Adjunctive bacteriophage therapy for prosthetic valve endocarditis due to *Staphylococcus aureus*

To the Editor: Infective endocarditis with *Staphylococcus aureus* is associated with a high mortality despite optimal antibiotic therapy.[1] The synergy between bacteriophages and antibiotics has been shown in vitro and in animal studies,[2] and bacteriophages have demonstrated their value in severe bacterial infections.[3] AB-SA01 (AmpliPhi Biosciences) is a bacterial DNA-free and protein-free highly purified preparation of three obligately lytic *Myoviridae*, each at 10^9 plaque-forming units per dose.[4] This preparation has been recently used successfully for staphylococcal sinusitis by local irrigation.[5] A protocol was established for bacteriophage therapy as an adjunct to standard care of severe staphylococcal infections under the auspices of the Therapeutic Goods Administration Special Access Scheme. Here, we report the first intravenous use of AB-SA01 in a case of severe staphylococcal sepsis with prosthetic valve endocarditis.

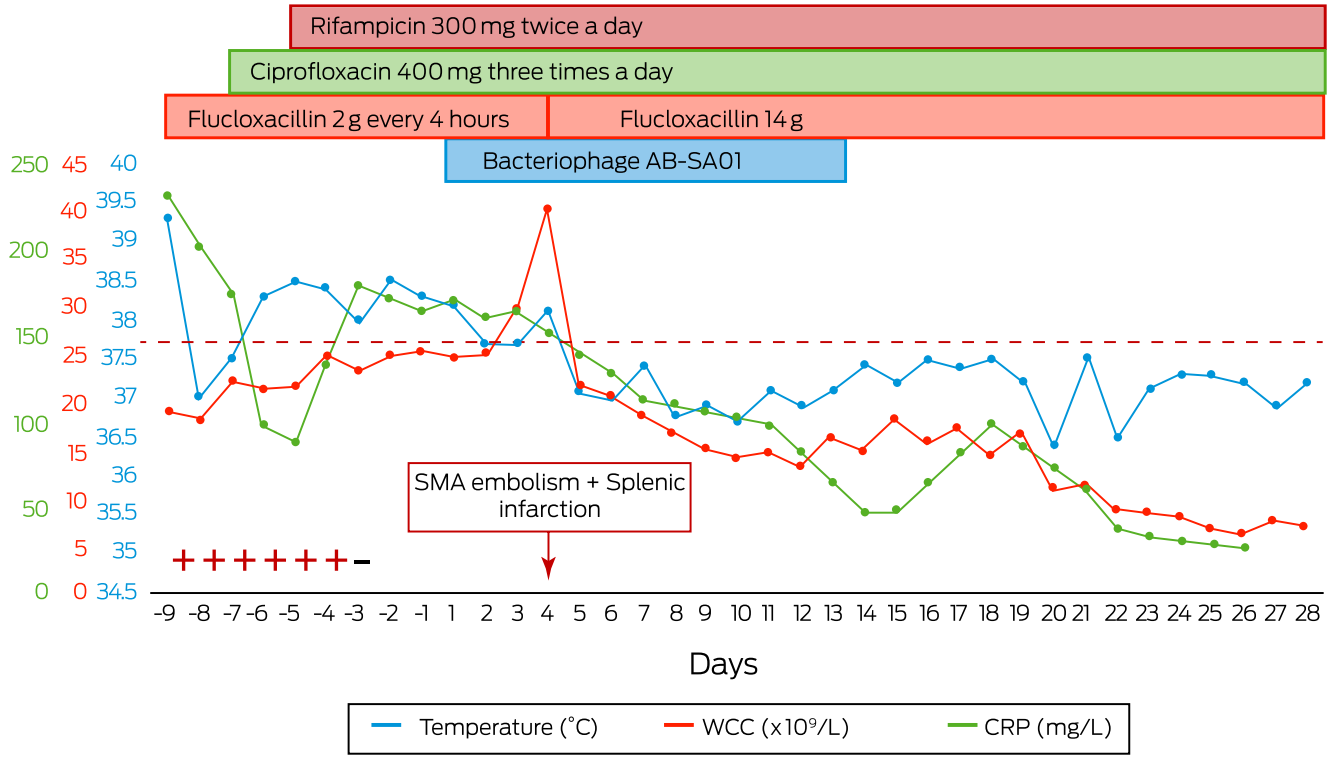
A 65-year-old man with a 30-year-old mechanical aortic valve presented with a week of malaise, severe exertional dyspnoea, and central pleuritic chest pain. He had been successfully treated for *Haemophilus aphrophilus* aortic valve endocarditis 8 years earlier with antibiotics alone. Examination revealed fever, tachypnoea, tachycardia and borderline hypotension (90–100 mmHg systolic), with a praecordial systolic murmur and click. There was no cardiac, renal or hepatic failure or any evident peripheral embolic sequelae of endocarditis (haematuria, splinter haemorrhages) at this stage. Blood cultures repeatedly grew an identical methicillin-sensitive *S. aureus* determined by whole genome sequencing, and the patient received high dose intravenous flucloxacillin, ciprofloxacin and rifampicin (Box).

Transoesophageal echocardiography confirmed vegetations on prosthetic aortic and native mitral valves, and the aortic root was thickened with possible paravalvular root abscess. Scheduled cardiopulmonary bypass for operative source control was postponed after a haemorrhagic infarction in the distribution of the left anterior cerebral artery on day –7 (ie, a week before starting bacteriophage therapy), despite concerns regarding development of an aortic root abscess, ongoing fevers and hypotension.

Intravenous AB-SA01 was administered twice a day for 14 days in conjunction with the patient's prescribed antibiotics, commencing (Day 1) 9 days after his first positive blood culture. Blood cultures were negative at onset of bacteriophage therapy, and the C-reactive protein, temperature, and white cell count results showed downward trends within 24 hours (Box). This trajectory was only interrupted by splenic infarction and occlusion of the superior mesenteric artery 48 hours after commencement, which was proven on computed tomography scan (not shown). No fevers, tachycardia, hypotension or rashes were detected after bacteriophage infusions and no adverse sequelae were attributable to the therapy.

The patient recovered after 40 days of antibiotic therapy and returned to his home state for follow-up. A positron emission tomography scan on Day 80 showed no fluorodeoxyglucose-avid lesions, including intracardiac lesions. Repeat echocardiogram on Day 98 for

Graphical representation of antimicrobial treatment, bacteriophage therapy and inflammatory markers



– = negative blood cultures; + = positive blood cultures; CRP = C-reactive protein; SMA = superior mesenteric artery; WCC = white cell count. ◆

progressive heart failure showed severely dilated left ventricle with moderate mitral and trivial aortic regurgitation. A possible mechanical aortic valve vegetation and paravalvular phlegmon were again demonstrated. Blood cultures were negative. He declined surgical intervention and died on Day 103.

To our knowledge, this was the first case of staphylococcal prosthetic valve endocarditis treated with intravenous bacteriophage (AB-SA01), which complies with good manufacturing practice standards.[4] Bacteriophage infusions were well tolerated. Future controlled trials are needed to evaluate adjunctive bacteriophage therapy, especially when surgical intervention is not feasible.

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Acknowledgements: This manuscript was prepared in collaboration with the Westmead Bacteriophage Therapy Team (WBTT) and AmpliPhi BioSciences.

We thank Patricia Fa for pharmacy support, Ruby Lin (WBTT project manager and scientific lead) for project support, and Belinda Dillon-Roychoudhry for technical assistance.

Competing interests: No relevant disclosures. ■

doi: 10.5694/mja2.50274

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