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Campylobacter infections of the pericardium and myocardium

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ABSTRACT

Members of the genus *Campylobacter* are notorious for their ability to cause gastroenteritis. However, increasing numbers of case reports now suggest that they may have a wider pathogenic repertoire. Pericarditis and myocarditis are increasingly being recognised as sequelae of *Campylobacter* infection. Although rare, these presentations are important, as misdiagnosis may result in inappropriate thrombolysis or angioplasty, with potential accompanying complications. Extraintestinal *Campylobacter* infections, and the resulting pathogenesis, remain an important challenge for the 21st century, particularly as immunocompromised patients are likely to become increasingly common.

Keywords *Campylobacter* spp., myocarditis, pericarditis

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The genus *Campylobacter* gained much of its notoriety from the ability of members of the genus to cause gastroenteritis. *Campylobacter jejuni* enteritis is the commonest enteric infection in the developed world, with an annual incidence as high as 1 in 1000. However, increasing numbers of case reports now suggest that *Campylobacter* spp. have a wider pathogenic repertoire than originally thought. Thus, *Campylobacter fetus*, type species, has been identified as the causative agent of pericarditis in at least ten documented cases [1–10]. In these cases, patients present typically with a history of several weeks of non-specific symptoms, including fever, weight loss, cough and chest pain. Significantly, there is no reported association with gastrointestinal symptoms in these cases. *C. jejuni* pericarditis is also an extremely rare entity, with only one reported case [11], in which the patient suffered from a congenital immunodeficiency, X-linked agammaglobulinaemia. The disease process ran an aggressive course, and the patient was hospitalised for 6 weeks. Pericarditis was an element in a presentation of systemic campylobacteriosis in which both lungs and pericardium were significantly invaded. *C. jejuni* was isolated from blood cultures, pleural effusion aspirate and pericardial effusion aspirate.

There have also been six reported instances of *C. jejuni*-associated myocarditis [12–17] and six cases of *C. jejuni*-associated myopericarditis [7–22], all of which involved immunocompetent hosts. The typical clinical presentation involved transient acute chest pain, with concomitant electrocardiogram changes and elevated levels of cardiac enzymes, in association with antecedent or coincident enteritis. In one case of *C. jejuni* myocarditis, left ventricular function was severely compromised for several months following infection [14]. In another, the patient suffered acute left ventricular failure on the second day of admission, which subsequently resolved within 24 h [16].

The precise mechanism by which *Campylobacter* mediates myopericarditis remains unknown, although there are several interesting putative mechanisms. The first involves direct attack of the pericardium or myocardium by the bacterium or its toxin following an episode of bacteraemia. However, while *C. fetus* is almost invariably isolated from blood in instances where the pathogen is linked to myopericarditis, the same cannot be said for *C. jejuni*. Thus, the infective agent was isolated from blood in nine of the ten cases of *C. fetus* pericarditis (in the remaining case it was isolated from the pericardial fluid [3]), while there was not a single instance among the

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12 cases of *C. jejuni*-associated myocarditis and myopericarditis in which the organism was isolated from blood. In these latter cases, the causative agent was identified on the basis of positive stool cultures and/or serological analyses.

Subtle differences in the presentation of *C. fetus* and *C. jejuni* myopericardial infections may be explained by nuances in their pathogenicity. Extraintestinal manifestations of *C. fetus* are legion, and result typically from direct pathogenic invasion. Conditions described include septic abortion, meningoencephalitis, brain abscesses, subdural empyema, septic arthritis, vertebral osteoarthritis, osteomyelitis and lung abscesses [5,6]. The spectrum of extraintestinal sites of infection has been linked to the pathogen's ability to elude the host immune system by means of surface-layer proteins. These proteins render the pathogen simultaneously impervious to complement attack and act as a means of antigenic variation. This 'S-layer protein' impedes the binding of complement C3b to the microbial surface, thereby rendering it resistant to antibody and phagocytic attack [23].

It is feasible that this protein coat, which affords *C. fetus* protection against the host's immune system, enables the pathogen to use the bloodstream as a system of transport from the gut to secondary sites of infection, particularly in a host whose immune system is weakened partially by chronic disease. Six of the case reports involved patients with concomitant chronic disease, namely rheumatic fever [1], lymphoma [2], hypothyroidism [3], polycystic kidneys [4], β-thalassaemia [5] and diabetes mellitus with hypertension [6]. *C. fetus* pericarditis appears to be the result of colonisation of the pericardium following bacteraemia and septicaemia; hence the presentation with non-specific symptoms such as fever, malaise and weight loss. *C. jejuni* lacks the S-layer protein coat, and appears to cause pernicious bacteraemia only in a profoundly immunocompromised host [11]. It may well be that direct microbial invasion of the pericardium via the blood is the patho-aetiogenesis of *C. fetus* pericarditis, but not of *C. jejuni* myopericarditis.

The second pathogenic paradigm involves a type II hypersensitivity reaction, in which antigens within *Campylobacter* and/or its toxin cross-react with pericardial antigens; alternatively, *Campylobacter* and/or its toxin may display antigens similar to those of the pericardium. This molecular mimicry may temper the host's immune response against the invader. Antibodies generated against the invading pathogen thus attack both pericardium and pathogen. There is typically a temporal window of several weeks between the primary infection and the development of hypersensitivity reactions.

In all except two of the cases in which *C. jejuni* has been implicated in myopericarditis and myocarditis, the gastrointestinal and cardiac symptomologies were coincident, making an immunological aetiology unlikely. In the two exceptions, both patients presented with cardiac involvement 2 weeks after the onset of enteric symptoms [18]. In addition, both patients suffered from concomitant reactive arthritis. Interestingly, *C. jejuni* has been linked to a number of pathologies by means of immunological mechanisms. Thus, reactive arthritis is a recognised complication in 1% of symptomatic *C. jejuni* enteric infections. Similarly *C. jejuni* enteritis is an antecedent event in 26–41% of patients suffering from Guillan–Barré syndrome. There is typically a period of several weeks between the onset of enteric symptoms and the development of these pathologies.

With the advent of antibiotics, it was thought that mankind would be finally victorious in the war against microbial infection. However, three interlinked phenomena have tilted the balance of power surreptitiously towards the pathogen. The first is antibiotic resistance, with the increasingly liberal use of antibiotics within human and animal populations [24]. The second is the increasingly common pathogenically or iatrogenically immunocomprised patient. The third is the phenomenon of increasingly epidemic enteric pathogens, such as *Campylobacter* spp. Such organisms use their pandemic status in the form of enteritis as springboards to attack other organ systems by novel pathogenic mechanisms, which currently remain unidentified. In particular, pericarditis and myocarditis are recognised increasingly as sequelae of *Campylobacter* infection. Although rare, they are noteworthy manifestations of infection with this pathogen, as misdiagnosis may result in inappropriate thrombolysis or angioplasty. Extraintestinal *Campylobacter* infections and pathogenicity remain a challenge for the 21st century, particularly as immunocompromised patients are likely to become increasingly common.

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