

A case report of *Enterobacter cloacae* endocarditis in a patient with a history of cotton fever

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Background

Cotton fever is a self-limited, febrile syndrome occurring after the injection of trace amounts of drugs, in particular heroin, extracted from reused cotton filters. It is characterized by non-specific findings, such as fever, tachycardia, and leucocytosis. The leading pathophysiologic explanation suggests it is the result of direct inoculation of the bloodstream with endotoxins from Gram-negative bacilli of the genus *Enterobacter*, known to colonize all parts of the cotton plant. Only one prior case report has suggested cotton fever as a potential risk factor of infective endocarditis (IE).

Case summary

We describe a case of a 57-year-old patient with a history of intravenous heroin use complicated by self-reported episodes of cotton fever. His presentation was notable for *Enterobacter cloacae* IE with bilateral septic pulmonary emboli. Transthoracic echocardiography findings included new tricuspid regurgitation and two mobile echodensities on the right atrial implantable cardioverter defibrillator (ICD) lead. Despite broad antibiotic coverage and extraction of the ICD leads, the patient passed away from septic shock.

Discussion

The present case report is only the second published report of endocarditis in a patient with a history of cotton fever. In both cases, bacteria of the *Enterobacter* genus were isolated in patients' blood cultures. This evidence supports the endotoxin theory as the leading pathophysiologic explanation for cotton fever and suggests cotton fever as a risk factor for Gram-negative IE. In the inpatient setting it informs proper antibiotic coverage, whereas in the outpatient setting it supports harm reduction interventions in the form of sterile cotton balls.

Keywords

Enterobacter endocarditis • Cotton fever • Tricuspid valve • Case report

ESC Curriculum

2.2 Echocardiography • 4.5 Tricuspid regurgitation • 4.11 Endocarditis • 5.10 Implantable cardioverter defibrillators • 6.2 Heart failure with reduced ejection fraction

Learning points

- To be aware of the association of *Enterobacter* endocarditis with cotton fever, a rarely recognized complication of IV drug use.
- To understand the importance of drug use practices, such as that of 'cotton shooting', when assessing the microbiologic aetiology of infectious endocarditis.

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Introduction

Cotton fever is a self-limited febrile syndrome occurring after the injection of drugs extracted from reused cotton filters.^{1,2} We report only the second case³ of infective endocarditis (IE) in a patient with a history of cotton fever. This limited clinical evidence may suggest that cotton fever could be an unrecognized risk factor for the development of *Enterobacter* endocarditis. This case provides clinicians with an appreciation of how drug use practices could increase the risk of IE, while offering key insights into microbiologic cause. Cotton fever occurs in up to 54% of persons who inject drugs,⁴ but there has been only one report on the association of this condition with endocarditis.³

Timeline

Day 0	<ul style="list-style-type: none"> – Hospitalization for worsening dyspnoea – Chest X-ray with evidence of bilateral consolidations – Initiation of community-acquired pneumonia coverage with ceftriaxone/doxycycline
Day 1	<ul style="list-style-type: none"> – First set of blood cultures to eventually grow <i>Enterobacter cloacae</i> – Sepsis was confirmed and the antibiotic regimen was changed to vancomycin/cefepime for broader coverage
Day 2	<ul style="list-style-type: none"> – Transthoracic echocardiography showing new tricuspid regurgitation and two mobile echodensities on the right atrial ICD lead
Day 3	<ul style="list-style-type: none"> – Computed tomography pulmonary angiogram showing new bilateral consolidations, left upper lobe cavitation, and bilateral septic pulmonary emboli – Second set of blood cultures to eventually grow <i>Enterobacter cloacae</i>
Day 7	<ul style="list-style-type: none"> – ICD lead extraction
Days 8–75	<ul style="list-style-type: none"> – Hospital course was complicated by respiratory failure necessitating intubation and multiple nosocomial infections treated with multiple rounds of antibiotics
Day 76	<ul style="list-style-type: none"> – Patient passed away

Case presentation

A 57-year-old man with a history of intravenous (IV) heroin use presented to the emergency department (ED) with a chief complaint of progressive dyspnoea. Other symptoms included chest pain on exertion, orthopnoea, and lower extremity swelling over the past 8 months. He also reported multiple instances of subjective fevers shortly after IV injection of heroin when reusing cotton filters. The patient's medical history was significant for chronic obstructive pulmonary disease, coronary artery disease status post-drug-eluting stent placement, ventricular fibrillation cardiac arrest status post implantable cardioverter defibrillator (ICD) placement, heart failure of probable ischaemic aetiology with reduced (last 40%) ejection fraction and polysubstance use disorder, including active use of intranasal cocaine, non-prescribed methadone, and IV heroin.

Presenting vital signs included: 134/90 mmHg, 105 beats/min, 36.2°C, 18 breaths/min, and oxygen saturation of 100% on room air. Physical examination revealed bilateral lower extremity oedema and track marks in the antecubital fossae. Admission labs were notable for anaemia (haemoglobin 10.4 g/dL), an elevated white blood cell count with bandemia (14.9 k/ μ L with 16% bands), as well as negative human immunodeficiency virus antibody and *Aspergillus* galactomannan antigen testing. Serial electrocardiograms and cardiac enzymes did not show evidence of ischaemia. A computed tomography pulmonary angiogram revealed new bilateral lung consolidations, left upper lobe cavitation, and bilateral septic pulmonary emboli (Videos 1 and 2 and Figure 1, Supplementary material online, Video S1). Two sets of blood cultures drawn on hospital days (HD) 1 and 3 speciated *Enterobacter cloacae* resistant to first-generation cephalosporins. No growth was observed in fungal blood cultures drawn on the same days. A transthoracic echocardiogram showed a severely reduced left ventricular ejection fraction (<30%), new tricuspid regurgitation, and two mobile echodensities on the right atrial ICD lead (Video 3 and Figure 2).

Upon presentation to the ED, ceftriaxone and doxycycline were initiated given concern for pneumonia on chest X-ray. With the development of hypotension and worsening tachycardia on HD 2, antibiotic coverage was empirically broadened to vancomycin/cefepime, then narrowed to cefepime monotherapy based on culture data. On HD 7, the patient underwent percutaneous laser lead extraction, with a set of cultures originating from the leads exhibiting no bacterial growth. Subsequently, the patient had a prolonged hospital course complicated by nosocomial infections, eventually passing away from septic shock.

Discussion

Persons who inject drugs (PWID) will often strain narcotic solutions through cotton balls to filter out particulate matter before IV injection.¹ Residual narcotic collects in reused cotton balls and can be extracted by boiling the cotton and injecting the resulting solution, a practice known as 'cotton shooting'.^{1,5} This practice can result in the onset of fever within 30 min of injection,^{1,3,6} a syndrome referred to as cotton fever that has been described as early as 1975.⁷ It has been reported primarily with the IV injection of heroin,^{3,5,7,8} but also of pentazocine and methylphenidate.¹ It is a self-limited syndrome resolving within 24–48 h and associated with leucocytosis and tachycardia, as well as non-specific symptoms including chills and shortness of breath.^{3,6} Given the overlap in its presentation with life-threatening conditions such as sepsis, cotton fever remain a diagnosis of exclusion.^{9–12} The presented patient engaged in the practice of 'cotton shooting' and endorsed multiple instances of subjective fevers shortly after IV injection. With 11 published case reports on cotton fever,^{1–11} this syndrome is well-recognized and self-reported by PWIDs.^{3,5,7} For example, a cross-sectional study of 557 PWIDs in France, estimated the self-reported prevalence of cotton fever at 54%.⁴

The leading pathophysiologic explanation suggests that cotton fever is the result of direct inoculation of the bloodstream with endotoxins from Gram-negative bacilli of the genus *Enterobacter*.^{3,4,6,8,11} The term 'cotton fever' was first used to describe a separate clinical

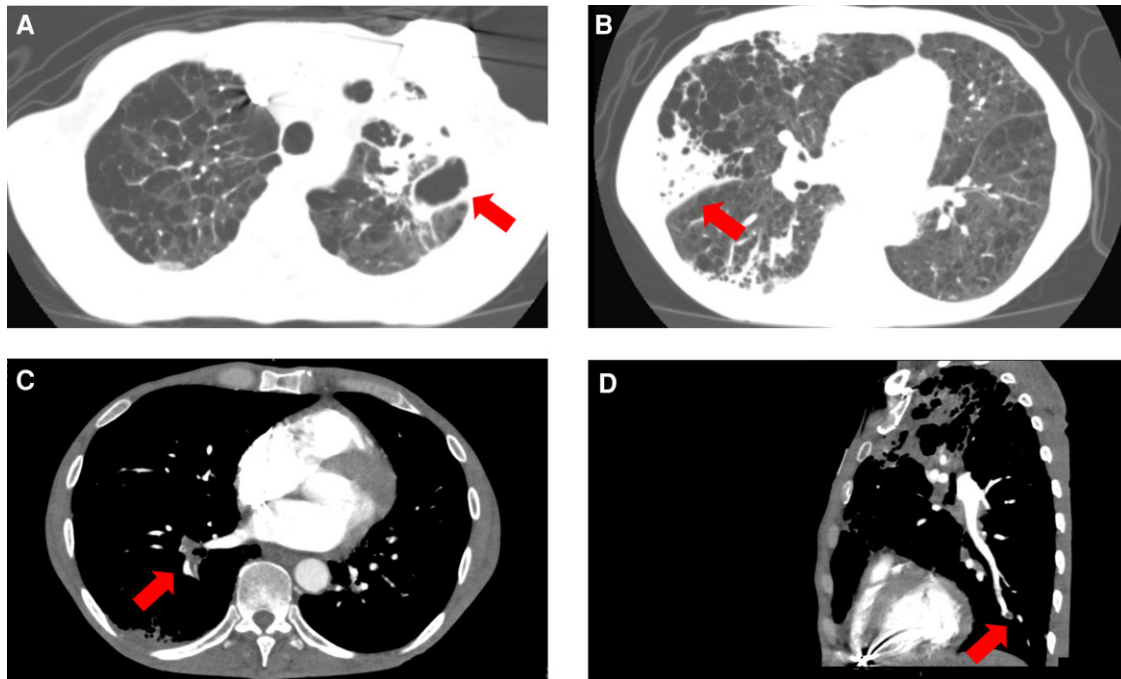


Figure 1 Computed tomography pulmonary angiogram. (A) Left upper lobe cavitation (arrow) with emphysematous changes in the right lung (axial plane, lung window). (B) Right middle lobe consolidation (axial plane, lung window, arrow). (C) Acute pulmonary embolism involving a segmental right lower lobe pulmonary artery branch (axial plane, mediastinal window, arrow). (D) Acute pulmonary embolism involving a subsegmental left lower lobe pulmonary artery branch (sagittal plane, mediastinal window, arrow).

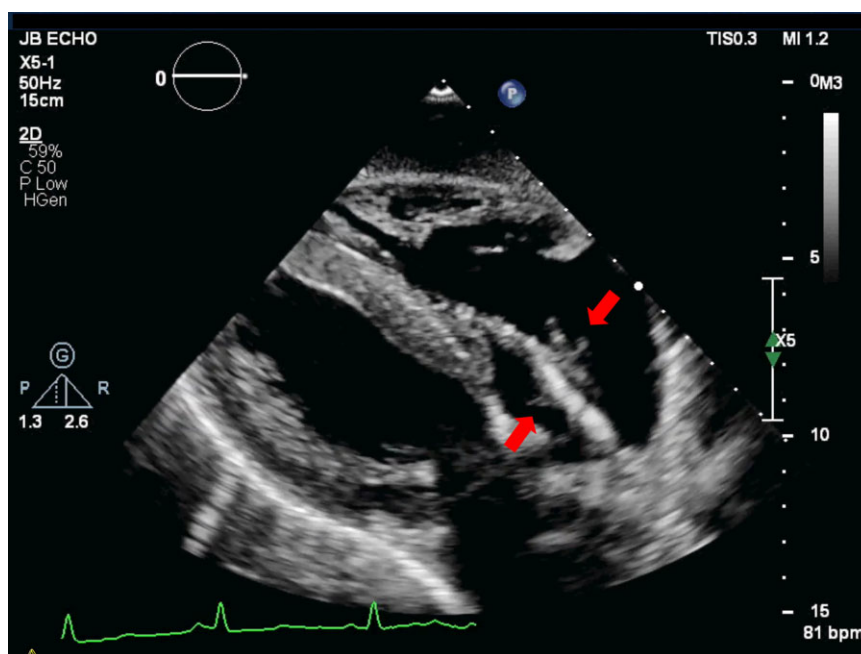
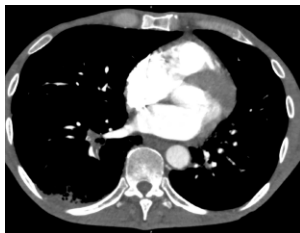


Figure 2 Snapshot of transthoracic echocardiogram (off axis right ventricular inflow view) showing two large, mobile vegetations (arrows) attached to the right atrial ICD lead with the largest one measuring approximately 2 × 1 cm.

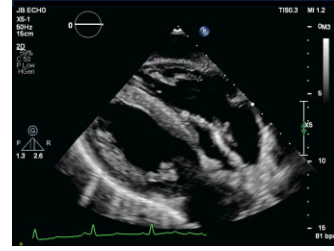


Video 1 Computed tomography pulmonary angiogram (axial plane, lung window) illustrating bilateral consolidations, emphysematous changes, and left upper lobe cavitation.

entity, namely a syndrome of cough, dyspnoea, and fever in cotton mill workers, also known as ‘mill fever’.^{1,13} Investigations of such cotton-related illnesses showed that all parts of the cotton plant are heavily colonized with *Enterobacter* and its produced endotoxin.¹³ In turn, extracts of cotton dust and endotoxin have been separately shown to induce IL-1-mediated neutrophil chemotaxis.^{1,13} Interestingly, the release of the water-soluble endotoxins into a water suspension of bacteria can be potentiated by heat, likely due to the denaturation of proteins in the endotoxin complex.¹³ This fact is relevant in our context, given the process of boiling reused cotton balls to extract residual narcotic. The strongest evidence supporting the endotoxin theory comes from a 1993 case report of cotton fever. *E. agglomerans* (since renamed *Pantoea agglomerans*)



Video 2 Computed tomography pulmonary angiogram (axial plane, mediastinal window) illustrating bilateral consolidations, left upper lobe cavitation, and acute bilateral pulmonary emboli involving segmental right lower lobe pulmonary artery extending into subsegmental branches, and a left subsegmental pulmonary arterial branch.



Video 3 Transthoracic echocardiogram (off axis right ventricular inflow view) showing two large, mobile vegetations attached to the right atrial ICD lead with the largest one measuring approximately 2 × 1 cm.

was isolated in both blood cultures and cultures of a reused cotton filter from a PWID presenting with cotton fever.²

In a 2019 case report, *E. asburiae*, a member of the *E. cloacae* complex, was isolated from blood cultures of a patient with a history of cotton fever presenting with IE.³ Similarly, we report only the second case of IE in a patient with a history of cotton fever isolating yet another *Enterobacter* species. It is important to note the microbiologic congruence (*Enterobacter* species) among studies of the cotton plant,¹³ the 1993 case report of cotton fever,² and these two cases of IE.³ This evidence may support the *Enterobacter* endotoxin theory as the leading pathophysiologic explanation for cotton fever. The present case report also suggests that cotton fever could be an unrecognized risk factor for the development of Gram-negative IE, specifically by *Enterobacter* species. We hypothesize that cotton fever and *Enterobacter* endocarditis exist on a continuum. More specifically, the *Enterobacter* inoculum size originating from the cotton, along with other risk factors (e.g. valvular damage, endovascular devices), could determine a primarily endotoxin-mediated, self-limited febrile course vs. bacterial seeding of the endocardium.

These findings inform both inpatient and outpatient clinical care. In the outpatient setting, it informs appropriate harm reduction interventions for PWIDs, such as the provision of sterile cotton balls and/or membrane filters.⁴ In the inpatient setting, it informs the need for early, broad-spectrum antibiotic treatment in this patient sub-population that would also cover for this otherwise rare cause of IE. This is especially important, given patients with non-HACEK Gram-negative bacillus endocarditis have poor outcomes with high rates of in-hospital mortality (as high as 24–37%) and complications.^{14,15} Although IV drug use has historically been considered a primary risk factor for non-HACEK Gram-negative bacillus endocarditis, recent data suggest a relatively greater risk contribution from implanted endovascular devices and nosocomial exposure.^{14,15}

Conclusions

We present clinical evidence supporting cotton fever as a potential risk factor for the development of *Enterobacter* endocarditis. Despite the typically benign and self-limited course associated with cotton fever, it is critical to rule out infectious complications, such as IE.

Lead author biography



Constantine Tarabanis received his Bachelor of Arts degree in Molecular and Cellular Biology from Harvard College and MD degree from Harvard Medical School. He is currently an internal medicine resident at New York University Langone Health. He has previously published basic research on cellular signalling pathways resulting in proteinuric kidney disease and on novel fabrication

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Supplementary material

[Supplementary material](#) is available at *European Heart Journal – Case Reports* online.

Slide sets: A fully edited slide set detailing these cases and suitable for local presentation is available online as [Supplementary data](#).

Consent: The authors confirm that written consent for submission of the case report including images and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: None declared.

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