Calciphylaxis complicated by NDM-1-producing *Pseudomonas aeruginosa*: first experience with cefepime–zidebactam alongside phage therapy in the USA

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We report a case of calciphylaxis—a rare vasculopathy characterised by arteriolar calcification and ischaemic skin necrosis—in a young woman with acute myeloid leukaemia. Her ulcerated skin lesions became superinfected with a pan-resistant New Delhi metallo-β-lactamase-1-producing *Pseudomonas aeruginosa*. Although such infections in the USA have largely been associated with international travel, our patient harboured one of the earliest domestically acquired isolates. Management required novel therapeutic strategies, including the first use of cefepime–zidebactam in the USA alongside bacteriophage therapy and calciphylaxis-directed treatment. This case highlights the diagnostic complexity of calciphylaxis in atypical populations and shows the potential for innovative therapeutic approaches to achieve favourable outcomes in this rare, potentially fatal condition.

Introduction

Calciphylaxis is a rare, life-threatening vasculopathy characterised by calcification of dermal and subcutaneous arterioles, resulting in ischaemic skin necrosis and severe pain.[1–3] Ulcerated lesions are highly susceptible to secondary infection, with sepsis representing the most lethal complication.[1,4–6] Although most cases occur in patients with end-stage renal disease, calciphylaxis can also arise in individuals with normal kidney function, where its exceptional rarity can delay diagnosis.[7–9] Superimposed infections with multidrug-resistant organisms pose a particularly urgent threat. Among these, New Delhi metallo-β-lactamase (NDM)-producing *Pseudomonas aeruginosa* can hydrolyse nearly all β lactams and is associated with high mortality.[10–12] Although most reported cases in the USA have been travel-associated, domestically acquired NDM infections are emerging, raising concern for pan-resistant infections that require innovative therapeutic strategies.[13–15] In this paper, we present a case that exemplifies these diagnostic and therapeutic challenges and detail the use of novel antimicrobial approaches when conventional therapies fail.

Case presentation

A woman aged 19 years with obesity presented to our children's hospital in May, 2023, with acute respiratory failure and was found to have acute myeloid leukaemia complicated by tumour lysis syndrome and multiorgan failure. She was emergently transferred to another facility on empirical meropenem for venovenous extracorporeal membrane oxygenation (ECMO) for 7 weeks and renal replacement therapy (for 4 months total). Despite these complications, she achieved remission after a single cycle of induction chemotherapy with cytarabine and dose-reduced daunorubicin. However, persistent multiorgan dysfunction prevented standard consolidation therapy. In late June, 2023, the patient developed new-onset fevers, escalating respiratory support, and new nodular opacities on chest CT. Cultures from bronchoalveolar lavage fluid grew multidrug-resistant *Pseudomonas aeruginosa*, and cefiderocol was initiated (750 mg intravenously every 12 h, dose-adjusted for renal replacement therapy). She returned to our hospital in early July, 2023, for intermittent renal replacement therapy and oncological care with a modified regimen of azacitidine and venetoclax (managed by CL, appendix p 1). On readmission, tobramycin was added, and a surveillance culture from a tracheal aspirate identified NDM-1-producing *P aeruginosa*, resistant to all β-lactams except cefiderocol (minimum inhibitory concentration 2 μg/mL, table). Although NDM-1 was not initially detected on the previous bronchoalveolar lavage isolate, later sequencing confirmed that both isolates represented the same strain. Her course was further complicated by *Enterococcus faecalis* bacteraemia and subsequent pulmonary infections with extended-spectrum β-lactamase-producing *Klebsiella oxytoca* and *Candida parapsilosis*. As a sequela of prolonged ECMO, she also developed bilateral lower-extremity dry gangrene, necessitating a left below-knee and a right transmetatarsal amputation. These complications led to intermittent cefiderocol therapy totalling about 3·5 months and pauses in her chemotherapy regimen. A summary timeline of her clinical course is shown in the appendix (p 2).

Despite initial stabilisation, new complications emerged in November, 2023, while she was still on cefiderocol. Exquisitely painful, erythematous-to-violaceous lesions appeared on bilateral thighs and pannus. Superficial wound cultures performed at that time yielded *Streptococcus* species and *E faecalis*. Although ampicillin was started, the lesions continued to progress to ulcerated, non-healing wounds (figure 1). Plasma cell-free DNA testing (Karius) later revealed extended-spectrum β-lactamase-producing *Klebsiella aerogenes*, prompting a switch from cefiderocol to ceftazidime–avibactam (2 g intravenously every 8 h as a 4 h extended infusion). In late December, 2023, concern for ecthyma gangrenosum arose when a deep tissue biopsy grew

Lancet Infect Dis 2026

Published Online June 9, 2026 https://doi.org/10.1016/S1473-3099(26)00176-3

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See Online for appendix

	July, 2023 (day –240)	December, 2023 (day –70)	February, 2024 (day –1)	March, 2024 (day 15)	April, 2024 (day 50)	June, 2024 (day 111)
Antibiotic	Tracheal aspirate	Right thigh	Right thigh	Left thigh	Right thigh	Left and right thigh
Cefepime–zidebactam	16 (S)	16–32 (S)	64 (S)	>512 (R)	512 (R)	64 (S)
Cefiderocol	2 (S)	16 (R)	32 (R)	16 (R)	16 (R)	4 (S) / 8 (I)†
Tobramycin	≤1 (S)	≤1 (S)	8 (R)	8 (R)	8 (R)	4 (R)
Amikacin	32 (I)	≥64 (R)	≥64 (R)	≥64 (R)	≥64 (R)	≥64 (R)
Ciprofloxacin	≥4 (R)	≥4 (R)	≥4 (R)	≥4 (R)	≥4 (R)	≥4 (R)
Levofloxacin	≥8 (R)	≥8 (R)	≥8 (R)	≥8 (R)	≥8 (R)	≥8 (R)
Colistin	0·5 (I)*	..	..	..	..	..
Piperacillin–tazobactam	≥128 (R)	≥128 (R)	256 (R)*	256 (R)*	≥128 (R)	256 (R)*
Cefepime	≥32 (R)	≥32 (R)	..	≥32 (R)	≥32 (R)	256 (R)*
Ceftazidime	≥64 (R)	≥64 (R)	≥64 (R)	≥64 (R)	≥64 (R)	≥64 (R)
Ceftazidime–avibactam	256 (R)*	256 (R)*	..	..	..	..
Ceftolozane–tazobactam	≥32 (R)	256 (R)*	..	≥32 (R)	..	..
Aztreonam	..	256 (R)*	..	..	..	..
Meropenem	≥16 (R)	≥16 (R)	≥16 (R)	≥16 (R)	≥16 (R)	32 (R)*
Meropenem–vaborbactam	32 (R)*‡	..	..	..	..	..
Imipenem–relebactam	32 (R)*	32 (R)*	..	..	..	..

Study days are relative to the initiation of therapy (day 0). Antimicrobials were administered as follows: bacteriophage KEN3 (days 0–48), cefepime–zidebactam (days 2–43), tobramycin (days 0–46), and cefiderocol plus sulbactam–durlobactam (days 43–57). Negative values indicate pre-therapy timepoints. MICs (μg/mL) were determined by broth microdilution unless noted (Etest). Interpretations use CLSI M100 breakpoints unless otherwise specified (EUCAST). CLSI=Clinical and Laboratory Standards Institute. EUCAST=European Committee on Antimicrobial Susceptibility Testing. I=intermediate. MIC=minimum inhibitory concentration. R=resistant. S=susceptible. ··=not tested. *Etest. †Left and right thigh wound cultures were identical for all antibiotics except cefiderocol (left: 4 μg/mL [S]; right: 8 μg/mL [I]). ‡EUCAST.

Table: **Serial antimicrobial susceptibility testing results for New Delhi metallo-β-lactamase-producing *Pseudomonas aeruginosa* isolates**

NDM-1-producing *P aeruginosa*, now resistant to cefiderocol (MIC 16 μg/mL, table). Aztreonam (2 g intravenous continuous infusion, MIC 256 μg/mL) was then added to ceftazidime–avibactam (MIC 256 μg/mL) for potential synergy, along with tobramycin (500 mg intravenously daily, MIC ≤1 μg/mL). The patient nonetheless continued to have fevers with an elevated C-reactive protein of 254·9 mg/L. As lesions continued to progress, serial debridement with vacuum-assisted closure (VAC) was initiated in January, 2024.

Over the subsequent month, pain intensified despite escalation of multimodal analgesia, necessitating intensive care unit-level care for opioid-related respiratory depression (appendix p 4). During this period, the patient was considering comfort care, leading to a temporary suspension of operative interventions. With ongoing deterioration, suspicion arose for calciphylaxis, even though histopathology was initially unrevealing. Re-examination of the first biopsy and a second biopsy 2 months later (February, 2024) showed arteriolar calcification, fat necrosis, and thrombosis, confirming the diagnosis (figure 2A). Radiographic imaging of her painful left wrist also revealed characteristic branching vascular calcifications (figure 2B).

Faced with calciphylaxis complicated by pan-resistant NDM-1-producing *P aeruginosa*, we urgently sought alternative therapeutic options. In response, extensive antibiotic susceptibility testing was done in the Ulloa Laboratory, as previously described.[16,17] Initial testing identified cefepime–zidebactam as a promising candidate, with combination testing later revealing synergy between cefiderocol and sulbactam–durlobactam. Concurrently, bacteriophage therapy was pursued through collaboration with the Van Tyne Laboratory (appendix p 6). In late February, 2024, the US Food and Drug Administration (FDA) and our hospital's Institutional Review Board approved emergency access to cefepime–zidebactam (Wockhardt 5222; Investigational New Drug #171182) and bacteriophage vB_Pae10145-KEN3 (KEN3, Investigational New Drug #30372). This authorisation marked the first clinical use of cefepime–zidebactam in the USA.

A comprehensive treatment approach was initiated, combining antimicrobial, surgical, and calciphylaxis therapies (appendix pp 2–3). After a successful 10% test dose, systemic phage therapy with KEN3 was started at 1×10^9 plaque-forming units (PFU) administered intravenously every 8 h. Persistent wound burden with incomplete bacterial clearance prompted escalation to 5×10^9 PFU intravenously every 4 h on day 11. Therapy continued for a total of 7 weeks, during which *P aeruginosa* isolates recovered during therapy were tested retrospectively for phage resistance (figure 3A; appendix p 6). Weekly plasma samples were also retrospectively analysed for neutralisation of phage activity (figure 3B; appendix p 6). Simultaneously, surgical debridement was reinstated with continuation of VAC. Topical phage therapy was applied with the use of a Surgifoam (Ethicon, Somerville,

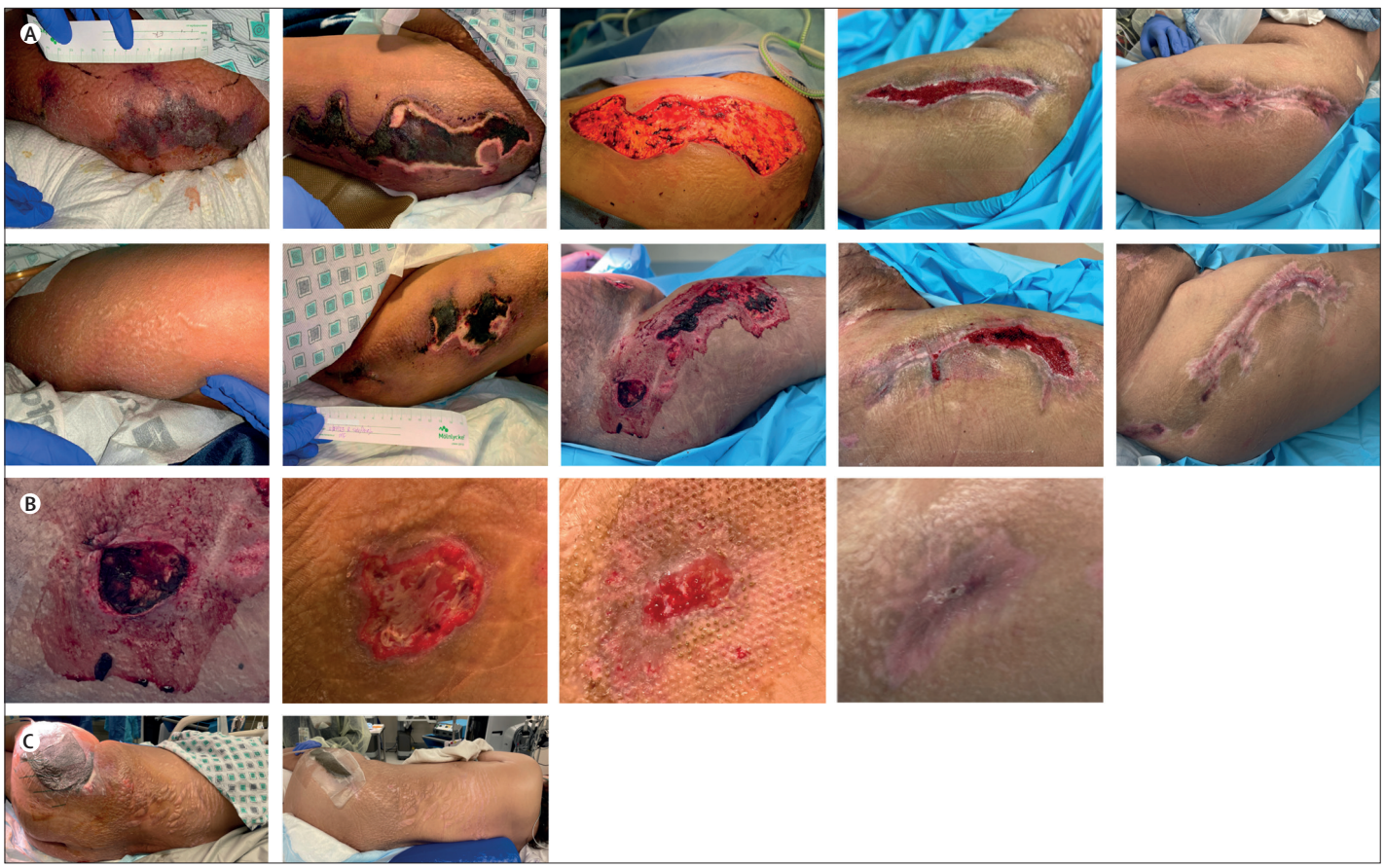


Figure 1: **Serial photographs of multifocal calciphylaxis showing disease progression and treatment response**
(A) Bilateral thighs (left thigh, top row; right thigh, bottom row) across five timepoints. The first two images (left to right) show pre-treatment disease progression, from livedo reticularis and reticulate purpura to violaceous plaques with extensive necrotic ulceration over four weeks (November to December, 2023). The subsequent three images (days 1, 111, and 225) document treatment response from March to October, 2024, culminating in near-complete healing one week prior to completion of nagtive-pressure wound therapy (October, 2024; day 225). (B) Right hip across four timepoints (days 1, 36, 71, and 139) over 5 months from March to July, 2024, demonstrating serial improvement. (C) Back showing cutaneous thickening and induration without ulceration (March, 2024; day 1) and improvement following calciphylaxis treatment (September, 2024; day 188).

NJ, USA) dressing soaked in phage solution (5×10^9 PFU in 150–250 mL normal saline) beneath layered non-adherent dressings under conventional negative-pressure therapy. This approach was discontinued after three doses due to concern for inadequate therapeutic phage exposure and the need for xenograft placement (ACell) to promote granulation tissue and wound healing.

In parallel, the patient received an 8-week course of antibiotics through to April, 2024, each dosed according to manufacturer guidelines and adjusted for her creatinine clearance (60–120 mL/min). This treatment course included 6 weeks of cefepime–zidebactam (3 g intravenously every 8 h; MIC 64 µg/mL) along with tobramycin, continued at an escalated dose (650 mg intravenously daily) despite an MIC of 8 µg/mL. Cefepime–zidebactam was discontinued when drug supply constraints limited availability, and resistance was retrospectively identified (table). The patient was then transitioned to a 2-week course of cefiderocol (1·5 g intravenously every 6 h; MIC 16 µg/mL) plus sulbactam–durlobactam (2 g intravenously every 6 h) as a bridge while chemotherapy was restarted (appendix p 1). During this time, intermittent fevers resolved and C-reactive protein decreased markedly to 20·1 mg/L (reference range 0–10 mg/L). To monitor bacterial clearance and resistance patterns, weekly wound cultures were obtained throughout her treatment course, with routine surveillance cultures performed 2 months after antibiotic discontinuation in June, 2024 (table).

Calciphylaxis management was also initiated in early March, 2024, with vitamin K (10 mg orally three times weekly) and sodium thiosulfate. Sodium thiosulfate was started at 12·5 g intravenously three times weekly and titrated to 25 g intravenously daily for a total 26-week course through to August, 2024. The patient was monitored closely for adverse effects, including hypotension, metabolic acidosis, and hypocalcaemia, with weekly electrocardiograms to assess corrected QT interval prolongation. After initiation of calciphylaxis therapy, she was able to begin a gradual wean of opioid analgesics over

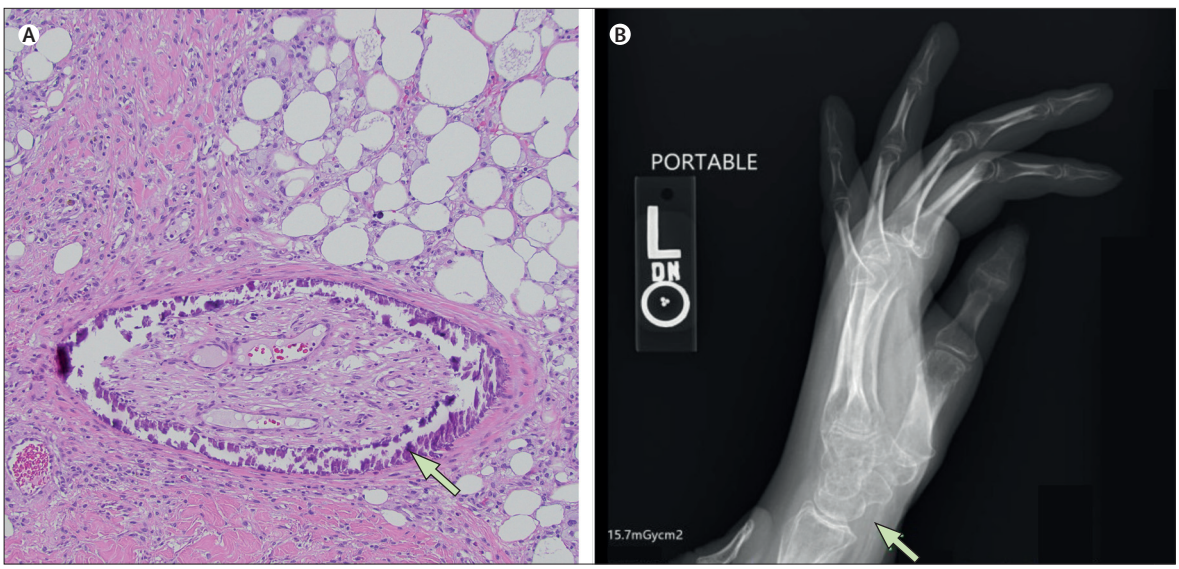


Figure 2: **Histopathological and radiographic features of calciphylaxis**
(A) Microscopic section of the wound excisional biopsy shows subcutaneous tissue with fat necrosis and inflamed granulation tissue. There are multiple calcified vessels with organised thrombi (arrow). Hematoxylin and Eosin stain, magnification ×100. (B) Radiograph of the left hand and wrist shows diffuse periarticular osteopenia and branching vascular calcifications (arrow).

the subsequent weeks (appendix p 4). Additionally, to control persistent hypercalcaemia despite sodium thiosulfate therapy, she received bisphosphonate treatment: a single dose of pamidronate 30 mg intravenously in April, 2024, followed by weekly oral alendronate 35 mg starting in June, 2024.

This multifaceted approach proved successful. After a 16·5-month hospitalisation, the patient was discharged home in September, 2024, with weekly wound VAC changes. She has been closely monitored for leukaemia relapse and, more than 18 months after completing chemotherapy, remains in complete remission without infectious complications. To our knowledge, this case represents the first clinical use of cefepime–zidebactam in the USA and the first reported case combining bacteriophage therapy with this novel β lactam–β-lactam enhancer combination for NDM-1-producing *P aeruginosa*.

Discussion and review

Calciphylaxis: a rare vascular complication

Calciphylaxis is a rare disorder characterised by calcification of the arteriolar microvasculature in the dermis and subcutaneous adipose tissue. Vessel occlusion and tissue ischemia result in severe pain that is nearly universal and often out of proportion to the visible lesions.[1–3] The disease carries high morbidity due to progressive tissue necrosis, risk of secondary infection, and few treatment options.[4,5] Also called calcific uremic arteriolopathy, calciphylaxis typically occurs in patients with end-stage renal disease on dialysis (incidence ~3·5–4·5 per 1000 patient–years).[18,19] But this condition can also arise in individuals with pre-dialysis chronic kidney disease, acute kidney injury, or normal kidney function.[7–9,20] In paediatric and young adult populations calciphylaxis is particularly rare, which can contribute to diagnostic delays.[21–26]

Our patient had several established risk factors for calciphylaxis, including female sex, obesity, history of dialysis, and chronic inflammation associated with her underlying malignancy, and prolonged hospitalisation.[1,3,18] Other recognised risk factors include hyperphosphataemia, warfarin use, diabetes, vitamin D supplementation, systemic glucocorticoids, and hypercoagulable states.[1,3,18] The pathogenesis remains incompletely understood but involves microvascular calcification driven by osteogenic signalling, deficiencies in calcification inhibitors (eg, fetuin-A and matrix Gla protein), and chronic inflammation.[3,27–30] These processes lead to arteriolar narrowing from calcium deposition, thrombosis, and subsequent tissue ischaemia and necrosis.

Clinically, calciphylaxis typically presents with extremely painful, violaceous skin lesions that progress to necrotic ulcers with black eschars.[31] Lesions most commonly affect areas of increased adiposity, including the thighs, abdomen, and buttocks, consistent with our patient's presentation.[3] The diagnosis is primarily clinical in patients with end-stage renal disease presenting with characteristic painful, ulcerated lesions, although skin biopsy might be necessary in atypical cases, as with our patient.[3] There are no specific laboratory markers for calciphylaxis. Some patients can have elevated parathyroid hormone, phosphorus, or calcium, but these findings are not consistently observed.[32] Our patient, for example, only had hypercalcaemia.

There are no high-quality studies to guide optimal treatment. Management focuses on mitigating risk

A

Phage activity detected No or reduced phage activity

	Phage treatment phase	Source	KEN3 titre (PFU/mL)
Day –15	Pre-therapy	Right abdomen	2·00E+11
Day –15	Pre-therapy	Right buttock	2·00E+10
Day –15	Pre-therapy	Right thigh	2·00E+10
Day –1	Pre-therapy	Right thigh	1·40E+10
Day 8	On therapy	Left hip	LA@E-3
Day 8	On therapy	Left hip	LA@E-3
Day 8	On therapy	Right hip	LA@E-3
Day 8	On therapy	Right hip	LA@E-2
Day 15	On therapy	Left thigh	No activity
Day 15	On therapy	Left thigh	LA@E-4
Day 15	On therapy	Right thigh	LA@E-3
Day 22	On therapy	Left thigh	LA@E-4
Day 22	On therapy	Left thigh	LA@E-3
Day 22	On therapy	Right thigh	LA@E-3
Day 50	Post-therapy (+2 days)	Right thigh	1·60E+10
Day 111	Post-therapy (+63 days)	Left thigh	2·00E+10
Day 111	Post-therapy (+63 days)	Right thigh	2·00E+10

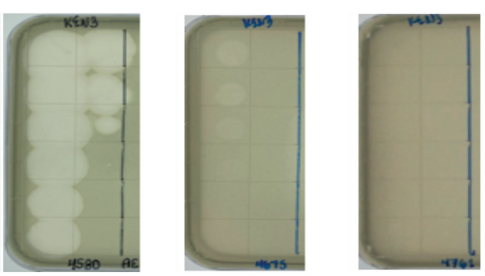
Day 0=phage therapy initiated

Day 48=phage therapy completed

Fully susceptible
Day –15 isolate
2·00E+10 PFU/mL

Lytic activity
Day 8 isolate
LA@E-3

Fully resistant
Day 15 isolate
No activity



B

Phage activity preserved; no or minimal neutralisation
Reduced phage activity; evidence of plasma neutralisation

	KEN3 titre	Titre ratio
Day 0	4·00E+10	2·0
Day 4	1·80E+10	0·9
Day 13	4·00E+07	0·002
Day 19	4·00E+06	0·0002
Day 26	1·00E+07	0·0005
Day 32	1·20E+06	0·00006
Control	2·00E+10	1·0

Phage incubated with buffer (control):

Phage incubated with plasma:

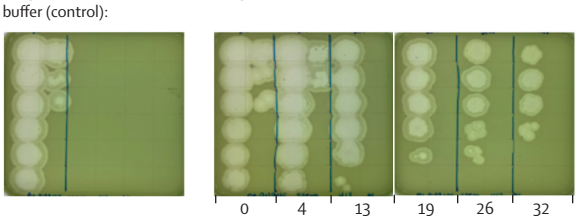


Figure 3: **Evolution of New Delhi metallo-β-lactamase-1 (NDM-1)-producing *Pseudomonas aeruginosa* susceptibility to bacteriophage KEN3 and development of plasma neutralisation during phage therapy**

(A) Phage susceptibilities. KEN3 phage titre results across serial NDM-1-producing *P aeruginosa* isolates collected from day –15 to day 111 (pre-therapy through to post-therapy follow-up). Phage therapy was administered from day 0 to day 48. Table values indicate plaque-forming units (PFU)/mL or lytic activity at the lowest dilution at which clearing was observed (eg, lytic activity @10^{-3}=lysis detectable at 10^{-3} dilution). These data show emergence of reduced phage susceptibility during therapy, followed by recovery after treatment cessation. Representative titration plates illustrate (left) full susceptibility (day –15 isolate; $2{\cdot}00 \times 10^{10}$ PFU/mL), (middle) reduced susceptibility (day 8 isolate; lytic activity @10^{-3}), and (right) complete resistance (day 15 isolate; no lytic activity). (B) Plasma neutralisation of phage activity. Table shows KEN3 titres after incubation with patient plasma collected longitudinally from day 0 to day 32 during active phage therapy, and corresponding titre ratios calculated relative to the buffer control. Progressive decline in titre ratios suggests development of neutralising anti-phage antibodies. Representative plaque assay plates depict phage incubated with (left) buffer control versus (right) patient plasma over time, demonstrating progressive neutralisation with reduced plaque formation. See appendix (p 6) for details.

factors, wound care, and pain control. However, growing evidence suggests that off-label intravenous sodium thiosulphate is associated with improvement or complete resolution of skin lesions in several studies.[33–35] Although not fully understood, postulated mechanisms include vasodilatory and antioxidant properties, as well as inhibition of adipocyte-induced vascular smooth muscle calcification.[36,37] Most experience with sodium thiosulfate involves patients on dialysis who receive the medication three to four times per week.[3] Our patient, who had recovered kidney function, received daily intravenous sodium thiosulfate, an approach with little published experience. This dosing regimen necessitated close monitoring for adverse effects, including hypotension, metabolic acidosis, electrolyte abnormalities, and QTc-interval prolongation.[3] The appropriate duration of therapy also remains unknown. Experts generally recommend a 3-month treatment course and earlier discontinuation if no clinical response is observed within 4 weeks.[38] Given our patient's extensive wounds and favourable response and tolerability, sodium thiosulfate therapy was continued for 26 weeks (6·5 months).

Vitamin K supplementation can further support vascular health by promoting carboxylation of matrix Gla protein, a key inhibitor of vascular calcification.[39] Patients with calciphylaxis have lower fractions of carboxylated matrix Gla protein, suggesting impaired vitamin K-dependent mechanisms.[28] This mechanism can explain why warfarin, a vitamin K antagonist, is a recognised risk factor for this condition.[39–42] Our patient received concurrent vitamin K therapy three times weekly alongside sodium thiosulfate, recognising the potential synergistic benefit of restoring calcification inhibitor function. She also received bisphosphonate therapy (intravenous pamidronate followed by oral alendronate) for persistent hypercalcaemia in the setting of immobilisation and calciphylaxis, as part of a comprehensive treatment approach. This strategy is occasionally employed in treatment-resistant calciphylaxis complicated by hypercalcaemia. Although evidence for bisphosphonates remain inconclusive—with meta-analyses showing no clear mortality benefit—observational studies suggest a potential reduction in amputation risk.[43]

Wound care and pain management are also essential components of treatment. Surgical debridement and negative-pressure wound therapy should be considered, particularly for infected or necrotic lesions, to promote healing.[38] Simultaneously, managing the severe pain associated with calciphylaxis often requires a multimodal regimen of analgesics targeting different mechanisms of action.[38] Our patient, for example, required fentanyl, hydromorphone, ketamine, and methadone during the acute phase of her illness. But as treatment progressed and tissue perfusion improved, her pain medications were successfully weaned (appendix p 4), reflecting the interdependence of source control, vascular healing, and symptom resolution.

Diagnostic uncertainty

Calciphylaxis carries high morbidity and mortality, largely due to infectious complications of ulcerated skin lesions, with 6-month mortality approaching 40%.[4,5] Recognition and aggressive multidisciplinary care, however, can lead to successful outcomes even in the context of extensively drug-resistant infections. In this case, the identification of pan-resistant NDM-1-producing *P aeruginosa* initially dominated the clinical focus. Necrotic skin lesions in an immunocompromised host also raised concern for ecthyma gangrenosum, further delaying the diagnosis of calciphylaxis. Other contributing factors included the exceptional rarity of this vasculopathy in young adults without end-stage renal disease and early unrevealing histopathology.[1,2,21–26] The paediatric hospital setting, where calciphylaxis is seldom encountered, might have further limited clinician familiarity with this condition. Since most adult cases occur in patients with advanced kidney disease, this patient's risk factors—female sex, obesity, previous dialysis, and chronic inflammation—did not initially trigger suspicion.[1,2,4,18,44] These combined factors illustrate the difficulty of recognising uncommon vascular calcification syndromes outside typical populations, particularly when complicated by a coexisting multidrug-resistant infection. Ultimately, the patient's excruciating pain coupled with progressive necrotic skin lesions led to a clinical diagnosis of calciphylaxis, which was confirmed by repeat biopsy and imaging. This diagnosis prompted initiation of sodium thiosulfate therapy alongside antimicrobial treatment and wound care. In retrospect, clinical improvement required the convergence of all three approaches, as any single intervention would have likely proven insufficient. This case underscores the importance of maintaining a high index of suspicion for calciphylaxis in patients with painful skin lesions and compatible risk factors, regardless of age or kidney function.

Therapeutic challenges and novel strategies for NDM-producing *P aeruginosa*

Whereas vascular pathology was the primary driver of lesion progression, local infection with pan-resistant *P aeruginosa* further complicated management, necessitating novel therapeutic approaches. NDM-producing *P aeruginosa* represents a major and emerging threat due to its extensive drug resistance and few therapeutic options.[12] This pathogen has multiple resistance mechanisms, including reduced membrane permeability, multidrug efflux pumps, and production of β lactamases across all four Ambler Classes (A–D).[12] Class B metallo-β-lactamases, which use zinc ions to hydrolyse virtually all β-lactams except monobactams, are particularly concerning. The three most clinically relevant metallo-β-lactamase families—imipenemase, Verona integron-encoded metallo-β-lactamase, and NDM—have spread globally, although they remain

relatively uncommon among *P aeruginosa* in the USA compared with other regions.[12,45]

Most US cases of NDM-producing *P aeruginosa* have been linked to international travel, but our patient harboured one of the first domestically acquired isolates.[14] Sequencing analysis traced her infection to the tertiary adult hospital where she received ECMO.[13,14] Among the eight patients in this nosocomial cluster, she was the only one to develop cefiderocol resistance.[14] The emergence of resistance was likely influenced by her exposure to intermittent cefiderocol totalling about 3·5 months between July and December, 2023, for recurrent fevers, infectious complications, and known colonisation with multidrug-resistant organisms (appendix p 2). This resistance prompted initiation of ceftazidime–avibactam plus aztreonam to leverage aztreonam's stability against metallo-β-lactamases—although reported synergy against metallo-β-lactamase-producing *P aeruginosa* is low (<10%).[46,47] It was only later that checkerboard testing confirmed a fractional inhibitory concentration index (FICI) of 2, indicating no synergy (FICI >0·5 to ≤4).[17]

With conventional options exhausted, our attention shifted to novel agents, including β-lactam enhancers, to address the patient's evolving resistance in the context of calciphylaxis. Zidebactam, the first clinically available β-lactam enhancer, both inhibits some β lactamases and shows potent binding affinity for penicillin-binding protein 2 (PBP2) in Enterobacterales, *P aeruginosa*, and *Acinetobacter* species.[48,49] The drug also inhibits Ambler Class A (including *Klebsiella pneumoniae* carbapenemases) and Class C β lactamases. Although not stable in vitro against Class B metallo-β-lactamases and Class D oxacillinases, its combination with cefepime demonstrates substantial activity against metallo-β-lactamase-producing *P aeruginosa* through its β-lactam enhancer mechanism.[50,51]

The enhancer effect arises from complementary PBP targeting: cefepime inhibits PBP1 and PBP3, whereas zidebactam engages PBP2, achieving at least 3 $\log_{10}$ bacterial killing.[50] Animal models show that this β-lactam enhancer activity lowers the cefepime pharmacodynamic target or fraction of time above the MIC from more than 60–100% to just 9–16% for an at least 1 $\log_{10}$ kill effect.[52,53] Notably, this occurs even when both drugs individually have high MICs, as the mechanism is independent of standard susceptibility cutoffs. Complementary PBP targeting also disrupts cell wall synthesis, leading to morphological changes—including spheroplast formation—that compromise bacterial membranes and accelerate cell death.[50,51]

These promising mechanistic and preclinical findings have spurred the clinical development of cefepime–zidebactam (Wockhardt 5222), which has entered multinational trials for complicated urinary tract infections in Europe and Asia.[54] In phase 1 studies, cefepime–zidebactam demonstrated linear pharmacokinetics without accumulation and about 90% renal excretion as unchanged drug.[55] The safety profile was also generally favourable, with mild adverse events, such as headache, diarrhoea, and infusion reactions. Under an FDA-approved Expanded Access application, our patient received cefepime–zidebactam (cefepime 2 g plus zidebactam 1 g) as a 60 min intravenous infusion every 8 h, based on her creatinine clearance (60–120 mL/min). At the start of therapy, the cefepime–zidebactam MIC was 64 μg/mL, which is at the upper limit but still within the Clinical and Laboratory Standards Institute investigational susceptible breakpoint (≤64 μg/mL). This relatively elevated MIC might have been influenced by the patient's preceding 3-month exposure to ceftazidime–avibactam (appendix p 2). Similar to zidebactam, avibactam is a diazabicyclooctane β-lactamase inhibitor that targets PBP2.[48,49] Selective pressure from avibactam might have driven PBP2 alterations, contributing to the initial cefepime–zidebactam MICs observed. With subsequent exposure to cefepime–zidebactam over 6 weeks, resistance ultimately emerged (MICs >512 μg/mL), exemplifying this pathogen's rapid capacity for adaptation. Whole-genome sequencing and analysis of resistance-associated mutations will be the focus of our future work.

Given both the emergence of resistance and constraints in drug supply, our salvage regimen was adjusted to combination therapy with cefiderocol and sulbactam–durlobactam for the remaining 2 weeks. Cefiderocol is a siderophore cephalosporin that exploits bacterial iron transport to cross the outer membrane, exerting its bactericidal activity primarily through inhibition of PBP3. This drug remains stable against most β lactamases, including metallo-β-lactamases.[56] That said, resistance can emerge through mutations in iron uptake systems or PBP3, and co-production of metallo-β-lactamases and serine β lactamases.[56–58] To address these additional resistance mechanisms, sulbactam–durlobactam was added. This agent combines a narrow-spectrum β-lactam β-lactamase inhibitor with no *Pseudomonas* activity (sulbactam) and a novel diazabicyclooctane β-lactamase inhibitor (durlobactam) that potently inhibits Class A, C, and D enzymes.[59,60] When used together, in-vitro checkerboard testing showed MIC reductions for cefiderocol (from 16 to 4 μg/mL) and sulbactam–durlobactam (from >16 to 0·50 μg/mL) against our patient's isolate, yielding an FICI of 0·266. Although such in-vitro synergy (FICI ≤0·50)[17] might not reliably predict clinical efficacy, similar findings have been reported with durlobactam restoring in-vitro imipenem susceptibility in *P aeruginosa*, alongside positive clinical outcomes.[60,61] This synergy likely reflects complementary targeting of distinct resistance mechanisms, with cefiderocol bypassing some metallo-β-lactamase-mediated resistance and sulbactam–durlobactam inhibiting co-existing non-metallo-β-lactamases.[62] Bacterial killing can be further enhanced through durlobactam's PBP2 inhibitory activity.[60] This effect can be particularly relevant when PBP3 function is compromised. Such a scenario has been observed in

cefiderocol-resistant NDM-producing Enterobacterales, where isolates with PBP3 mutations are resensitised by durlobactam.[58] However, this phenomenon has not yet been reported in *P aeruginosa*. Whether such PBP2-mediated killing additionally involves β-lactam enhancer mechanisms—beyond complementary multi-PBP targeting—also remains to be determined.

Considering our patient's underlying immunosuppressive state and extensive lesions, we opted for an 8-week antibiotic course. The optimal duration of antimicrobial therapy for infected calciphylaxis ulcers is not established. Variation in wound healing, host factors, and microbiological findings often necessitates individualised, prolonged courses. In our patient, this extended duration was chosen to support tissue repair while allowing concurrent modified oncological therapy to resume safely (appendix p 1).

Bacteriophage therapy for pan-resistant infections

Given the pan-resistant profile of our patient's isolate, bacteriophage therapy emerged as a promising therapeutic option. Phages are naturally occurring viruses that specifically target and lyse bacterial hosts, offering a mechanism distinct from traditional antibiotics.[63] Phage therapy was first described over a century ago, however, its clinical application was largely abandoned in Western societies with the advent of antibiotics in the 1940s. However, the rise of extensively drug-resistant pathogens has renewed interest in this therapeutic modality.[64,65]

Growing clinical experience with bacteriophage therapy has demonstrated encouraging safety profiles.[66] For instance, in a case series of 100 patients receiving personalised phage therapy, 15 adverse events were reported, including seven non-serious drug reactions suspected to be treatment-related.[67] Another analysis of 63 patients identified phage-related adverse events in only nine cases, most of which were mild and transient.[68] The most significant reaction involved fever and dyspnoea occurring 2 h after infusion of 1×10^{11} PFU/mL, which resolved with supportive care and did not recur when the same phage was subsequently administered at a lower dose (1×10^{10} PFU/mL).[69]

Optimal phage dosing remains undefined, as clinical outcomes depend on multiple variables including phage-specific characteristics (ie, burst size, adsorption rate, and stability), bacterial inoculum, multiplicity of infection or phage-to-bacteria ratios, and pre-therapeutic bacterial genetic diversity—which is particularly pronounced in *Pseudomonas*.[68,70] As a result, clinical dosing regimens have varied widely, ranging from 1×10^{3} to 1×10^{11} PFU per dose, with treatment durations extending from a single dose to 16 weeks of daily therapy.[68] Pharmacokinetic considerations are also important as intravenous phages undergo rapid clearance through mononuclear phagocyte uptake and neutralising antibody formation.[68] Direct administration at infection sites can achieve higher local concentrations and has been successfully used for infections of the skin and soft tissue, prosthetic joints, ventricular assist devices, and the respiratory tract.[68]

For our patient, bacteriophage therapy was coordinated with the Van Tyne Laboratory. The overall process, from initial laboratory contact to treatment initiation, took about 4 weeks. Within roughly 1 week, susceptibility testing identified phage KEN3, a podovirus in the genus Bruynoghevirus.[71] The phage was subsequently manufactured at 1×10^{9} PFU per dose, with endotoxin levels of 80 endotoxin units per dose and undetectable *Pseudomonas* exotoxin A (<0·64 ng per dose). Regulatory clearance followed, including FDA Emergency Investigational New Drug and local Institutional Review Board approvals. Sterility testing was required before treatment authorisation and represented the rate-limiting step, taking approximately 2·5 weeks to complete. To our knowledge, there are no previous reports describing phage therapy for superinfected ulcerated calciphylaxis lesions. Therefore, initial dosing was guided by published clinical experience in wound infections, available manufacturing titres, and expert consultation.[66,68] All dosing was also carefully coordinated to remain within FDA-specified endotoxin limits of five endotoxin units/kg per h. Treatment began with a 10% test dose (1×10^{8} PFU intravenously over 10 min), which was well tolerated. Systemic therapy was then administered at 1×10^{9} PFU intravenously every 8 h. After 11 days, the dose was increased to 5×10^{9} PFU intravenously every 4 h in response to persistent, albeit reduced, *P aeruginosa* growth. This dose adjustment was not guided by real-time phage resistance testing, as this was only performed retrospectively. Phage therapy was continued for a total of 7 weeks, initially alongside cefepime–zidebactam and later with cefiderocol plus sulbactam–durlobactam. The full phage course was well tolerated, with no treatment-related adverse events.

Beyond systemic therapy, comprehensive wound management was essential. Our patient was taken to the operating room at least weekly for negative-pressure dressing changes, debridement, and application of ACell, a porcine-derived extracellular matrix scaffold. We also attempted topical phage delivery to maximise local antimicrobial activity. Despite various delivery methods described in the literature including phage-immobilised dressings, hydrogels, and liposome-encapsulated formulations,[72] only liquid phage preparations were available for our clinical use. This formulation constraint made irrigating wound vacuum systems—which allow controlled fluid instillation and dwell periods—an attractive option. Such systems have been shown to enhance biofilm reduction in vitro with phage dwell times of at least 1 h.[73] However, only conventional negative-pressure wound therapy was feasible in our case. Surgifoam sponges soaked in phage solution were therefore placed directly on the open wounds, followed

by coverage with Mepitel and Adaptic (non-adhering) dressings before reapplying the wound VAC. Yet this approach faced practical limitations. Surgifoam is not optimised for controlled phage release, and concurrent negative-pressure wound therapy likely reduced sustained local delivery. Given these concerns and the need for xenograft placement (ACell), topical phage therapy was discontinued after three doses. Instead, the wound beds were soaked in a hypochlorous acid–containing, saline-based irrigant (VASHE Wound Cleanser Solution) before ACell application.

Throughout treatment, wound cultures remained polymicrobial—most often growing organisms such as *E faecalis* (cleared with targeted therapy), coagulase-negative staphylococci, and *Candida glabrata*—with NDM-1-producing *P aeruginosa* persisting despite our interventions. In this context, distinguishing active infection from colonisation was challenging. In our immunocompromised patient, deep tissue culture positivity together with progressive clinical decline and systemic features—including persistent fevers and elevated inflammatory markers—favoured active infection. After antimicrobial treatment, fevers resolved and inflammatory markers declined substantially. Nevertheless, the relative contribution of antimicrobial therapy versus calciphylaxis-directed interventions to the favourable outcome could not be definitively determined, as the wounds ultimately healed under the comprehensive treatment regimen.

Over the course of treatment, the patient's *P aeruginosa* isolate became resistant not only to cefepime–zidebactam (MIC >512 µg/mL) but also to phage KEN3, as evidenced by declining PFU (figure 3A). Although complete bacterial eradication was not achieved, therapy appeared to select for a slow-growing *P aeruginosa* phenotype (data not shown). In published reports, phage-driven resistance in multidrug-resistant *P aeruginosa* has been associated with beneficial evolutionary trade-offs, including reduced bacterial virulence or restored antibiotic susceptibility—a phenomenon sometimes referred to as phage steering or the see-saw effect.[74,75] Even with the emergence of phage resistance, many cases have nonetheless resulted in favourable clinical outcomes.[67,76] Such positive outcomes can also reflect synergistic interactions between phages and antibiotics, as shown in vitro against metallo-β-lactamase-producing *P aeruginosa*.[67,77,78] That said, real-time testing of phage–antibiotic combinations was not done in this case, representing an opportunity for future optimisation. Beyond bacterial resistance, weekly plasma sampling retrospectively revealed the development of plasma neutralisation of phage activity within 13 days of initiating therapy (figure 3B). Yet the effect of this neutralisation remains unclear, as successful outcomes have been reported even in patients with high anti-phage antibody titres.[79,80]

Phage and antibiotic resistance exhibited different kinetics after therapy cessation. Phage resistance reverted rapidly to susceptibility—within 2 days of stopping therapy—suggesting a high fitness cost (figure 3A). In contrast, antibiotic resistance declined more gradually (table). Follow-up cultures obtained 2 months after discontinuation of all antimicrobials (June, 2024) showed isolates were again susceptible to cefepime–zidebactam (MICs decreased from >512 to 64 µg/mL) and cefiderocol (MIC 4–8 µg/mL, within the susceptible–intermediate range). Together, these findings suggest that in-vivo selective pressures from prolonged phage and antibiotic exposure might have imposed fitness costs that became disadvantageous once therapy was withdrawn, permitting re-emergence of susceptibility over time.

Conclusion

This case represents the first reported use of bacteriophage therapy combined with a novel β-lactam enhancer targeting NDM-1-producing *P aeruginosa* in a young adult patient with calciphylaxis. Our report highlights the intricate interplay between rare vascular pathology and emerging antimicrobial resistance, offering important lessons for clinical practice. Early suspicion and diagnosis of calciphylaxis in atypical patients, particularly when complicated by multidrug-resistant infections, are key to improving outcomes. In this case, addressing the concomitant resistant infection required rapid bedside-to-bench testing that enabled the rational selection of antimicrobial agents that otherwise would not have been considered. Successful management ultimately required a multifaceted approach, combining novel antimicrobial strategies, calciphylaxis-directed therapy, surgical intervention, and rigorous wound care. The favourable outcome—with complete wound healing 8 months after therapy and ongoing leukaemia remission more than 18 months post-chemotherapy—illustrates the value of persistence and multidisciplinary collaboration in managing complex, life-threatening conditions.

Contributors

ERU designed and managed the antimicrobial, phage, and calciphylaxis treatment approach, coordinated multidisciplinary care, performed microbiological analyses (including cefepime–zidebactam, cefiderocol, and sulbactam–durlobactam testing), created figures, and revised and finalised the manuscript. DJ designed and directed the wound care and surgical management. MTT wrote the initial draft and assisted with medication management. CL and HT managed oncological therapy. ERU and DC obtained Institutional Review Board and regulatory approvals, and DC assisted with sample collection. AN performed histopathological examination and interpretation. SUN provided calciphylaxis expertise. MPN directed the original isolation and characterisation of phage KEN3. DVT performed phage susceptibility testing, phage manufacturing, and plasma neutralisation testing. ERU, DJ, MTT, CL, and HT were involved in patient care, had full access to all clinical data, and verified the underlying data. All authors critically reviewed and approved the final manuscript.

Declaration of interests

We declare no competing interests.

Acknowledgments

Written informed consent was obtained from the patient for the publication of data and photographs. This work was supported by a US

National Institute of Allergy and Infectious Diseases K08 award (K08AI151253 to ERU), a US National Center for Advancing Translational Sciences UM1 award (UM1TR004927 to ERU), the Children's Hospital of Orange County (to ERU), a Congressionally Directed Medical Research Program grant (PR182667 to MPN), and the US Department of Medicine at the University of Pittsburgh School of Medicine (to DVT). The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Defense Health Agency, Department of War, nor the US Government. We thank Wockhardt, India, for facilitating the timely supply of cefepime–zidebactam; Lillian Musila (Kenya Medical Research Institute and Walter Reed Army Institute of Research [WRAIR]-Africa, Nairobi, Kenya) for the original isolation of phage KEN3; the WRAIR Wound Infections Department team for the initial characterisation of phage KEN3, including genomic analysis; George Sakoulas (Sharp Rees-Stealy Medical Group, San Diego, CA, USA) for key clinical input; and Chloe Castells for her unwavering support throughout. We are grateful to the CHOC Clinical Microbiology Laboratory for processing serial wound cultures, and to the CHOC Pharmacy team for coordinating receipt, handling, and administration protocols for investigational antimicrobials (bacteriophage KEN3 and cefepime–zidebactam). We also thank the CHOC palliative care team and the CHOC oncology physicians, nurse practitioners, and nursing staff for their exceptional care of the patient throughout her prolonged hospitalisation.

References

1 Nigwekar SU, Kroshinsky D, Nazarian RM, et al. Calciphylaxis: risk factors, diagnosis, and treatment. *Am J Kidney Dis* 2015; **66:** 133–46.

2 Nigwekar SU. Calciphylaxis. *Curr Opin Nephrol Hypertens* 2017; **26:** 276–81.

3 Nigwekar SU, Thadhani R, Brandenburg VM. Calciphylaxis. *N Engl J Med* 2018; **378:** 1704–14.

4 McCarthy JT, El-Azhary RA, Patzelt MT, et al. Survival, risk factors, and effect of treatment in 101 patients with calciphylaxis. *Mayo Clin Proc* 2016; **91:** 1384–94.

5 Gabel CK, Nguyen ED, Chakrala T, et al. Assessment of outcomes of calciphylaxis. *J Am Acad Dermatol* 2021; **85:** 1057–64.

6 Adrogué HJ, Frazier MR, Zeluff B, Suki WN. Systemic calciphylaxis revisited. *Am J Nephrol* 1981; **1:** 177–83.

7 Nigwekar SU, Wolf M, Sterns RH, Hix JK. Calciphylaxis from nonuremic causes: a systematic review. *Clin J Am Soc Nephrol* 2008; **3:** 1139–43.

8 Bajaj R, Courbebaisse M, Kroshinsky D, Thadhani RI, Nigwekar SU. Calciphylaxis in patients with normal renal function: a case series and systematic review. *Mayo Clin Proc* 2018; **93:** 1202–12.

9 Yu WY-H, Bhutani T, Kornik R, et al. Warfarin-associated nonuremic calciphylaxis. *JAMA Dermatol* 2017; **153:** 309–14.

10 Shanthi M, Sekar U, Kamalanathan A, Sekar B. Detection of New Delhi metallo beta lactamase-1 (NDM-1) carbapenemase in *Pseudomonas aeruginosa* in a single centre in southern India. *Indian J Med Res* 2014; **140:** 546–50.

11 Wu W, Feng Y, Tang G, Qiao F, McNally A, Zong Z. NDM metallo-β-lactamases and their bacterial producers in health care settings. *Clin Microbiol Rev* 2019; **32:** e00115–18.

12 Tenover FC, Nicolau DP, Gill CM. Carbapenemase-producing *Pseudomonas aeruginosa*—an emerging challenge. *Emerg Microbes Infect* 2022; **11:** 811–14.

13 Gray HK, Beaird OE, Smith EA, Schaenman JM, Yang S. Domestically acquired NDM-1-producing *Pseudomonas aeruginosa*, southern California, USA, 2023. *Emerg Infect Dis* 2023; **29:** 2382–85.

14 Garrigues JM, Gray HK, Ison RP, et al. Outbreak of New Delhi metallo-β-lactamase carbapenemase-producing *Pseudomonas aeruginosa* infections in a Southern California hospital. *Am J Infect Control* 2025; **53:** 977–84.

15 Rankin DA, Stahl A, Sabour S, et al. Changes in carbapenemase-producing carbapenem-resistant Enterobacterales, 2019 to 2023. *Ann Intern Med* 2025; **178:** 1818–21.

16 Clinical & Laboratory Standards Institute. M100: performance standards for antimicrobial susceptibility testing. Clinical & Laboratory Standards Institute, 2021.

17 Leber. Clinical microbiology procedures handbook, vol 5, 5th edn. American Society for Microbiology, 2023.

18 Nigwekar SU, Zhao S, Wenger J, et al. A nationally representative study of calcific uremic arteriolopathy risk factors. *J Am Soc Nephrol* 2016; **27:** 3421–29.

19 Toussaint ND, Davies CE, Bongetti E, et al. Calciphylaxis episodes in the Australia and New Zealand dialysis and transplant registry. *Kidney Int Rep* 2024; **9:** 951–59.

20 Desai P, Derby C, Cioffi MA, et al. Calciphylaxis in the setting of acute kidney injury. *Cureus* 2025; **17:** e82018.

21 Araya CE, Fennell RS, Neiberger RE, Dharnidharka VR. Sodium thiosulfate treatment for calcific uremic arteriolopathy in children and young adults. *Clin J Am Soc Nephrol* 2006; **1:** 1161–66.

22 Feng J, Gohara M, Lazova R, Antaya RJ. Fatal childhood calciphylaxis in a 10-year-old and literature review. *Pediatr Dermatol* 2006; **23:** 266–72.

23 Stârcea M, Gavrilovici C, Elsayed A, et al. A case report of pediatric calciphylaxis—a rare and potentially fatal under diagnosed condition. *Medicine* 2018; **97:** e11300.

24 Distel HL, Purohit PJ, Ingraham SE, Feng AK. Calciphylaxis in a pediatric patient with multisystem inflammatory syndrome. *JAAD Case Rep* 2023; **35:** 80–83.

25 Imam AA, Mattoo TK, Kapur G, Bloom DA, Valentini RP. Calciphylaxis in pediatric end-stage renal disease. *Pediatr Nephrol* 2005; **20:** 1776–80.

26 Timmis A, Morgan H. Calciphylaxis in a paediatric patient. *BMJ Case Rep* 2010; **2010:** bcr0520102989.

27 Au S, Crawford RI. Three-dimensional analysis of a calciphylaxis plaque: clues to pathogenesis. *J Am Acad Dermatol* 2002; **47:** 53–57.

28 Kramann R, Brandenburg VM, Schurgers LJ, et al. Novel insights into osteogenesis and matrix remodelling associated with calcific uraemic arteriolopathy. *Nephrol Dial Transplant* 2013; **28:** 856–68.

29 Nigwekar SU, Jiramongkolchai P, Wunderer F, et al. Increased bone morphogenetic protein signaling in the cutaneous vasculature of patients with calciphylaxis. *Am J Nephrol* 2017; **46:** 429–38.

30 Tian F, Patterson AT, Davick JJ, et al. The cutaneous expression of vitamin K-dependent and other osteogenic proteins in calciphylaxis stratified by clinical features and warfarin use: a case control study. *J Am Acad Dermatol* 2016; **75:** 840–842.e1.

31 Weenig RH. Pathogenesis of calciphylaxis: Hans Selye to nuclear factor kappa-B. *J Am Acad Dermatol* 2008; **58:** 458–71.

32 Fine A, Zacharias J. Calciphylaxis is usually non-ulcerating: risk factors, outcome and therapy. *Kidney Int* 2002; **61:** 2210–17.

33 Zitt E, König M, Vychytil A, et al. Use of sodium thiosulphate in a multi-interventional setting for the treatment of calciphylaxis in dialysis patients. *Nephrol Dial Transplant* 2013; **28:** 1232–40.

34 Nigwekar SU, Brunelli SM, Meade D, et al. Sodium thiosulfate therapy for calcific uremic arteriolopathy. *Clin J Am Soc Nephrol* 2013; **8:** 1162–70.

35 Hackett BC, McAleer MA, Sheehan G, Powell FC, O'Donnell BF. Calciphylaxis in a patient with normal renal function: response to treatment with sodium thiosulfate. *Clin Exp Dermatol* 2009; **34:** 39–42.

36 Hayden MR. Calciphylaxis and the cardiometabolic syndrome: the emerging role of sodium thiosulfate as a novel treatment option. *J Cardiometab Syndr* 2008; **3:** 55–59.

37 Chen NX, O'Neill K, Akl NK, Moe SM. Adipocyte induced arterial calcification is prevented with sodium thiosulfate. *Biochem Biophys Res Commun* 2014; **449:** 151–56.

38 Chewcharat A, Nigwekar SU. Ten tips on how to deal with calciphylaxis patients. *Clin Kidney J* 2025; **18:** sfaf098.

39 Wallin R, Cain D, Sane DC. Matrix Gla protein synthesis and gamma-carboxylation in the aortic vessel wall and proliferating vascular smooth muscle cells—a cell system which resembles the system in bone cells. *Thromb Haemost* 1999; **82:** 1764–67.

40 Nigwekar SU, Bhan I, Turchin A, et al. Statin use and calcific uremic arteriolopathy: a matched case-control study. *Am J Nephrol* 2013; **37:** 325–32.

41 Hayashi M, Takamatsu I, Kanno Y, et al. A case-control study of calciphylaxis in Japanese end-stage renal disease patients. *Nephrol Dial Transplant* 2012; **27:** 1580–84.

42 Coates T, Kirkland GS, Dymock RB, et al. Cutaneous necrosis from calcific uremic arteriolopathy. *Am J Kidney Dis* 1998; **32:** 384–91.

43 Udomkarnjananun S, Kongnatthasate K, Praditpornsilpa K, et al. Treatment of calciphylaxis in CKD: a systematic review and meta-analysis. *Kidney Int Rep* 2018; **4:** 231–44.

44 Brandenburg VM, Kramann R, Rothe H, et al. Calcific uraemic arteriolopathy (calciphylaxis): data from a large nationwide registry. *Nephrol Dial Transplant* 2017; **32:** 126–32.

45 Wang M-G, Liu Z-Y, Liao X-P, et al. Retrospective data insight into the global distribution of carbapenemase-producing *Pseudomonas aeruginosa*. *Antibiotics* 2021; **10:** 548.

46 Mauri C, Maraolo AE, Di Bella S, Luzzaro F, Principe L. The revival of aztreonam in combination with avibactam against metallo-β-lactamase-producing Gram-negatives: a systematic review of in vitro studies and clinical cases. *Antibiotics* 2021; **10:** 1012.

47 Tamma PD, Heil EL, Justo JA, Mathers AJ, Satlin MJ, Bonomo RA. Infectious Diseases Society of America 2024 guidance on the treatment of antimicrobial-resistant gram-negative infections. *Clin Infect Dis* 2024; **72:** e169–e183.

48 Rajavel M, Kumar V, Nguyen H, et al. Structural characterization of diazabicyclooctane β-lactam 'enhancers' in complex with penicillin-binding proteins PBP2 and PBP3 *of Pseudomonas aeruginosa*. *MBio* 2021; **12:** e03058–20.

49 Papp-Wallace KM, Nguyen NQ, Jacobs MR, et al. Strategic approaches to overcome resistance against Gram-negative pathogens using β-lactamase inhibitors and β-lactam enhancers: activity of three novel diazabicyclooctanes WCK 5153, zidebactam (WCK 5107), and WCK 4234. *J Med Chem* 2018; **61:** 4067–86.

50 Moya B, Barcelo IM, Bhagwat S, et al. WCK 5107 (zidebactam) and WCK 5153 are novel inhibitors of PBP2 showing potent 'β-lactam enhancer' activity against *Pseudomonas aeruginosa*, including multidrug-resistant metallo-β-lactamase-producing high-risk clones. *Antimicrob Agents Chemother* 2017; **61:** e02529–16.

51 Hujer AM, Marshall SH, Mack AR, et al. Transcending the challenge of evolving resistance mechanisms in *Pseudomonas aeruginosa* through β-lactam-enhancer-mechanism-based cefepime/zidebactam. *MBio* 2023; **14:** e0111823.

52 Monogue ML, Tabor-Rennie J, Abdelraouf K, Nicolau DP. In vivo efficacy of WCK 5222 (cefepime-zidebactam) against multidrug-resistant *Pseudomonas aeruginosa* in the neutropenic Murine thigh infection model. *Antimicrob Agents Chemother* 2019; **63:** e00233–19.

53 Kidd JM, Abdelraouf K, Nicolau DP. Efficacy of human-simulated bronchopulmonary exposures of cefepime, zidebactam and the combination (WCK 5222) against MDR *Pseudomonas aeruginosa* in a neutropenic murine pneumonia model. *J Antimicrob Chemother* 2020; **75:** 149–55.

54 ClinicalTrials.gov. Study of cefepime-zidebactam (FEP-ZID) in complicated urinary tract infection (cUTI) or acute pyelonephritis (AP). 2025. https://clinicaltrials.gov/ct2/show/NCT04979806 (accessed Sept 25, 2025).

55 Preston RA, Mamikonyan G, Mastim M, et al. Single-center investigation of the pharmacokinetics of WCK 4282 (cefepime-tazobactam combination) in renal impairment. *Antimicrob Agents Chemother* 2019; **63:** e00873–19.

56 Sato T, Yamawaki K. Cefiderocol: discovery, chemistry, and in vivo profiles of a novel siderophore cephalosporin. *Clin Infect Dis* 2019; **69** (suppl 7)**:** S538–43.

57 Wang Q, Jin L, Sun S, et al. Occurrence of high levels of cefiderocol resistance in carbapenem-resistant *Escherichia coli* before its approval in China: a report from China CRE-network. *Microbiol Spectr* 2022; **10:** e0267021.

58 Aitken SL, Pierce VM, Pogue JM, et al. The growing threat of NDM-producing *Escherichia coli* with penicillin-binding protein 3 mutations in the United States—is there a potential role for durlobactam? *Clin Infect Dis* 2024; **79:** 834–37.

59 McLeod SM, O'Donnell JP, Narayanan N, Mills JP, Kaye KS. Sulbactam-durlobactam: a β-lactam/β-lactamase inhibitor combination targeting *Acinetobacter baumannii*. *Future Microbiol* 2024; **19:** 563–76.

60 Pogue JM, Harrington J, Wangchinda W, Kaye KS. New perspectives on antimicrobial agents: sulbactam–durlobactam. *Antimicrob Agents Chemother* 2025; **69:** e0108624.

61 McLeod SM, Miller AA, Rana K, Altarac D, Moussa SH, Shapiro AB. Clinical outcomes for patients with monomicrobial *vs polymicrobial Acinetobacter baumannii-calcoaceticus* complex infections treated with sulbactam-durlobactam or colistin: a subset analysis from a phase 3 clinical trial. *Open Forum Infect Dis* 2024; **11:** ofae140.

62 Dorazio AJ, Kline EG, Squires KM, et al. Restoring ceftolozane susceptibility: a role for diazabicyclooctane β-lactamase inhibitors? *Antimicrob Agents Chemother* 2025; **69:** e0154324.

63 Rohwer F, Segall AM. In retrospect: a century of phage lessons. *Nature* 2015; **528:** 46–48.

64 El Haddad L, Harb CP, Gebara MA, Stibich MA, Chemaly RF. A systematic and critical review of bacteriophage therapy against multidrug-resistant ESKAPE organisms in humans. *Clin Infect Dis* 2019; **69:** 167–78.

65 Sawa T, Moriyama K, Kinoshita M. Current status of bacteriophage therapy for severe bacterial infections. *J Intensive Care* 2024; **12:** 44.

66 Uyttebroek S, Chen B, Onsea J, et al. Safety and efficacy of phage therapy in difficult-to-treat infections: a systematic review. *Lancet Infect Dis* 2022; **22:** e208–20.

67 Pirnay J-P, Djebara S, Steurs G, et al. Personalized bacteriophage therapy outcomes for 100 consecutive cases: a multicentre, multinational, retrospective observational study. *Nat Microbiol* 2024; **9:** 1434–53.

68 Suh GA, Lodise TP, Tamma PD, et al. Considerations for the use of phage therapy in clinical practice. *Antimicrob Agents Chemother* 2022; **66:** e0207121.

69 Aslam S, Lampley E, Wooten D, et al. Lessons learned from the first 10 consecutive cases of intravenous bacteriophage therapy to treat multidrug-resistant bacterial infections at a single center in the United States. *Open Forum Infect Dis* 2020; **7:** ofaa389.

70 Abedon ST. How simple maths can inform our basic understanding of phage therapy. *Clin Infect Dis* 2023; **77** (suppl 5)**:** S401–06.

71 Burke KA, Urick CD, Mzhavia N, Nikolich MP, Filippov AA. Correlation of *Pseudomonas aeruginosa* phage resistance with the numbers and types of antiphage systems. *Int J Mol Sci* 2024; **25:** 1424.

72 Chang RYK, Morales S, Okamoto Y, Chan H-K. Topical application of bacteriophages for treatment of wound infections. *Transl Res* 2020; **220:** 153–66.

73 Nebeluk N, Van Tyne D, Saharia K, Doub JB. What are the optimal irrigating wound vacuum parameters when using bacteriophage therapeutics? *Surg Infect* 2025; **26:** 557–60.

74 Gurney J, Pradier L, Griffin JS, et al. Phage steering of antibiotic-resistance evolution in the bacterial pathogen, *Pseudomonas aeruginosa*. *Evol Med Public Health* 2020; **2020:** 148–57.

75 Ashworth EA, Wright RCT, Shears RK, et al. Exploiting lung adaptation and phage steering to clear pan-resistant *Pseudomonas aeruginosa* infections in vivo. *Nat Commun* 2024; **15:** 1547.

76 Chan BK, Stanley GL, Kortright KE, et al. Personalized inhaled bacteriophage therapy for treatment of multidrug-resistant *Pseudomonas aeruginosa* in cystic fibrosis. *Nat Med* 2025; **31:** 1494–501.

77 Comeau AM, Tétart F, Trojet SN, Prère M-F, Krisch HM. Phage-antibiotic synergy (PAS): beta-lactam and quinolone antibiotics stimulate virulent phage growth. *PLoS One* 2007; **2:** e799.

78 Paranos P, Vourli S, Pournaras S, Meletiadis J. In vitro interactions between bacteriophages and antibacterial agents of various classes against multidrug-resistant metallo-β-lactamase-producing *Pseudomonas aeruginosa* clinical isolates. *Pharmaceuticals* 2025; **18:** 343.

79 Łusiak-Szelachowska M, Zaczek M, Weber-Dąbrowska B, et al. Phage neutralization by sera of patients receiving phage therapy. *Viral Immunol* 2014; **27:** 295–304.

80 Łusiak-Szelachowska M, Żaczek M, Weber-Dąbrowska B, et al. Antiphage activity of sera during phage therapy in relation to its outcome. *Future Microbiol* 2017; **12:** 109–17.