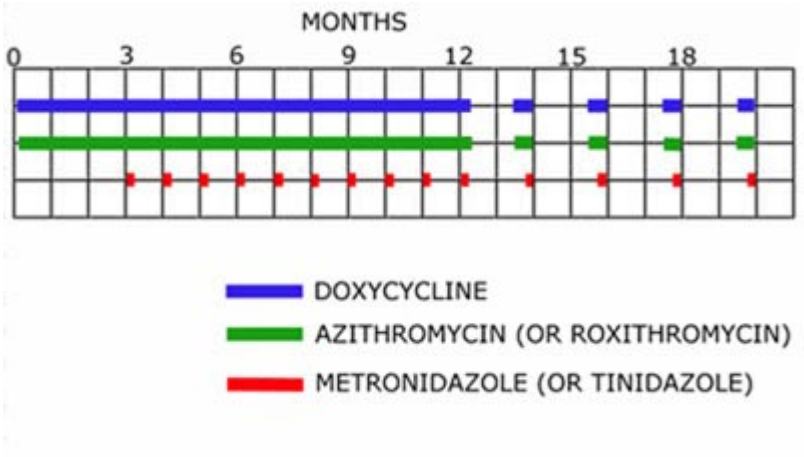
The dosage of metronidazole is 400mg three times a day. If it is suspected that a patient may have a heavy chlamydial load a smaller daily dose may be given initially.

N-acetyl cysteine (NAC) 600mg daily - 1,200mg twice a day, should be taken continuously. This is a commonly-taken dietary supplement, available at health-food stores. It is an acetylated sulphur-containing amino-acid, and may be expected to cause chlamydial EBs to open prematurely, killing them. NAC should be started at the lower dose of 600mg daily; the dose should be doubled when well-tolerated. NAC offers liver protection; this may be useful, as rapid bacterial die-off may compromise hepatic function. If NAC produces unpleasant reactions, its administration may be delayed until antibiotics are well tolerated. Doxycycline and azithromycin may be expected to slowly deplete the chlamydial EB load by destroying them as they enter host cells.

The period of continuous treatment needs to be of the order of a year. This is very important, as the organisms are extremely difficult to remove from certain cell-types. The recommendations for acute infection (typically 2 - 6 weeks monotherapy with doxycycline or a macrolide) *are totally insufficient. The organism is not killed by such treatment, but is instead driven deeper into a persistent state.* This is recognised but not widely appreciated. [See: Woessner R, Grauer MT, Frese A et al., Long-term Antibiotic Treatment with Roxithromycin in Patients with Multiple Sclerosis. Infection. 2006; 34(6): 342-4.] Roxithromycin alone for three 6-week periods did not help these patients; this outcome was predictable. The difficulties of treating persistent chlamydial infections with traditional antimicrobial schedules are ably discussed by Villareal and co-authors [Villareal C, Whittum-Hudson JA, Hudson AP. Persistent Chlamydiae and chronic arthritis. Arthritis Res. 2002;4(1):5-9.] Effective treatment needs to be addressed to all stages of the organism's life-cycle.

The eventual aim is to give all three agents intermittently so that there is some respite from antibiotics. This, the final leg of treatment, may entail a 14 day course of doxycycline and roxithromycin, with a five day course of metronidazole in the middle. This course is given once a month. After several months the intervals between the antibiotics may be cautiously extended. Rifampicin is not suitable for intermittent use, and azithromycin may be given instead.

Here is a graphic representation of a possible course of treatment. The details will vary according to suspected bacterial load:



Adjuncts

The brain has extraordinary powers of repair, but must be provided with the building-blocks by which to do it. This infection is intracellular; the organism interferes with mitochondria, the cells' powerhouses. Many of the symptoms of the disease - particularly the fatigue - may be due to mitochondrial exhaustion. Toxins known as free radicals are released as various synthetic pathways are disrupted. If this oxidative stress continues unchecked for too long irreversible mitochondrial damage may occur. A combined dietary supplementation of antioxidants is strongly recommended. (See Syburra C, Passi S. Oxidative stress in patients with multiple sclerosis. *Ukr Biokhim Zh.* 1999 May-Jun;71(3):112-5.)

Vitamin C 1G daily
E 800iu daily
Omega 3 fish oil daily
Evening primrose oil 1G daily
Acetyl L-Carnitine 500mg daily
Alpha Lipoic acid 150mg daily
Ubiquinone (Coenzyme Q10) 200mg daily
Selenium 200 micrograms daily.
N-acetyl cysteine 600mg twice daily
melatonin 1.5mg at night may be considered.

This may seem like polypharmacy, but there are good reasons to consider these agents. This is because the mitochondrial membrane is the bottle-neck for numerous key cellular reactions, and it is exactly here that chlamydiae hover as they control the host cell and steal its vital molecules via tiny projections. These agents are available at health food stores and are obtainable on-line.

More details on how antioxidants can act synergistically to enhance their effects, and to regenerate each other can be found on page 7.

Apart from mitochondrial support, Vitamin D is needed. There is evidence that a relative Vitamin D deficiency is common in MS, and may allow the disease process to begin. High dose supplementation - 4000iu is recommended. (less may be needed in infections other than MS) This is discussed on page 11.

In addition, B complex, Magnesium, 300mg and Calcium 500mg supplements in the evening (remote from the time of taking doxycycline) daily.

High-dose sublingual Vitamin B12 (methylcobalamin) should be taken; initially 4000 - 5000 micrograms several times a day, reducing to once daily after three months. This is to flood the system with methylcobalamin as there is often a functional B12 deficit, as evidenced by raised serum methylmalonate or homocysteine. Vitamin B12 (together with B6 and folate) counteracts the hyperhomocysteinaemia which

frequently accompanies chronic *Chl pneumoniae* infection and which is thought to cause connective tissue damage. Excess homocysteine is a potent neurotoxin with activity against cortical and hippocampal neurones. [1. Kruman II, Culmsee C, Chan SL, et al., Homocysteine elicits a DNA damage response in neurons that promotes apoptosis and hypersensitivity to excitotoxicity. *J Neurosci* 2000;20:6920-6:] [2. Den Heijer T, Vermeer SE, Clarke R, Oudkerk M, Koudstaal PJ, Hofman A, et al. Homocysteine and brain atrophy on MRI of non-demented elderly. *Brain* 2002;126:170-5:] [3. Leblhuber F, Walli J, Artner-Dworzak E, Vrecko K, Widner B, Reibnegger G, et al. Hyperhomocysteinemia in dementia. *J Neural Tansm* 2000;107:1469-74.] An excellent review of Vitamin B12 and multiple sclerosis can be recommended here: [Miller A, Korem M, Almog R, Galboiz Y. Vitamin B12, demyelination, remyelination and repair in multiple sclerosis. *J Neurol Sci* 2005 Jun 15;233(1-2):93-7.]

Regular *Lactobacillus acidophilus*, daily, either as a supplement or in capsules. This is to maintain bowel flora in the face of antibiotic treatment. Tablets of *Lactobacillus sporogenes* spores may be considered. These have the advantage of getting into the small bowel in large numbers.

It would be wise to avoid foods containing artificial trans-fats. These are hard fats made from unsaturated oils which, after heating under pressure, are hydrogenated in the presence of a catalyst. They are widely used because they have a long shelf life and are inexpensive. With certain exceptions hydrogenated fats are not found in nature, and are metabolized with difficulty in the body. They alter cell and mitochondrial membrane functions. Two studies in animal models have found that artificial trans-fats affect mitochondrial efficiency as measured by a reduction of ATP synthesis. [Blomstrand R, Svensson L. The effects of partially hydrogenated marine oils on the mitochondrial function and membrane phospholipid fatty acids in rat heart. *Lipids*. 1983 Mar;18(3):151-70; De Schrijver R, Privett OS. Energetic efficiency and mitochondrial function in rats fed trans fatty acids. *J Nutr*. 1984 Jul;114(7):1183-91.] Dietary intake of trans-fats increases systemic inflammatory markers in humans. [Mozaffarian D, Pischon T, Hankinson SE, et al. Dietary intake of trans-fatty acids and systemic inflammation in women. *Am J Clin Nutr.* 2004;79:606–12.; Baer DJ, Judd JT, Clevidence BA, Tracy RP. Dietary fatty acids affect plasma markers of inflammation in healthy men fed controlled diets: a randomized crossover study. *Am J Clin Nutr.* 2004;79:969–73.] If the words 'hydrogenated oil' or 'partially hydrogenated oil' appear in a list of ingredients then trans-fats are likely to be present. (It may be noted that dairy products and animal fats also contain a small proportion of trans-fats, but these naturally occurring trans-fats are digestible and were beneficial in animal studies; evidence is less clear-cut in humans. [reviewed by Wang Y, Jones PJ. Dietary conjugated linoleic acid and body composition. *Am J Clin Nutr.* 2004 Jun; 79(6 Suppl): 1153S - 1158S.])

Turmeric, the yellow spice used in Indian cooking, may be very useful. The active ingredient, curcumin, moderates the pro-inflammatory effects of bacterial endotoxin, probably by restraining the activation of nuclear factor-kappa B. 'Nuclear factor kappa B has been implicated in autoimmune and inflammatory diseases, infection, cell survival, and cell transformation with subsequent promotion of cancer.' [Reviewed by Holmes-McNary M. Nuclear factor kappa B signaling in catabolic disorders. *Curr Opin Clin Nutr Metab Care.* 2002 May;5(3):255-63.]

A cautionary note must be sounded. All this is very new and much of it is speculative. It is linking up the work of others. But an empirical trial of antibiotic treatment is surely worthwhile: it would be attempted in any other disease were there even indirect evidence of a treatable pathogen. As an example, one might consider culture-negative endocarditis, where long-term antibiotics are given (often successfully) in the absence of a demonstrable pathogen. MS, as it progresses, can be just as devastating and antibiotics are very cheap by the standards of conventional treatment. In comparison with other drugs they are relatively (but not completely) risk-free.

In treating the disease, it makes sense to use a schedule of antimicrobial agents which is effective against other potential pathogens of the CNS including *Borrelia garini* and *B burgdorferi.* These spirochaetes have been known to cause a serologically negative MS-like illness. Chronic infections with these organisms are generally difficult to detect serologically; the EIA test is particularly prone to giving false negative results. Chronic borreliosis may be much more prevalent than is now believed; *B. burgdorferi* has been identified in avian ticks infesting songbirds [Morshed MG, Scott JD, et al., Migratory songbirds disperse ticks across Canada, and first isolation of the Lyme disease spirochete, *Borrelia burgdorferi*, from the avian tick, *Ixodes auritulus*. J Parasitol. 2005 Aug;91(4):780-90.] and has been posited as a reservoir of borrelial infection in Europe [Comstedt P,

Bergstrom S, Olsen B, et al., Migratory passerine birds as reservoirs of Lyme borreliosis in Europe. Emerg Infect Dis. 2006 Jul;12(7):1087-95.] Given the likelihood of chronic *C pneumoniae* infection causing a decreased efficiency of host systems, one might speculate that chronic *C pneumoniae* infection may prevent resolution of borreliosis. It would also make sense to cover for *Rickettsiae* and *Mycoplasma sp*. and cell-wall deficient forms. MS and other initially relapsing-remitting but ultimately progressive diseases may have a polymicrobial phase: the punctured vasculitis caused by *Chl pneumoniae* would provide an easy portal of tissue-entry for blood-borne organisms. Microbiologists are beginning to recognise that, in many chronic infections, an altered host physiology provides a niche for a host of secondary organisms: an obvious example is chronic HIV disease, where the pathogen which initiates the disease is rarely the pathogen which causes the final event which results in death.

There seem to be a number of factors which need to be in place before MS develops, including chronic *C. pneumoniae* infection and a genetic inheritance which determines a certain kind of response to this infection. Some people have a disease-form which is primarily driven by the infection; it is characterised by rapid progression and intoxication with bacterial metabolites. Untreated it results in a swift decline. This is the form that Sarah had. Paradoxically, it seems very responsive to treatment. Other people seem to have a disease-form where the host reaction predominates; the infection is slow, bacterial numbers are probably few. This seems to be less amenable to antibacterial treatment, and the disease may remain active until the remains of the dead bacteria (endotoxins) are removed. This may be problematic in an enclosed area like the brain. One might speculate that there are even some disease forms where autoimmunity persists autonomously. I think that most people with MS fall somewhere within these extremes. My own experience from advising many people with MS is that those with relapsing-remitting disease and early progressive disease can do well. Patients with later progressive disease respond less well, though this is not always the case. Generally speaking, the earlier that treatment is begun the better the result is likely to be and the more complete the resolution.

People with dense neurological deficits which have been in place for many years and which are situated in confined anatomical bottlenecks such as the cord or cerebellum may recover little function, but treatment may halt disease progression.

In considering treatment, one must make an analysis of risk versus benefit. I believe that a trial of twelve months' doxycycline plus roxithromycin / azithromycin is worthwhile even in late disease, metronidazole being added if benefits occur and / or progression is halted. It is important to go into the trial without undue expectation. Nothing at all can be guaranteed.

Written 29th November 2003; updated 24th June 2007

[This is a version of http://www.davidwheldon.co.uk/ms-treatment.html The webpage is regularly updated.]