

Case Report

Correspondence

Aman Dalal
amandalal@hotmail.com

Received 12 May 2008
Accepted 9 June 2008

Endocarditis due to *Corynebacterium amycolatum*

Aman Dalal,¹ Carl Urban^{1,2} and Sorana Segal-Maurer^{1,3}

¹Division of Infectious Diseases, New York Hospital Queens, Flushing, NY, USA

²Department of Microbiology, Weill Cornell Medical College, NY, USA

³Department of Medicine, Weill Cornell Medical College, NY, USA

Corynebacterium amycolatum, a normal inhabitant of human skin, is a Gram-positive, non-spore-forming, mycolic acid-free, aerobic or facultative anaerobic bacillus. Since its description in 1988, it has only rarely been associated with infective endocarditis. This paper describes a case of infective endocarditis successfully treated by combination therapy with daptomycin and rifampicin. To the best of our knowledge, this is the first case report of *C. amycolatum* endocarditis from the USA successfully treated with these agents.

Case report

The patient was an 84-year-old female resident in a long-term care facility with end-stage renal disease requiring haemodialysis three times a week via a left subclavian haemodialysis catheter, and with atherosclerotic heart disease, hypertension and congestive heart failure. The patient was referred to our hospital from a dialysis centre with fever and hypotension. On physical examination, her blood pressure was 92/78 mmHg, her temperature was 39.8 °C and a new loud cardiac murmur localized in the mitral area was evident. No peripheral stigmata of endocarditis were present.

Initial blood work showed 17 800 leukocytes μl^{-1} (84% neutrophils, 16% lymphocytes), and blood cultures performed at admission resulted in the growth of Gram-positive rods within 24 h in all four bottles. These were later identified as *Corynebacterium amycolatum* using the API Coryne database 2.0 (bioMérieux). Susceptibility by Etest gave the following MICs ($\mu\text{g ml}^{-1}$): penicillin, 16; ampicillin, 32; erythromycin, 16; levofloxacin, 16; rifampicin, 0.004; daptomycin, 0.19; linezolid, 0.38; and vancomycin, 0.5. Transthoracic echocardiography revealed normal functioning valves, without evidence of vegetation, thrombi or pericardial effusion. Transoesophageal echocardiography on hospital day 2 detected a small mobile echodensity attached to the mitral valve, consistent with a vegetation. Urine and sputum cultures remained negative for bacterial growth.

The patient initially received 1 g vancomycin intravenously after every haemodialysis and 1 g ceftriaxone intravenously every 12 h. Once *C. amycolatum* was identified on day 3, ceftriaxone was discontinued and oral rifampicin (300 mg every 12 h) was added. The patient refused to remove the haemodialysis catheter. Blood cultures from days 2–4 remained positive for *C. amycolatum*. On day 4, vancomycin was discontinued and daptomycin at a dose of 8 mg kg^{-1} every 48 h was administered intravenously.

Subsequent blood cultures from days 5–8 during antibiotic therapy remained negative for bacterial growth. The patient received a total of 6 weeks of daptomycin and 4 weeks of rifampicin treatment. Transoesophageal echocardiography carried out on completion of antibiotic therapy did not reveal any vegetation. The patient had a complete recovery with no elevated creatine phosphokinase levels or other adverse events.

Discussion

The taxonomy of coryneform bacteria has undergone significant modification since 1896 when Lehman and Neumann proposed that bacteria morphologically resembling the diphtheria bacillus be incorporated into the genus *Corynebacterium* (Lipsky *et al.*, 1982). *C. amycolatum* is a normal inhabitant of human skin and was first described in 1988 as a Gram-positive, non-spore-forming, mycolic acid-free, aerobic or facultative anaerobic bacillus (Collins *et al.*, 1988).

Physicians often disregard blood cultures that yield *Corynebacterium* species, as these organisms are usually classified as skin contaminants or ‘colonizers’. This is likely to be true when there is a single, isolated positive culture; however, multiple positive blood cultures, when performed in an appropriate aseptic manner, are more indicative of true bacteraemia. In a review, van Scoy *et al.* (1977) suggested that diphtheroids account for 10% of blood culture contaminants. Another study reported that *Corynebacterium* species accounted for 5% of the Gram-positive organisms that caused bacteraemia during trial VIII of the International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer (Zinner, 1999).

A Medline search revealed 14 cases (De Miguel-Martinez *et al.*, 1996; Berner *et al.*, 1997; Vaneechoutte *et al.*, 1998;

Clarke *et al.*, 1999; De Miguel *et al.*, 1999; Oteo *et al.*, 2001; Knox & Holmes, 2002; Daniëls *et al.*, 2003; Chiu *et al.*, 2005; Adderson *et al.*, 2008) of invasive infections due to *C. amycolatum*, which are summarized in Table 1 together with the present case. These included five cases of neutropenic septicaemia; two cases of native valve infective endocarditis and single cases each of septic shock in a premature infant, septic arthritis, cardioverter lead electrode infection, pneumonia, peritonitis, post-surgical septicaemia and empyema. Von Graevenitz *et al.* (1998) described *C. amycolatum* infections following prosthetic joint insertion and open fractures without additional details. Paviour *et al.* (2002) described the isolation of *C. amycolatum* strains from three patients with mastitis. A meta-analysis of 129 cases of *Corynebacterium* endocarditis involving nine species revealed that only *C. amycolatum* has a predilection for women (Belmares *et al.*, 2007). The majority of infections due to *C. amycolatum* were in either immunocompromised patients or patients with intravascular devices (De Miguel-Martinez *et al.*, 1996; Berner *et al.*, 1997; Vaneechoutte *et al.*, 1998; De Miguel *et al.*, 1999; Oteo *et al.*, 2001; Knox & Holmes, 2002; Chiu *et al.*, 2005; Adderson *et al.*, 2008). To date, they remain an uncommon cause of infective endocarditis (Knox & Holmes, 2002; Daniëls *et al.*, 2003), even though other non-diphtherial corynebacteria, particularly *Corynebacterium jeikeium*, are becoming an increasingly common group of opportunistic pathogens. To the best of our knowledge, this is the first case report of *C. amycolatum* endocarditis from the USA treated with daptomycin and rifampicin.

Due to several modifications and the inclusion of new species into the genus *Corynebacterium*, it is becoming increasingly difficult to identify these organisms. Methods that reliably differentiate related species, such as mycolic acid chromatography, GLC and molecular amplification techniques, are not used in a routine clinical microbiology laboratory setting. From 1987 to 1995, 11 new *Corynebacterium* species were described (Funke *et al.*, 1997). *C. amycolatum* has recently been included in the updated API Coryne database 2.0 (Wauters *et al.*, 1998). The presence of only two reports of *C. amycolatum* causing endocarditis in the literature may be due to its misidentification, as other non-lipophilic fermentative *Corynebacterium* species, including *Corynebacterium xerosis* and *Corynebacterium minutissimum*, are associated with human disease (Funke *et al.*, 1996a; Zinkernagel *et al.*, 1996). Letek *et al.* (2006) described a molecular method for rapid identification of *C. amycolatum* from the closely related *Corynebacterium striatum*, *C. minutissimum* and *C. xerosis*, without the requirement for further molecular analysis, based on the use of different primers for amplification of the cell-division *divIVA* gene using conventional or real-time PCR (Letek *et al.*, 2006). Again, these techniques are not performed routinely in clinical microbiology laboratories.

Published material provides useful schema for differentiating *C. amycolatum*, *C. minutissimum* and *C. striatum*

using colonial morphology, carbohydrate assimilation tests and sensitivity to amoxicillin and the vibriostatic compound O/129, in conjunction with the API Coryne and API 20NE systems. Antibiotic sensitivity patterns may support identification, with *C. amycolatum* and *C. jeikeium* generally resistant to multiple antibiotics (Renaud *et al.*, 1998). In contrast, *C. striatum*, *C. minutissimum* and *C. xerosis* are generally sensitive to a wide range of antibiotics.

Sánchez Hernández *et al.* (2003) tested 58 strains of *C. amycolatum* (including 33 multidrug-resistant strains); they showed no resistance to teicoplanin or linezolid and 1 strain was resistant to quinupristin/dalfopristin. Goldstein *et al.* (2003) showed that 29/31 strains of *Corynebacterium* species, including *C. jeikeium*, *C. amycolatum* and *Corynebacterium pseudodiphtheriticum*, were inhibited by $\leq 0.25 \mu\text{g}$ daptomycin ml^{-1} . The Clinical and Laboratory Standards Institute (CLSI, 2006a, b) does not report susceptibility criteria for *Corynebacterium* species and therefore susceptibility data generated in the microbiology laboratory should be interpreted with caution, as data linking MIC results to clinical outcomes are lacking.

C. amycolatum is quite sensitive to glycopeptide/lipopeptide antibiotics, as was the isolate presented in this report (Funke *et al.*, 1996b; Sánchez Hernández *et al.*, 2003). Thirteen of the fifteen patients with *C. amycolatum* infections for whom treatment data were available were given at least a glycopeptide antibiotic, as listed in Table 1. Because of the paucity of documented case reports, there is no consensus on the optimal treatment *C. amycolatum* endocarditis. Knox & Holmes (2002) successfully treated a case of endocarditis due to *C. amycolatum* with vancomycin and oral rifampicin for 16 months. In our case, we switched to daptomycin as our patient was on haemodialysis and was bacteraemic on vancomycin therapy for 4 days. Whilst daptomycin is only approved for bacteraemia and right-sided endocarditis caused by *Staphylococcus aureus*, the exquisite bactericidal nature and ease of administration of this agent prompted our switch in therapy. Her bacteraemia cleared after 24 h on daptomycin therapy and she had a favourable outcome after 6 weeks of daptomycin and 4 weeks of rifampicin.

In summary, *C. amycolatum* is classified as a fermentative, non-lipophilic, mycolic acid-free *Corynebacterium* species and is capable of causing serious human infections. *C. amycolatum* isolated in this and other reported cases of endocarditis was susceptible to vancomycin or daptomycin in the laboratory, and patients treated with these antimicrobial agents in combination with rifampicin had successful microbiological and clinical outcomes. The description of further cases treated with vancomycin and daptomycin, alone or in combination, may lead to more formal therapeutic guidelines. With the increase in newer identification schemes routinely performed in clinical laboratories, non-diphtherial *Corynebacterium* species are likely to be implicated in a growing number of infections.

Table 1. Infections due to *C. amycolatum*

Reference	Age/sex	Co-morbidity	Diagnosis	Associated IVD	Antibiotic susceptibility	Treatment	Outcome
De Miguel-Martinez <i>et al.</i> (1996)	75 years/F	Acute non-lymphocytic leukaemia, DM	Neutropenic septicaemia	None	Teicoplanin, vancomycin,	Piperacillin/tazobactam, amikacin, teicoplanin	Survived
Berner <i>et al.</i> (1997)	2 days/M	Premature	Septic shock syndrome	None	Imipenem, vancomycin, erythromycin, clindamycin	Piperacillin, netilmicin, dopamine, dobutamine, norepinephrine	Died
Vaneechoutte <i>et al.</i> (1998)	42 years/F	ACD, SVC syndrome, recurrent ACD pocket infections	Cardioverter lead electrode infection	ACD	Vancomycin	Ampicillin, vancomycin, fluconazole and removal of ACD and electrode	Survived
Clarke <i>et al.</i> (1999)	63 years/M	HTN, OA	Septic arthritis	None	Teicoplanin, vancomycin, gentamicin, fusidic acid, doxycycline, ciprofloxacin	Flucloxacillin, vancomycin, rifampicin, doxycycline	Survived
De Miguel <i>et al.</i> (1999)	75 years/F	DM, acute leukaemia	Neutropenic septicaemia	None	No data	Ceftazidime, amikacin, teicoplanin	Survived
De Miguel <i>et al.</i> (1999)	53 years/F	Acute leukaemia	Neutropenic septicaemia	None	No data	Piperacillin/tazobactam, amikacin, teicoplanin	Survived
Oteo <i>et al.</i> (2001)	70 years/M	Laryngeal carcinoma, chronic bronchitis, DM, DVT	Incarcerated umbilical hernia, RLL pneumonia	None	Doxycycline, vancomycin, rifampicin	Vancomycin	Survived
Oteo <i>et al.</i> (2001)	70 years/F	DM	Left hip fracture with ORIF, septicaemia	None	Doxycycline, vancomycin	Vancomycin	Died
Oteo <i>et al.</i> (2001)	53 years/M	Adenocarcinoma of stomach	Empyema, haemothorax	CVC	Doxycycline, vancomycin	Vancomycin	Died
Knox & Holmes (2002)	74 years/F	ANCA vasculitis	Native mitral valve endocarditis	Right IJ HD catheter	No data	Vancomycin, rifampicin	Survived
Daniëls <i>et al.</i> (2003)	88 years/M	LVH, AS, decubitus ulcer	Native aortic valve endocarditis	None	No data	Cefuroxime	Died
Chiu <i>et al.</i> (2005)	65 years/F	ESRD, CAPD	Peritonitis	Tenckhoff catheter	No data	Cefazolin, ceftazidime, vancomycin	Survived
Adderson <i>et al.</i> (2008)	4 years/F	ALL, disseminated histoplasmosis, hyperglycemia	Neutropenic septicaemia	CVC	No data	Vancomycin, meropenem	No data
Adderson <i>et al.</i> (2008)	9 years/M	ALL, SCT, GVHD	Neutropenic septicaemia	CVC	No data	Vancomycin, cefepime, removal of CVC	No data
Present case	84 years/F	ESRD, ASHD, HTN, CHF	Native mitral valve endocarditis	Left subclavian HD catheter	Vancomycin, linezolid, daptomycin, rifampicin	Vancomycin, daptomycin, rifampicin	Survived

ACD, Automated cardioverter defibrillator; ALL, acute lymphocytic leukaemia; ANCA, anti-neutrophilic cytoplasmic antibody; AS, aortic stenosis; ASHD, atherosclerotic heart disease; CAPD, continuous peritoneal ambulatory peritoneal dialysis; CHF, congestive heart failure; CVC, central venous catheter; DM, diabetes mellitus; DVT, deep venous syndrome; ESRD, end-stage renal disease; F, female; GVHD, graft-versus-host disease; HD, haemodialysis; HTN, hypertension; IJ, internal jugular; IVD, intravascular device; LVH, left ventricular hypertrophy; M, male; OA, osteoarthritis; ORIF, open reduction and internal fixation; RLL, right lower lobe; SCT, stem-cell transplant; SVC, superior vena cava.

The increasing number of immunocompromised patients and the burgeoning use of intravascular access devices have also contributed to this phenomenon.

References

- Adderson, E. E., Boudreaux, J. W. & Hayden, R. T. (2008).** Infections caused by coryneform bacteria in pediatric oncology patients. *Pediatr Infect Dis J* **27**, 136–141.
- Belmares, J., Deterline, S., Pak, J. B. & Parada, J. P. (2007).** *Corynebacterium* endocarditis species-specific risk factors and outcomes. *BMC Infect Dis* **7**, 4.
- Berner, R., Pelz, K., Wilhelm, C., Funke, A., Leititis, J. U. & Brandis, M. (1997).** Fatal sepsis caused by *Corynebacterium amycolatum* in a premature infant. *J Clin Microbiol* **35**, 1011–1012.
- Chiu, Y. L., Wu, V. C., Wun, K. D. & Hsueh, P. R. (2005).** Recurrent peritonitis caused by *Corynebacterium amycolatum* in a patient undergoing continuous ambulatory peritoneal dialysis. *Clin Nephrol* **63**, 241–242.
- Clarke, R., Qamruddin, A., Taylor, M. & Panigrahi, H. (1999).** Septic arthritis caused by *Corynebacterium amycolatum* following vascular graft sepsis. *J Infect* **38**, 126–127.
- CLSI (2006a).** *Performance Standards for Antimicrobial Disk Susceptibility Tests*, 9th edn, approved standard M2-A9. Wayne, PA: Clinical and Laboratory Standards Institute.
- CLSI (2006b).** *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*, 7th edn, approved standard M7-A7. Wayne, PA: Clinical and Laboratory Standards Institute.
- Collins, M. D., Burton, R. A. & Jones, D. (1988).** *Corynebacterium amycolatum* sp. nov, a new mycolic acid-less *Corynebacterium* species from human skin. *FEMS Microbiol Lett* **49**, 349–352.
- Daniëls, C., Schoors, D. & van Camp, G. (2003).** Native valve endocarditis with aorta-to-left atrial fistula due to *Corynebacterium amycolatum*. *Eur J Echocardiogr* **4**, 68–70.
- De Miguel, I., Rodríguez, E. & Martín, A. M. (1999).** *Corynebacterium amycolatum*: sepsis in hematologic patients. *Enferm Infecc Microbiol Clin* **17**, 340–341.
- De Miguel-Martinez, I., Fernández-Fuertes, F., Ramos-Macias, A., Bosch-Benitez, J. M. & Martín-Sánchez, A. M. (1996).** Sepsis due to multiply resistant *Corynebacterium amycolatum*. *Eur J Clin Microbiol Infect Dis* **15**, 617–618.
- Funke, G., Lawson, P. A., Bernard, K. A. & Collins, M. D. (1996a).** Most *Corynebacterium xerosis* strains identified in the routine clinical laboratory correspond to *Corynebacterium amycolatum*. *J Clin Microbiol* **34**, 1124–1128.
- Funke, G., Punter, V. & Von Graevenitz, A. (1996b).** Antimicrobial susceptibility patterns of some recently established coryneform bacteria. *Antimicrob Agents Chemother* **40**, 2874–2878.
- Funke, G., Von Graevenitz, A., Clarridge, J. E. & Bernard, K. A. (1997).** Clinical microbiology of coryneform bacteria. *Clin Microbiol Rev* **10**, 125–159.
- Goldstein, E. J., Citron, D. M., Merriam, C. V., Warren, Y. A., Tyrrell, K. L. & Fernandez, H. T. (2003).** In vitro activities of daptomycin, vancomycin, quinupristin-dalfopristin, linezolid, and five other antimicrobials against 307 Gram-positive anaerobic and 31 *Corynebacterium* clinical isolates. *Antimicrob Agents Chemother* **47**, 337–341.
- Knox, K. L. & Holmes, A. H. (2002).** Nosocomial endocarditis caused by *Corynebacterium amycolatum* and other nondiphtheriae corynebacteria. *Emerg Infect Dis* **8**, 97–99.
- Letek, M., Ordóñez, E., Fernández-Natal, I., Gil, J. A. & Mateos, L. M. (2006).** Identification of the emerging skin pathogen *Corynebacterium amycolatum* using PCR-amplification of the essential *divIVA* gene as a target. *FEMS Microbiol Lett* **265**, 256–263.
- Lipsky, B. A., Goldberger, A. C., Tompkins, L. S. & Plorde, J. J. (1982).** Infections caused by non-diphtheriae corynebacteria. *Rev Infect Dis* **4**, 1220–1235.
- Oteo, J., Aracil, B., Ignacio Alós, J. & Luis Gómez-Garcés, J. (2001).** Significant bacteremias by *Corynebacterium amycolatum*: an emergent pathogen. *Enferm Infecc Microbiol Clin* **19**, 103–106.
- Paviour, S., MUSAAD, S., Roberts, S., Taylor, G., Taylor, S., Shore, K., Lang, S. & Holland, D. (2002).** *Corynebacterium* species isolated from patients with mastitis. *Clin Infect Dis* **35**, 1434–1440.
- Renaud, F. N. R., Dutaur, M., Daoud, S., Aubel, D., Reigel, P., Monget, D., Freney, J. & other authors (1998).** Differentiation of *Corynebacterium amycolatum*, *C. minutissimum* and *C. striatum* by carbon assimilation tests. *J Clin Microbiol* **36**, 3698–3702.
- Sánchez Hernández, J., Mora Peris, B., Yagüe Guirao, G., Gutiérrez Zufiaurre, N., Muñoz Bellido, J. L., Segovia Hernández, M. & García Rodríguez, J. A. (2003).** In vitro activity of newer antibiotics against *Corynebacterium jeikeium*, *Corynebacterium amycolatum* and *Corynebacterium urealyticum*. *Int J Antimicrob Agents* **22**, 492–496.
- van Scoy, R. E., Cohen, S. N., Geraci, J. E. & Washington, J. A. (1977).** Coryneform bacterial endocarditis: difficulties in diagnosis and treatment, presentation of three cases, and review of literature. *Mayo Clin Proc* **52**, 216–219.
- Vanechoutte, M., De Bleser, D., Claeys, G., Verschraegen, G., De Baere, T., Hommez, J., Devriese, L. A. & Riegel, P. (1998).** Cardioverter-lead electrode infection due to *Corynebacterium amycolatum*. *Clin Infect Dis* **27**, 1553–1554.
- Von Graevenitz, A., Frommelt, L., Pünter-Streit, V. & Funke, G. (1998).** Diversity of coryneforms found in infections following prosthetic joint insertion and open fractures. *Infection* **26**, 36–38.
- Wauters, G., van Bosterhaut, B., Janssens, M. & Verhaegen, J. (1998).** Identification of *Corynebacterium amycolatum* and other nonlipophilic fermentative corynebacteria of human origin. *J Clin Microbiol* **36**, 1430–1432.
- Zinkernagel, A. S., Von Graevenitz, A. & Funke, G. (1996).** Heterogeneity within *Corynebacterium minutissimum* strains is explained by misidentified *C. amycolatum* strains. *Am J Clin Pathol* **106**, 378–383.
- Zinner, S. H. (1999).** Changing epidemiology of infections in patients with neutropenia and cancer: emphasis on Gram-positive and resistant bacteria. *Clin Infect Dis* **29**, 490–494.