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Review Article

Bacterial Infections and the Pathogenesis of Autoimmune Conditions

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Abstract
Bacterial infections are associated with many autoimmune diseases involving chronic inflammation and demyelination. The possible mechanisms of bacterial involvement as aetiological agents or in the exacerbation of these diseases have been investigated intensively. This review focuses the role of bacterial infections in the pathogenesis of autoimmune, inflammatory and demyelinating diseases. Possible modes of pathogenic action of bacteria are discussed, viz. the role of cytokines, Toll-like receptor signalling, the interaction of heat shock proteins with the immune system, and the role of nitric oxide. An auto-regulatory loop might exist in the interaction of bacteria with the host and in pathogenic signal processing. These studies reveal potential therapeutic targets.

Abbreviations: AQP4 Aquaporin-4; AS ankylosing spondylitis; CSF cerebrospinal fluid; EAE autoimmune encephalomyelitis; GB Guillain-Barre syndrome; HLA human leukocyte antigens; HSP heat shock protein; IL interleukin; LPS lipopolysaccharides; MAM Mycoplasma arthritidis antigen; MHC [proteins encoded by] major histocompatibility gene complex; MS multiple sclerosis; NK natural killer cells; NMO neuromyelitis optica; NO nitric oxide; NOS nitirc oxide synthase; PCR polymerase chain reaction; RA rheumatoid arthritis; SLE systemic lupus erythematosus; TLR Toll-like receptors; TNF tumour necrosis factor

Introduction

Bacterial and viral infections are commonplace in a variety of autoimmune and chronic illnesses such as the chronic fatigue syndrome (myalgic encephalomyelitis), fibromyalgia syndrome, Gulf War illnesses and rheumatoid conditions[1-3]. Much attention is focused at present on the role of bacteria and the possible mechanisms of their involvement in the pathogenesis of several diseases. The route of infection and penetration and the immune responses of the host can not only make any bacterial infection pathogenic but probably can also determine the aggressiveness of the disease and the chance for full recovery. Therefore the two basic elements addressed here are the association between bacterial infection and autoimmune disease and the involvement of the immune system in the disease process.

Bacterial infections in rheumatoid conditions

A wide variety of bacterial infections have been associated with rheumatoid conditions. Rheumatic diseases might have a manifold aetiology with varying genetic susceptibility, but bacteria-related autoimmunity might be an important factor[4].

Mycoplasma infection, e.g. by M. pneumoniae, M. salivarum, and M. fermentans, has been strongly associated with RA (rheumatoid arthritis)[5-8]. There is often systemic infection of more than one species[8]. Mycoplasma antigens induce both cell-mediated and humoral immune responses. Enhanced levels of antibodies against MAM (Mycoplasma arthritidis antigen) have been found in sera from RA patients in comparison with antibodies against Staphylococcal enterotoxins A and B. Also antibody titers were higher in RA serum than in systemic lupus erythematosus, ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome, or healthy controls.

The mycoplasma antigen MAM can activate T cells. MAM contains two domains, one of which can inhibit lymphocyte proliferation; the second domain, which contains concanavalin A motif-β, is required for T cell activation[9]. It can also up regulate natural killer cell activity[10]. Furthermore, synovial tissues of RA patients contain T-cells, which bear the same T-cell receptors as used by MAM. The mitogen seems to be capable of initiating and exacerbating arthritic changes[11, 12]. MAM is a zinc-dependent antigen that binds to MHC class II molecules. Zinc induces MHC protein dimerisation required for MAM binding, MHC-induced cell-cell adhesion, and efficient T cell activation[13, 14]. As discussed in later sections, MAM can alter cytokine expression profiles and activate and modulate nitric oxide synthase (NOS) signalling pathways.

Bacterial DNA isolated from rheumatoid arthritis (RA) and juvenile arthritis has included Haemophilus influenzae, Bordatella and Yersinia as possible infecting organisms[15]. Lyme arthritis, which resembles rheumatoid synovial infiltration by Borrelia burgdorferi, has often been suggested to be an autoimmune condition. The B. burgdorferi surface protein A (OspA161-175) is recognised by T-cells and HLA (human leukocyte antigen)-DR molecules that bind this T-cell epitope and to these events is attributed the development of autoimmunity following B. burgdorferi infection. However, these decline with antibiotic therapy[16]. Therefore, in spite of the perceived association, Drouin et al.[17] diligently searched for peptides with sequence homology with OspA (165-173) and have concluded from their study that molecular mimicry might not be significant to pathogenesis. The epitope OspA (163-175) is the predominant epitope associated with Lyme disease. Serum reactivity against OspA is also found in RA patients[18]. Our knowledge concerning the interaction of B. burgdorferi with host tissues and cells is rather scant. Ghosh et al.[19] have suggested cytokeratin 10 as a potential autoantigen. Gavanescu et al.[20] reported that mycoplasma infections can result in the production of autoantibodies against centrosomes. It is not known if this cellular organelle is involved with autoimmunity in RA.

B. burgdorferi seems to be able to induce inflammatory responses including secretion of cytokines and cellular responses of the T-helper cell-1 (Th-1) type[21]. Beermann et al.[22] generated lipoprotein vesicles (LV) from this bacterium and incorporated them into peripheral blood mononuclear cells. The resultant LV-T cells were predominantly the immune effector CD8+. Furthermore, these cells destroyed autologous T-cells carrying LV. These data do indeed support the existence of an autoimmune condition. Overall, a conservative conclusion would be that the molecular mimicry and autoimmunity thesis is yet to be fully tested.

Proteus mirabilis has been implicated in the pathogenesis of RA[23-26] and in osteoarthritis (OA)[27, 28]. Again, the HLA DRB1 alleles appear to be the major genetic susceptibility factors as postulated some years ago[29].

Bacterial infection associated with other autoimmune conditions

Bacterial infections have been identified in association with other autoimmune conditions besides RA. Members of the Enterobacteriaceae family are associated with autoimmune conditions such as Kawasaki syndrome and Graves' disease. Demyelinating diseases have been a focus of active investigation in the past few years. Kollef et al.[30] suggested that central and peripheral nerve demyelination might occur following M. pneumoniae infection. Since then patients with the autoimmune condition SLE (systemic lupus erythematosus) have been investigated for mycoplasma infections. Early studies revealed differences between SLE patients and control subjects in respect of genitourinary mycoplasma infections[31]. However, the deployment of more sensitive methods of detection has not supported these early claims. Runge et al.[32], for instance, found no difference in the incidence of Ureaplasma urealyticum in SLE patients, and they discount the notion that this mycoplasma species has any role to play in the pathogenesis of SLE. Nonetheless, there should be no serious doubts that mycoplasma infection can lead to demyelination.

The demyelinating neuropathy known as Guillain-Barre (GB) syndrome often has pathogenic association with bacterial infections. Campylobacter jejuni, Haemophilus influenzae and M pneumoniae have been implicated as possible causative agents of GB. C. jejuni is the major infecting organism here together with M. pneumoniae infection in some cases[33, 34]. GB is associated with the presence of antibodies against galactocerebroside, which is a major component of myelin[35, 36]. Some bacterial LPS (lipopolysaccharides) apparently bear molecular similarity to the human gangliosides GM1, GM1b, GD1a, and GalNAc-GD1a of the motor axolemma and are said to be the target epitopes for antibodies occurring in the GB subtype acute motor axonal neuropathy. The antiganglioside antibodies cause axonal neuropathy[37]. The host immune response to LPS moieties of the HB93-13 strains of C. jejuni cross-reacts with human nerve gangliosides and induce GBS[38]. .

Multiple sclerosis (MS) is a chronic inflammatory and demyelinating disease of the central nervous system. The pathogenesis of MS is possibly a consequence of autoimmune condition or infection by viral or bacterial agents. Both infections lead to the development of demyelinating plaques. Bacterial infections can evoke immune responses and induce demyelination. Infections of the brain parenchyma are sequestered from the immune system. Matyszak[39] has postulated a loss of the integrity of the blood-brain barrier at the foci of infection by a delayed-type hypersensitivity response leading to demyelination. Nitric oxide (NO), which enhances the permeability of the blood brain barrier, is found in greater quantities in the CSF (cerebrospinal fluid) of MS patients than of control subjects[4]. Also NO metabolite levels reportedly correlate with disease activity[41]. Other explanations have also been advanced. Gay[42] has drawn attention to the putative link of bacterial nasopharyngeal infections with optic neuritis, optochiasmatic arachnoiditis and MS. The possibility is aired that the blood barrier may be by-passed. Gay[42] points out the physical connection between CSF and the lymphatic drainage channels of the nasopharyngeal mucosa. So in the event, the CNS could be exposed to bacterial toxins and generate an immunological response. Many autoimmune diseases involve HLAs. The latter play a key role in antigen presentation to CD4+ Th cells. Specific regions of HLA e.g. HLA-C have robust association with MS and Graves' disease[43].

More recently serology and PCR (polymerase chain reaction) have provided ample evidence of Chlamydia pneumoniae, Borrelia burgdorferi, Mycoplasma species, human herpesvirus-1 and -6, among others in MS, amyotrophic lateral sclerosis Alzheimer's and Parkinson's disease[3]. Parratt et al.[44] looked at Chlamydia pneumoniae-specific immune complexes and have reported that C. pneumoniae infection is more frequent in MS patients and detected early in the course of the disease, presumably indicating an aetiological link. A tentative relationship between MS and streptococcal infection has been suggested[45]. But Budak et al.[46] have found no evidence of C. pneumoniae DNA in CSF samples. Similarly no Mycoplasma-specific nucleic acid sequences were detected[47] (Casserly et al. 2007). Lindsey and Patel[48] found no trace of bacterial 16S

DNA in the CSF of MS patients with progressive diseases or patients in remission. They tested for Campylobacter, Mycoplasma, Chlamydia, Bartonella, Mycobacteria and Streptococcus.

The aetiology and pathogenesis of MS and neuromyelitis optica (NMO) have been studied intensively from another angle in recent years. MS and NMO are related conditions; NMO could be a variant of greater severity than MS. Specific autoantibody responses have been identified in NMO patients. These are AQP4 (Aquaporin-4) antibodies generated against the water channel protein AQP4[49, 50] and they selectively target astrocytic end feet at the glia limitans (the external glial limiting membrane).

AQP4 antibodies are regarded as autoantibodies and so associated with the pathogenesis of NMO. The occurrence of lesions in the brain and spinal cord of NMO patients are consistent with the degree of AQP-4 expression[51]. The damage of astrocytes encountered in NMO is attributed to these antibodies. Serum IgG from patients with NMO binds to the extracellular domain of aquaporin-4; it is predominantly IgG1. Antibody binding to membranes expressing aquaporin-4 probably initiates demyelination[52]. HSP (heat shock protein) 70 has also been implicated in the autoimmune response leading to demyelination[53].

Possible modes of pathogenic action of bacteria

Molecular mimicry in pathogenesis

Most autoimmune diseases are associated with HLA types. RA and AS (ankylosing spondylitis) are classical examples of the association of HLA with rheumatoid conditions. More than 90% of RA patients possess HLA-DR1 or other sub-type and >96% of AS patients reportedly possess HLA-B27[54]. HLA-B27 antigen is also involved in reactive arthritis[55]. Spondyloarthropathies (SAP) are a group of HLA-B27-linked diseases, characterised by inflammatory pain in the spine and asymmetrical arthritis in the lower limbs. HLA-B27 transgenic mice spontaneously develop arthritis and they are susceptible to collagen-induced arthritis[56]. The involvement of HLA antigens in the pathogenesis of autoimmune diseases has been suggested to be due to the molecular similarities between certain bacterial antigens and HLA antigens. But there are no cross-reactive antibodies against bacteria and HLA-B27 in significant titres[57].

The autoimmune conditions of Graves' disease and Kawasaki syndrome are a result of the hyperactivation of the immune system. Bacterial infections have been implicated in both disease states. Yersinia enterocolitica, a member of the Enterobacteriaceae family, produces lipoproteins that are well known for their mimicry of the extracellular domain of the human thyrotropin receptor protein[58, 59]. This lipoprotein is mitogenic to B-cells[60] and induces the production of autoantibodies against the thyrotropin receptor. This could be the cause of hyperthyroidism associated with Graves' disease.

Chlamydial infection occurs commonly in chronic and acute diseases of the upper and lower respiratory tract and. also with atherosclerosis and asthma. Rheumatic autoimmune conditions also often show antibodies against the ribosomal protein L7. The L7 protein has been reported to contain epitopes bearing homology with a specific aminoacid sequence of the C. trachomatis RNA polymerase[61]. This has led to the suggestion that certain rheumatoid conditions could be due to the molecular similarity between L7 and the homologous sequence of the polymerase and generation of autoantibodies.

The autoimmune condition of SLE causes glomerulonephritis, arthritic changes and neurological alterations. SLE is another example of pathogenesis attributable to molecular mimicry between antigens of infecting agents and autologous proteins. As stated earlier, Campylobacter jejuni is the major infecting agent in patients with this disease. Hughes et al.[62] demonstrated the presence of antibodies against the ganglioside GM1 in SLE patients. Campylobacter infection has been linked with the perceived molecular mimicry of bacterial LPS with the human gangliosides of the motor axolemma and these are the target epitopes for antibodies that are believed cause axonal neuropathy[37].

The role of cytokines in the pathogenesis of autoimmune conditions

Another line of evidence that links bacterial infections with RA and other inflammatory autoimmune conditions is the demonstration that bacterial antigens, such as MAM, induce the synthesis of pro-inflammatory cytokines, interleukin (IL)-1, IL-6, and IL-8[63, 64]. Furthermore, the modulation of the synthesis of cytokines by MAM corresponds with the induction of arthritic changes in mice[65]. The induction of IL-13 expression appears to be up regulated in human fibroblast cell lines when the cell cultures are contaminated by mycoplasmas[66]. IL-6 and IL-8 are induced in human gingival fibroblasts by a host of mycoplasma species, e.g. M. hominis, M. arthritidis, M. arginini, M. fermentans, M. penetrans, M. pirum and M. pneumoniae[64]. Glycolipid antigens of M. fermentans have been identified as important mediators of pathogenicity. The induction of TNF (tumour necrosis factor) together with cytokines and prostaglandins was reported some years ago[67, 68]. TNF is produced in response to M. fermentans antigens[69]. TNF-β induced by M. fermentans appears to enhance cytokines that can modulate the immune system. Exposure of human lung fibroblasts to M. fermentans induces IL-6, IL-10 and IL-12, IL-1β, IL-8 (now designated as CXCL8), the monocyte chemoattractant protein-1 (MCP-1) also known as CCL2 (CC chemokine ligand 2), and the chemokine (C-X-C motif) ligand 1 (CXCL1) production[69, 70]. Kawahito et al.[71] used monoclonal antibody against the M. fermentans glycolipid antigen GGPL-III and detected it in synovial tissues from RA patients. The antigen was not detectable in OA or normal synovial tissues. Furthermore, GGPL-III induced TNF-α and IL-6 production by peripheral blood mononuclear cells, and also induced proliferation of synovial fibroblasts. However, anti-phospholipid antibodies are generated in response to a number of bacterial infections[72]. So their presence alone might not be clearly linked with pathogenesis.

Toll-like receptor signalling in immune responses to infection

The generation of immune responses to lipopolysaccharides (LPS) is mediated by a class of receptors called Toll-like receptors (TLRs). These are transmembrane receptors that activate immune cell responses. TLR can recognise molecular patterns associated with pathogenic infectious agents; among them of note are LPS, viral RNA, and unmethylated CpG-oligonucleotides.

The TLR signalling mechanism has been the focus of much attention. Exposure of cells to LPS or other toxins induces the expression of different forms of TLR and different pro-inflammatory interleukins and interferons[73]. Inflammatory responses to M. arthritidis lipoproteins require TLRs[74]. MAM of M. arthritidis has been shown to interact with TLRs[75]. MAM generates a differential immune reactivity mediated by different TLR types. The co-stimulatory molecules associated with the immune stimulation determine the outcome in terms of IL isoform produced and this depends upon which co-stimulatory factor interacts with MAM. Thus inhibition of co-stimulatory factor B7-1 leads to a shift from IL-2 to IL-1[76]. TLR signalling also involves caspases required for processing the precursors of IL-1β and IL-18. The TLRs use the adapter protein MyD88 and the so-called adapter-like MyD88 to activate signaling pathways, but only the latter interacts with caspase[77]. So here we have another potential means of regulating the expression pattern of pro-inflammatory cytokines. In other words, IL production pattern is determined by the co-operation TLRs. TLRs can synergistically or competitively modulate IL expression in immune response to infectious agents[78]. Equally, one can attribute specific TLRs of T-cells with the ability to directly stimulate Th1 and Th2 effector function and modulate the synthesis of cytokines and interferons, and influence cell proliferation and survival[79]. TLR function is closely related to Fcγ receptor (FcγR) expression. The cells of the immune system express receptors for the Fc region of Ig isotypes. FcγR for IgG links IgG mediated responses of the immune system[80]. TLR4 up regulates the expression of FcγR. IL10 is said to be involved in and mediate this up regulation[81]. Probably, as Loof et al.[82] have implied, TLRs might be functioning as a cohort of signalling channels interacting with one another rather than acting individually to generate an immune outcome. TLR signalling might be autoregulated; a concept that is worthy of investigation.

LPS seems to induce the production of interleukins via a TLR-mediated pathway. Exposure of the macrophage RAW264.7 cell line to LPS leads to Janus kinase (JAK)2 tyrosine phosphorylation with TLR4 mediation, then down stream to the phosphorylation of JNK {c-jun N terminal kinase) resulting in IL production[83].

Finally, TLR signalling is involved in the activation of innate immunity in defence from infections not only bacterial, but also viral and parasitic. NK cells, macrophages, dendritic cells are all capable of enlisting TLRs signalling in their function. The recognition of bacterial infection by NK cells seems to be mediated by TLR[84, 85]. Other infections e. g. by the parasitic protozoan Leishmania major, result in the induction of IL-12 in bone marrow-derived dendritic cells, IFN-γ expression and activation of NK cells. These events are mediated by TLR9[86].

The interaction of heat shock proteins with the immune system

Heat shock proteins (HSP) are a highly conserved family of stress-related proteins with diverse function such as protein folding and chaperoning, and novel and differential modes of function have now been ascribed to their functional repertoire. HSPs might chaperone antigenic peptides.

Antibodies against a number of HSPs have been detected in autoimmune diseases. Marked increases in antibodies against HSP70 and HSP90 occur in patients with RA[87], Klebsiella pneumoniae HSP60 in ankylosing spondylitis patients[88], HSP27 and HSP90 antibodies in patients with arthritis accompanying cystic fibrosis[89] and so on. T lymphocytes react to heat shock proteins and this probably plays an important regulatory role in the progression of autoimmune diseases. HLA-DR-T cell epitopes have been identified in HSP60 and HSP70[90-92]. In experimental systems HSP60 induces the production of IL-8 and TNF (tumor necrosis factor)-α and this is enhanced by HSP auto-antibodies. Sera from RA patients with higher anti-HSP60 auto-antibody titers also markedly increased the IL-8 production induced by HSP60 in a human monocytic cell line[93]. As yet, it is unclear what role HSP auto-antibodies might play in pathogenesis.

HSP are known to be able to influence both innate and adaptive immune response and induce the expression of interleukins under a variety of experimental conditions. Some HSPs induce and other can inhibit the production of interleukins. Bacterial HSPs bear sequence homology to human HSPs, and immunisation with bacterial HSPs has often inhibited disease progression[94]. Several HSP receptors have been identified to-date on antigen presenting cells. Among them are the Toll-like receptors TLR2 and TLR4. HSPs are recognised by appropriate receptors to initiate their participation in the signalling cascade[95, 96]. Singh et al.[97] showed that heat shock activated transcription factor HSF-1 (heat shock factor-1) binds to heat shock responsive elements in the promoter of genes coding for certain interleukins.

The TLR signalling pathway has been robustly implicated in HSP function. HSPs recognise and bind to pathogen-associated molecules and activate TLR mediated signalling. It appears possible that different HSPs might differentially activate TLRs thus determining the functional pathway. Thus HSP60 is said to bind to TLR1 but not to TLR2[98]; this could have differing consequences in terms of induction of cytokines. HSP70 bound to the cell membrane is said to specifically activate NK cells, whilst intracellular HSP70 exerts immunomodulatory effects by binding specifically to TLR2 and TLR4. In vitro studies have suggested that HSP70 is actively released in response to heat shock and induces the production of IL-10 in fibroblast-like synoviocytes by TLR4 signalling[99]. HSP72 induces IL-8 expression by activating TLR4 and NF-kappa B[100].

<u>The role of nitric oxide in the pathogenesis of autoimmune, inflammatory and demyelinating diseases</u>

Nitric oxide (NO) is synthesised by NO synthase (NOS) which occurs as neuronal, endothelial and inducible isoforms. NO subserves many functions. Most prominently, it is a vasoactive agent regarded as contributing significantly to the pathogenesis of inflammatory immune and neurodegenerative diseases. RA, SLE, MS, and experimental autoimmune encephalomyelitis (EAE), an experimental model of MS, all show associated synthesis of NO, superoxide and their toxic products. Upon infection bacterial components bind to macrophages using TLRs and this leads to the production of TNF-α, which in turn induces to the synthesis of NO. NO is also expressed by cells when exposed to IFN-γ. NOS is required for bacterial clearance during infection[101]. The general and overall effects would be bactericidal in nature.

Arthritic changes occurring in an animal model called adjuvant-induced arthritis, which exhibits features similar to those of RA, accompany the induction of NOS. Furthermore, NOS inhibitors suppress the arthritic changes[102]. Mouse peritoneal macrophages and a macrophage cell line have been reported to synthesise NO in response to MAM. This is enhanced by LPS possibly via TLR2 but not TLR4 signalling[103, 104]. M. hominis lipophilic component also interacts with TLR2 not TLR4[105]. M. synoviae lipoprotein lipid moiety induces NO secretion by chicken macrophages[106].

Nitric oxide (NO) enhances the permeability of the blood brain barrier. The invasion of the CNS by inflammatory cells and the development of EAE are prevented if the toxic product peroxynitrite of NO and superoxide are scavenged[107]. Both constitutive isoforms of NOS, neuronal and endothelial, and inducible NOS are active in the demyelination process[108]. NOS has also been implicated in the pathogenesis of Parkinson's disease[109].

Demyelination can be induced by mycoplasmas. NO, inflammatory cytokines, and prostaglandins are induced when glial cells are exposed to M. fermentans antigens[68]. Heat shock inhibits both NO and iNOS (inducible NOS)[110, 111]. Bacterial LPS-induced expression of NOS can be inhibited by exposure of cells to hyperthermia at 43°C. Transfection of HSP70 reduces iNOS expression[111, 112]. From the foregoing discussions one can visualize a complete regulatory picture of the involvement of HLAs, HSPs, cytokines and nitric oxide in the pathogenesis of inflammatory immune diseases.

Although NO is harmful to bacteria, it can induce apoptosis in some cell systems[113] and cause necrosis (see Naito et al.[114]). The toxicity of NO can result in immune suppression and in turn lead to enhanced infection[115]. Bacteria also seem to have evolved protective mechanisms against these deleterious effects. So host resistance to bacterial infections and the ability of bacteria to initiate inflammatory and demyelinating conditions leading to pathogenesis are finely tuned. The understanding of the control mechanisms has not only expanded our knowledge of the possible modes of bacterial involvement in pathogenesis, but it has also led to the identification of potential targets for therapy. The activation of signalling pathways mediated by TLRs has afforded an avenue of therapeutic approaches to autoimmune conditions. TLR signalling together with its cognate receptors and adapter molecules can conceivably be employed as specific targets for therapeutic intervention. The TLR agonists have been found to enhance immune responses, especially against tumours[116]. Some agonists have been approved for the treatment of certain human disease conditions[117, 118]. There is also much scope for the detection of bacterial infections via TLRs. As discussed earlier the TLR signalling pathway might be implicated in potential crosstalk with other interacting signalling systems. In other words, a composite regulatory operation of many pathways involving TLRs can be delineated in the pathogenesis of autoimmune diseases.

It would not be out of place to inquire here into the potential clinical benefits of studying the role of bacterial infections and the mode of their participation in the disease process. The prevention of disease progression is one of the benefits, in which not only the identification of the infecting agent but also the mode by which the infectious agents might trigger initiation and progression would make a valuable contribution. Specifically targeted intervention modalities using antibacterial therapy can evolve and develop from such basic research. Also these would find much application in the development of healthcare facilities such as antimicrobial 'stewardship' programmes and infection control programmes to monitor effects of treatment and treatment costs[119]. Unavoidably the cost effectiveness of treatment regimes comes into reckoning. This makes it imperative that factors which determine antibiotic-resistance of bacteria are identified and adequately addressed.

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COMPETING INTERESTS
None Declared

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