A Dangerous Duo: A Rare but Severe Case of Coinfection

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Case Presentation

- **71-year-old man** with **relapsed stage IV diffuse large B-cell lymphoma**, admitted for **COP chemotherapy.**
- Past history: hypertension, dyslipidemia, carotid atherosclerosis, coronary artery disease (non-significant), glaucoma, asthma, hepatic steatosis.
- Recent prolonged travel in North Africa.
- **Shortly after chemotherapy:** developed fever, productive cough, hypotension (BP 55/39 mmHg), **septic shock.**
- Required ICU admission, vasopressors, high-flow nasal oxygen; new atrial fibrillation on amiodarone.

Investigations

- **Bronchoalveolar lavage (single sample):**
  - **Methicillin-resistant *Staphylococcus aureus* (MRSA)** (vancomycin susceptible)
  - **Non-typhoidal *Salmonella enterica*** (ceftriaxone susceptible)
- **Serial blood cultures:**
  - Day 1: **MRSA** 2/2 positive
    Salmonella enterica 2/2 positive
  - Day 2: **MRSA** 4/4 positive
    Salmonella enterica 2/4 positive
  - Day 3: negative
  - Day 4: **MRSA** 1/2 positive
  - Days 5–7: negative
  - Day 8: **MRSA** 1/2 positive

Investigations (continued)

- **Urine culture:** MRSA positive
- **Chest CT:** Left upper lobe **cavitary necrotizing pneumonia** + multifocal bilateral infiltrates
- **Abdominal CT:** splenic & bilateral renal infarcts, mild ascites
- **Brain CT:** ischemic stroke with hemorrhagic transformation.
- **TEE:** no endocarditis.

Relevant negative labs:

- **BAL additional testing:**
  - Negative for fungi, *Nocardia*, *Legionella*, cultures
  - *Aspergillus* galactomannan and *Pneumocystis jirovecii* antigens: negative
  - Multiplex respiratory PCR panel: negative
  - *Mycobacterium* culture: pending
- HIV, hepatitis B & C serologies: negative
- CMV: IgG positive, IgM negative

Pending tests:

- Interferon-gamma release assay: pending
- *Strongyloides* serology: pending
- Stool ova & parasites: pending
- Stool culture: pending

Diagnosis

Necrotizing pneumonia with persistent bacteremia due to MRSA + non-typhoidal *Salmonella enterica*, complicated by systemic septic emboli (splenic, renal, cerebral)

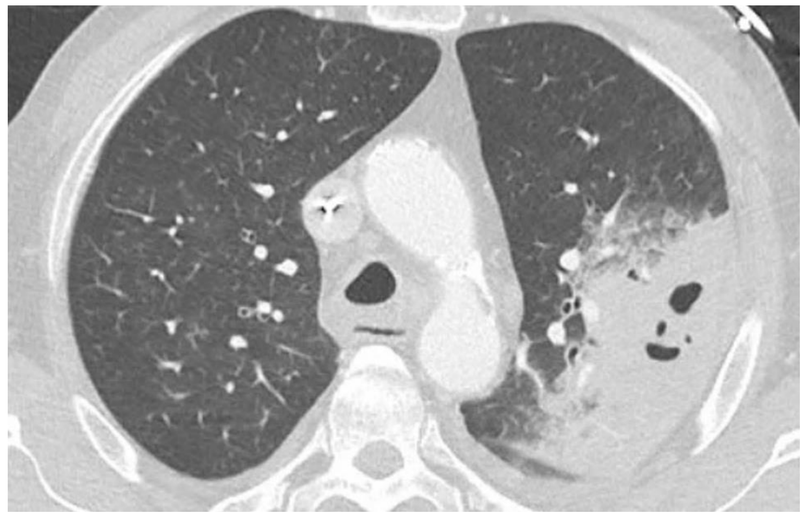

Figure 1: Cavitary necrotizing pneumonia

Clinical Course

- Initial empiric therapy with piperacillin-tazobactam and vancomycin was narrowed to ceftriaxone and vancomycin.
  - Despite this regimen, **blood cultures remained persistently positive** (see Investigations).
- Central venous line was removed due to concern for line-associated infection.
- Antibiotics were escalated:
  - **Clindamycin** added for **toxin suppression**
  - Ceftriaxone replaced by **ceftobiprole** for **MRSA pneumonia** coverage (Ceftobiprole also tested on Salmonella strain: susceptible).
  - Switch from vancomycin to **daptomycin** was planned for **MRSA bacteremia**, given persistent bacteremia with vancomycin.

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Clinical Course (continued)

- However, initiation of daptomycin was delayed:
  - The patient had a concomitant intramuscular iliopsoas hematoma with elevated creatine kinase
  - Daptomycin known to further increase CK

- Given the epidemiologic risk factors, empiric ivermectin was administered as a precaution while disseminated *Strongyloides stercoralis* infection had not yet been excluded, even though suspicion was low.
  - *Strongyloides* serology was still pending

- Repeat chest CT demonstrated progression with new multilobar cavitary lesions.
  - An FDG-PET scan was ordered to evaluate for metastatic infectious foci, given embolic phenomena, but was not performed because of severe dyspnea and worsening respiratory failure.

- Despite antimicrobial escalation and supportive measures, the patient deteriorated clinically.
  - He was transitioned to comfort care, and subsequently deceased.

- Pending investigations were not pursued/processed due to the change in care level.

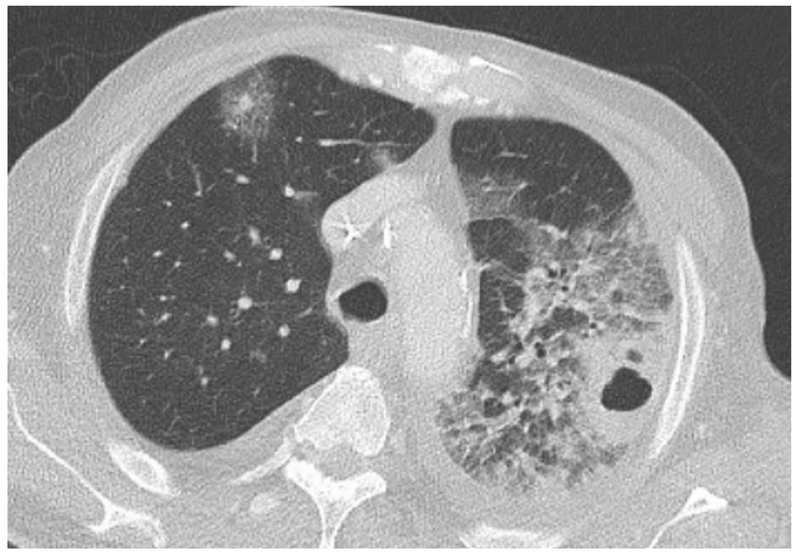

Figure 2: Progressive cavitary pneumonia

Discussion

Invasive non-typhoidal *Salmonella* disease, such as pneumonia, is exceptionally rare and occurs almost exclusively in immunocompromised patients, with high morbidity and mortality.[1,2]

This patient also presented with MRSA bacteremia that was persistent despite vancomycin therapy. Persistent MRSA bacteremia is a well-recognized poor prognostic factor, and each additional day of bacteremia has been shown to increase mortality. Current guidance emphasizes prompt evaluation for metastatic or endovascular foci (e.g., with transesophageal echocardiography or FDG-PET imaging).[3,4]

Discussion (continued)

Removal of potentially infected intravascular catheters, and aggressive source control, including drainage of abscesses and debridement of infected tissue, is essential for improving outcomes.[3,4]

When vancomycin fails, escalation to second-line, site-specific therapies is recommended.

Ceftobiprole

Ceftobiprole can be used in the treatment of MRSA pneumonia when vancomycin therapy has failed, particularly in cases of community-acquired pneumonia (CAP) or hospital-acquired pneumonia (HAP) not associated with mechanical ventilation. Ceftobiprole is a new generation cephalosporin with documented bactericidal activity against MRSA, including strains with reduced susceptibility to vancomycin.[5,6]

Daptomycin

Daptomycin, although ineffective in the lungs due to inactivation by surfactant and not recommended for the treatment of pneumonia, is highly effective in bloodstream infection. It is recommended by clinical guidelines for persistent MRSA bloodstream infections (bacteremia), especially in cases of vancomycin treatment failure or when the vancomycin MIC is elevated.[7]

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Discussion (continued)

Ceftobiprole-Daptomycin Synergy

Ceftobiprole–daptomycin combination therapy has shown promising synergy in invasive MRSA infections, particularly in the context of persistent bacteremia and endocarditis.

This synergy was demonstrated in vitro in 2014, where the combination enhanced daptomycin binding and achieved sustained bactericidal activity across multiple MRSA strains, including vancomycin-intermediate isolates.[8]

A systematic review in 2022 confirmed that ceftobiprole–daptomycin combinations are among the most consistently synergistic across in vitro and in vivo studies.[9]

In 2022, Boni et al. reported a case of MRSA native valve endocarditis treated with ceftobiprole + daptomycin, providing pharmacokinetic evidence of effective valve tissue penetration by both agents and supporting their potential role in endovascular infections.[10]

In this patient, the presence of persistent bacteremia with distal embolic phenomena strongly suggested an underlying endovascular source or endocarditis, which could not be fully investigated (no TEE or FDG-PET performed). This scenario provides a rationale for considering combination therapy.

Discussion (continued)

Role of clindamycin in necrotising pneumonia

Clindamycin is recommended as adjunctive therapy in necrotizing pneumonia when a toxin-mediated infection is suspected, such as with PVL-positive *Staphylococcus aureus* or group A *Streptococcus*.

In vitro, Stevens et al. (2007) showed that clindamycin suppresses translation of key exotoxins in *S. aureus*, notably PVL, TSST-1, and α-hemolysin, whereas nafcillin and vancomycin failed to suppress and even enhanced toxin production.[12]

Clinically, Soavi et al. (2011) reported a case of PVL-positive necrotizing MRSA pneumonia where the patient deteriorated on ampicillin-sulbactam and vancomycin but improved only after initiation of the toxin-suppressing agents clindamycin and linezolid.[13]

More recently, the CASSETTE pilot randomized controlled trial (Campbell et al., 2022) provided the first randomized data on adjunctive clindamycin in severe *S. aureus* infections, showing feasibility, no safety concerns, and a signal toward lower mortality in the clindamycin arm despite small numbers.[14]

Discussion (continued)

Considerations for off-label ceftobiprole use in non-typhoidal Salmonella infection

Ceftobiprole, in addition to its activity against MRSA, also covers many Gram-negative bacteria, including non-ESBL-producing *Enterobacterales*.[11]

Clinical and surveillance studies have not included *Salmonella* isolates, and ceftobiprole has therefore not yet been established as effective against *Salmonella* species.

However, in this particular case, treatment with ceftriaxone + vancomycin had failed, and for the MRSA component of the pneumonia, linezolid was contraindicated due to thrombocytopenia + anemia following recent COP chemotherapy.

These considerations prompted us to use a ceftobiprole–daptomycin regimen for their reported synergy against MRSA. At the same time, the **patient's *Salmonella*** isolate **was** confirmed to be **susceptible** to **ceftobiprole**, supporting its use for concomitant Salmonella coverage.

It must nevertheless be emphasized that the use of ceftobiprole for *Salmonella* is off-label and is not currently recommended in guidelines. Third-generation cephalosporins remain the standard of care.

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Learning objectives

1. Recognize second-line anti-MRSA treatment options when vancomycin fails (e.g., ceftobiprole for MRSA pneumonia; daptomycin for MRSA bacteremia).
2. Identify key management principles in persistent MRSA bacteremia, including evaluation for endovascular and metastatic foci and prompt removal of potentially infected intravascular catheters or devices.

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Conflicts of Interest

	Co-author	Conflict disclosures
1	Yu Shi Wang	No conflicts to disclose
2	Patrice Savard	No conflicts to disclose