Association between HACEK bacteraemia and endocarditis

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We retrospectively examined medical records of 87 patients with bacteraemia caused by members of the HACEK group (Haemophilus parainfluenzae, Aggregatibacter actinomycetemcomitans, Aggregatibacter aphrophilus, Aggregatibacter paraphrophilus, Cardiobacterium spp., Eikenella corrodens and Kingella spp.) to determine whether endocarditis was present, as defined by the Duke criteria. The overall positive predictive value (PPV) of HACEK bacteraemia for endocarditis was 60 %. The PPV varied with different HACEK species from 0 % (E. corrodens) to 100 % (A. actinomycetemcomitans).

METHODS

A case was defined as a patient with at least one positive blood culture with a HACEK bacterium. Definitions of definite and possible infectious endocarditis were according to the Duke criteria (Li et al., 2000).

Cases were identified from May 1979 to February 2011, through electronic databases from microbiology laboratories at Christchurch Hospital (Christchurch, New Zealand), Auckland City Hospital (Auckland, New Zealand), Middlemore Hospital (Auckland), North Shore Hospital (Auckland) and Wellington Hospital (Wellington, New Zealand).

The clinical notes of all cases were reviewed and the relevant clinical information transcribed onto a standard data sheet. The clinical data obtained included patient demographics and co-morbidities, number of positive blood cultures, echocardiography findings, antibiotic therapy and mortality at 1 year. During review of the clinical notes, the diagnosis of endocarditis was determined in accordance with the modified Duke criteria by an infectious diseases physician or trainee, and was subsequently recorded in the data sheet. All data sheets were then analysed by H. S. Y., S. T. C. and D. R. M.

Ethics approval was obtained from the New Zealand Ministry of Health Multi-region Ethics Committee.

RESULTS

Overall, 87 cases of HACEK bacteraemia were identified, of which 81 were from the period between 1995 and 2010. In total, 52 of the 87 cases had endocarditis (PPV 60 %). The characteristics of the cases by HACEK species are shown in...
Tables 1 and 2. The PPV of bacteraemia for endocarditis varied with HACEK species, ranging from 100% for *A. actinomycetemcomitans* and *A. paraphrophilus* to 0% for *E. corrodens*.

The eight cases of *H. parainfluenzae* bacteraemia who did not have endocarditis had the following foci of infection identified: meningitis (one case), appendicitis (one case), epidural abscess (one case), urosepsis (one case), presumed contaminant (one case) and unknown focus (three cases).

Of the 18 cases of *A. actinomycetemcomitans* bacteraemia, all had a diagnosis of endocarditis. Three cases had either reinfection or relapse (Chu et al., 2005; Tornos et al., 2011). The first case had a mechanical aortic valve and diabetic nephropathy requiring dialysis, was treated with 42 days of ceftriaxone, became reinfected 9 months later and died. The second case had a mechanical mitral valve and had reinfection 3 years later. This was treated with 42 days of ceftriaxone but relapsed 11 days later, before a curative reoperation with mitral valve replacement was performed. The third case had a pulmonary artery homograft valve with 10 days of antibiotic therapy. This patient also had a biopsyprosthetic aortic valve replacement in the setting of a congenital ventricular septal defect and was treated with 42 days of ceftriaxone but relapsed 6 months later. *A. actinomycetemcomitans* was cultured during each repeat episode and is the only HACEK bacterium associated with repeated endocarditis in this study.

Five of the nine *A. aphrophilus* cases were diagnosed with endocarditis, and other foci of infection identified were sacroilitis (one case), pneumonia (one case), presumed contaminant (one case) and unknown focus (one case).

Among the eight cases of *Cardiobacterium* bacteraemias, six were *Cardiobacterium hominis*, one was *Cardiobacterium valvarum* and one was not identified to the species level. Six of the seven cases of *Cardiobacterium endocarditis* affected the aortic valve. The single case without endocarditis had radiographic pneumonia, which was successfully treated with 10 days of antibiotic therapy. This patient also had a bioprosthetic aortic valve replacement. Delayed transthoracic echocardiogram 4 months later and transoesophageal echocardiogram 7 months later showed no evidence of endocarditis.

None of the 11 cases of *E. corrodens* bacteraemia was diagnosed with endocarditis, although echocardiography was performed in only three cases. Four had cancer (oesophageal cancer, colon cancer, diffuse large B-cell lymphoma or metastatic prostate cancer), one had end-stage alcoholic liver disease and three had acute appendicitis. The foci of infection identified were appendicitis (two cases), gingivitis (one case), oesophagitis (one case), liver abscess (one case), mediastinitis (one case), gastrointestinal tract (one case), central line infection or contaminant (one case), presumed contaminant (one case) and unknown focus (two cases). Six (55%) had died at 1 year.

Among the 19 cases of *Kingella* bacteraemia, 17 were *Kingella kingae*, one was *Kingella denitrificans* and one was not identified to the species level. Thirteen cases were aged between 0 and 3 years and the remaining six cases were ages 21–61 years. Among the paediatric cases, five (38%) were diagnosed with endocarditis, and three of these cases were complicated by cerebral emboli. Among the adult cases, three (50%) were diagnosed with endocarditis and none of these suffered from embolic complications. Of the 19 *Kingella* cases, nine (47%) did not have echocardiography performed. Of the 11 cases that did not have a diagnosis of endocarditis, the foci of infection identified were septic arthritis (three cases), stomatitis (two cases), pharyngitis (one case), presumed contaminant (one case) and unknown focus (four cases).

If a single blood culture with a HACEK bacterium was considered as a major Duke criterion for endocarditis and applied to our cases, eight cases (three *Kingella* spp., three *H. parainfluenzae* and two *E. corrodens*) without endocarditis would be reclassified as ‘possible endocarditis’, and five cases (four *A. actinomycetemcomitans* and one *H. parainfluenzae*) of ‘possible endocarditis’ would be reclassified as ‘definite endocarditis’.

Of the 87 cases, 60 were investigated with an echocardiogram. Of these 60 cases, 21 had only a transthoracic

### Table 1. Characteristics of the cases of HACEK bacteraemia and the PPV for endocarditis

<table>
<thead>
<tr>
<th>Micro-organism</th>
<th>No. cases (%)</th>
<th>Median age in years (range)</th>
<th>Sex (male/female)</th>
<th>No. positive blood cultures (mean)</th>
<th>Total no. endocarditis cases (definite/possible) by Duke criteria</th>
<th>PPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>H. parainfluenzae</em></td>
<td>18 (20.7)</td>
<td>38.5 (0–67)</td>
<td>11/7</td>
<td>2.4</td>
<td>10 (7/3)</td>
<td>55</td>
</tr>
<tr>
<td><em>A. actinomycetemcomitans</em></td>
<td>18 (20.7)</td>
<td>45.5 (20–76)</td>
<td>12/6</td>
<td>3.3</td>
<td>18 (9/9)</td>
<td>100</td>
</tr>
<tr>
<td><em>A. aphrophilus</em></td>
<td>9 (10.3)</td>
<td>51.0 (18–85)</td>
<td>6/3</td>
<td>2.7</td>
<td>5 (3/2)</td>
<td>55</td>
</tr>
<tr>
<td><em>A. paraphrophilus</em></td>
<td>4 (4.6)</td>
<td>55.0 (38–58)</td>
<td>4/0</td>
<td>2.8</td>
<td>4 (4/0)</td>
<td>100</td>
</tr>
<tr>
<td><em>Cardiobacterium spp.</em></td>
<td>8 (9.2)</td>
<td>55.0 (45–85)</td>
<td>7/1</td>
<td>4.5</td>
<td>7 (5/2)</td>
<td>88</td>
</tr>
<tr>
<td><em>E. corrodens</em></td>
<td>11 (12.6)</td>
<td>67.0 (18–81)</td>
<td>9/2</td>
<td>1.0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><em>Kingella</em> spp.</td>
<td>19 (21.8)</td>
<td>1.0 (0–57)</td>
<td>11/8</td>
<td>1.8</td>
<td>8 (7/1)</td>
<td>42</td>
</tr>
<tr>
<td>Total</td>
<td>87 (100)</td>
<td>45 (0–85)</td>
<td>60/27</td>
<td>2.5</td>
<td>52 (35/17)</td>
<td>60</td>
</tr>
</tbody>
</table>
A. actinomycetemcomitans is a major causative agent of localized aggressive periodontitis (Henderson et al., 2002), and this is due to the bacterium’s ability to express a host of virulence factors. These include factors that promote colonization and persistence in host tissues, factors that interfere with host defences, factors that destroy host tissues and factors that inhibit repair of host tissues (Fives-Taylor et al., 1999). A number of these virulence factors are likely to be implicated in the pathogenesis of A. actinomycetemcomitans endocarditis. Examples are LtxA protein (a leukotoxin that causes leukocyte apoptosis), cytolethal distending toxin (a cell-cyle-inhibitory protein), Omp34 protein (an Fc-binding protein) and Flp-1 protein (a fimbrial protein that enables tight auto-adhesion) (Henderson et al., 2002).

The isolation of Cardiobacterium spp. from blood was also strongly associated with endocarditis in our study. This is not surprising given that almost all reported cases of Cardiobacterium spp. infection have endocarditis (Graevenitz et al., 2007; Steinberg & Burd, 2010). One review found 61 cases of endocarditis among 63 cases of bacteraemia (Malani et al., 2006). The predilection to affect the aortic valve is also consistent with the experience of others (Brouqui & Raoult, 2001).

In contrast, isolation of E. corrodens in blood was not associated with a clinical diagnosis of endocarditis in our study. Sheng et al. (2001) described a series of 43 patients with invasive E. corrodens infection, of whom eight were bacteraemic. Only one patient was diagnosed with endocarditis. Interestingly, among their patients, 15 (35%) had underlying malignancies. Due to the lack of echocardiography data in our study, we are unable to draw firm conclusions regarding the PPV of E. corrodens bacteraemia for endocarditis. The lack of these data may reflect the severe underlying co-morbidities found in this group and the reluctance to investigate further.

Although only 38% of the paediatric cases of Kingella bacteraemia in our study were diagnosed with endocarditis, this is a higher proportion than has been reported previously. Dubnov-Raz et al. (2008) described 42 children with K. kingae bacteraemia, of whom only 16 underwent echocardiography and four were diagnosed with endocarditis. A subsequent study of 296 paediatric cases of invasive K. kingae disease found 169 cases of skeletal infection (48 were bacteraemic), 140 cases of occult bacteraemia, eight cases of endocarditis and four cases of bacteraemic pneumonia.

### DISCUSSION

To our knowledge, this is the first study describing the PPV of HACEK bacteraemia for endocarditis. Overall, 60% of cases of HACEK bacteraemia had endocarditis, although this varied by HACEK species.

A major finding from our study is that detection of A. actinomycetemcomitans in blood cultures was always associated with endocarditis. Previous reports of invasive A. actinomycetemcomitans infection have also found a high prevalence of endocarditis. Wang et al. (2010) described 10 patients with A. actinomycetemcomitans bacteraemia, of whom eight were diagnosed with endocarditis, one with pneumonia and one with periauricular osteoradionecrosis in the setting of nasopharyngeal carcinoma. The case with pneumonia had transthoracic (but not transoesophageal) echocardiography performed, whereas the case with osteoradionecrosis did not have echocardiography performed. Paju et al. (2003) also described a series of patients with non-oral A. actinomycetemcomitans infections, three of whom had bacteraemia; one was diagnosed with endocarditis, one with septicemia and one with fever of unknown origin. It was unclear what diagnostic measures were undertaken in these patients.

A. actinomycetemcomitans is a major causative agent of periodontal disease, particularly a condition known as localized aggressive periodontitis (Henderson et al., 2002), and this is due to the bacterium’s ability to express a host of virulence factors. These include factors that promote colonization and persistence in host tissues, factors that interfere with host defences, factors that destroy host tissues

### Table 2. Characteristics of the cases of HACEK endocarditis

Valve type: A, aortic; M, mitral; P, pulmonary; T, tricuspid.

<table>
<thead>
<tr>
<th>Micro-organism</th>
<th>No. cases</th>
<th>Valve</th>
<th>Valve type</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A M A and M P T Not clear Prosthetic Native</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>H. parainfluenza</em></td>
<td>10</td>
<td>3 (30%) 4 (40%) 2 (20%) 1 (10%) 0 0 2 (20%) 8 (80%)</td>
<td></td>
</tr>
<tr>
<td><em>A. actinomycetemcomitans</em></td>
<td>18</td>
<td>5 (28%) 8 (44%) 3 (17%) 1 (6%) 0 1 (6%) 14 (78%) 4 (22%)</td>
<td></td>
</tr>
<tr>
<td><em>A. aphrophilus</em></td>
<td>5</td>
<td>0 2 (40%) 1 (20%) 0 0 2 (40%) 1 (20%) 4 (80%)</td>
<td></td>
</tr>
<tr>
<td><em>A. paraphrophilus</em></td>
<td>4</td>
<td>4 (100%) 0 0 0 0 2 (50%) 2 (50%)</td>
<td></td>
</tr>
<tr>
<td><em>Cardiobacterium spp.</em></td>
<td>7</td>
<td>6 (86%) 1 (14%) 0 0 0 0 4 (57%) 3 (43%)</td>
<td></td>
</tr>
<tr>
<td><em>E. corrodens</em></td>
<td>0</td>
<td>0 0 0 0 0 0 0 0</td>
<td></td>
</tr>
<tr>
<td><em>Kingella spp.</em></td>
<td>8</td>
<td>1 (13%) 5 (63%) 0 1 (12%) 1 (12%) 0 1 (13%) 7 (87%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>52</td>
<td>19 (36%) 20 (38%) 6 (12%) 3 (6%) 1 (2%) 3 (6%) 23 (44%) 29 (56%)</td>
<td></td>
</tr>
</tbody>
</table>

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IP: 54.70.40.11
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(Dubnov-Raz et al., 2010). Interestingly, 95% of these infections were in children younger than 4 years old, which is consistent with our findings.

*Actinobacillus paraphrophilus* bacteraemia was also highly predictive of endocarditis in our study, but the number of cases was small. Approximately half of the *H. parainfluenzae, A. aphrophilus* and *Kingella* spp. cases had a diagnosis of endocarditis. Although detection of these organisms in blood cultures was not always predictive of endocarditis, this remained the most common diagnosis.

The major limitations of our study are the reliance on retrospective assessment of case notes for data collection and the lack of echocardiographic data from quite a number of cases. Consequently, we may have underestimated the proportion of cases with endocarditis. HACEK bacteraemia is relatively uncommon, and the number of cases for some HACEK species was small, thereby affecting the precision of our PPV estimates. Lastly, the study was conducted in the New Zealand population only, which may limit applicability to other populations.

In conclusion, we have preliminary evidence to suggest that isolation of *A. actinomycetemcomitans* from a single blood culture should be considered a major Duke criterion for the diagnosis of infective endocarditis. The same may also apply to *Cardiobacterium* spp. and *A. paraphrophilus*. More data are required to confirm these findings.

**ACKNOWLEDGEMENTS**

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**REFERENCES**


