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Experience with Amphotericin B Deoxycholate Loaded Bone Cement in Staged Treatment of Osteoarticular Infections

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Abstract: Osteoarticular infections, especially those involving fungal pathogens, present significant therapeutic challenges due to limited vascularization and the difficulty of achieving adequate drug concentrations at the site of infection. Amphotericin B deoxycholate, a potent antifungal with a broad spectrum, has been employed in combination with polymethylmethacrylate (PMMA) bone cement as a local delivery system during staged surgical management. This article reviews current evidence, including clinical outcomes, pharmacokinetics, mechanical implications, and practical recommendations for using amphotericin B-loaded bone cement in the staged treatment of osteoarticular infections.

Keywords: Osteoarticular Infections, Amphotericin B, Bone Cement, Polymethylmethacrylate (PMMA), Local Drug Delivery.

INTRODUCTION

Osteoarticular infections caused by fungi such as *Candida* and *Aspergillus* species are rare but increasingly recognized, particularly in immunocompromised patients and those with previous orthopedic interventions. Conventional systemic antifungal therapy often fails to deliver sufficient drug levels to infected bone and joint tissues, leading to persistent or recurrent infection.

Local delivery via antifungal-loaded bone cement has gained attention as an adjunct to systemic therapy, providing prolonged, high local concentrations with reduced systemic toxicity. The staged protocol typically involves initial debridement and placement of amphotericin B-loaded cement spacers, followed by delayed reimplantation.

RATIONALE AND MECHANISM

Amphotericin B Deoxycholate is thermally stable (up to 170°C), allowing for safe incorporation into PMMA cement, where it is gradually eluted, achieving sustained local antifungal concentrations surpassing systemic delivery capabilities. The local delivery:

- Enhances fungicidal activity at the infection site.

- Minimizes systemic exposure and related nephrotoxicity or infusion reactions.
- Permits high local doses with manageable risks[1][2][3][4].

METHODS: CEMENT PREPARATION AND SURGICAL PROTOCOL

Cement Loading and Formulation

- Typical loading: 0.3–1.0 g amphotericin B deoxycholate per 40g PMMA.
- Some protocols combine with antibiotics (e.g., vancomycin) for mixed infections[5][6].
- Cement is shaped as beads or spacers for easy removal in second-stage surgery.

Staged Treatment Protocol

1. **Initial Stage:**
   - Radical surgical debridement of infected tissue.
   - Implantation of amphotericin B-loaded cement spacers.
   - Systemic antifungal therapy as indicated.
2. **Inter-stage Period:**
   - Monitoring of infection markers, wound healing, and local status.
   - Cement provides continuous local antifungal release.
3. **Second Stage:**
   - Removal of spacer, further debridement if needed.
   - Reimplantation of prosthesis or definitive fixation.

Clinical Experience and Outcomes

Case Series and Literature Reports

- *Successful eradication*: Multiple reports demonstrate infection eradication using amphotericin B-loaded cement as part of a two-stage revision for fungal prosthetic joint infection (PJI) and osteomyelitis[2][7][5][6].
- *Drug levels*: Amphotericin B concentrations in bone reached up to 5.1μg/g at 4 months post-implantation, with undetectable serum levels, limiting systemic toxicity[1][3].
- *Infection-free survival*: 81 out of 101 reported cases achieved infection-free survival (IFS) at 12–144 months follow-up, with an average spacer duration of 25 weeks[5].
- *Clinical tolerance*: No major adverse reactions attributable to local amphotericin B use have been reported, aside from rare local inflammation.

Table 1: Reported Outcomes in Clinical Series

Reference	Cases	Cement Dose (g/40g PMMA)	IFS (%)	Avg. Follow-Up (mo)	Spacer Duration (wk)
Marra et al.	1	0.75	100	12	10
Anagnostakos et al.	101	0.3–1.0	81.2	38	25
Wang et al.	5	0.1	100	24	8

Graph: Infection-Free Survival After Amphotericin B Cement

A bar graph would illustrate IFS percentages across major case series, consistently above 80% when protocols are followed.

Pharmacokinetics and Elution Characteristics

- **Elution**: Deoxycholate amphotericin B elutes from PMMA cement in measurable quantities, though generally less efficiently than liposomal formulations[8][4].
- **Porosity effect**: Adding high-dose poragens (e.g., cefazolin as filler) increases antifungal release, but reduces mechanical strength, limiting use for definitive implant fixation[9][10].
- **Mechanical integrity**: Standard amphotericin B loading does not significantly compromise compressive strength; however, overloading or excessive porosity may be detrimental[9][11].

Table 2: Elution Profiles and Mechanical Strength

Formulation	Cumulative Elution (%)	Compressive Strength (MPa)
Standard (200mg/40g)	<0.05	~80 (stable)

High poragen (200mg + cefazolin)	0.5	Decreases (to ~46 @ 30d)
Liposomal amphotericin	Higher	Not routinely used

DISCUSSION

Benefits

- **High local concentrations** can overcome biofilm resistance, a major challenge in chronic osteoarticular infections[4].
- **Safety**: Low systemic absorption reduces nephrotoxicity risk, which is significant with intravenous amphotericin B.

Limitations and Risks

- *Elution is modest*: Deoxycholate amphotericin B does not elute as effectively as liposomal preparations, but sufficient local levels are often achievable[8][4].
- *Mechanical trade-off*: Excessive poragen undermines cement stability[9].
- *Lack of standardization*: Optimal dosing and cement formulations remain under investigation.

Current Recommendations

- Employ amphotericin B deoxycholate loaded cement as a local adjunct in two-stage surgery for refractory fungal osteomyelitis or prosthetic joint infection.
- Combine with systemic antifungals tailored to pathogen and susceptibility.
- Use standard doses to balance elution and mechanical needs; avoid overloading with poragens if definitive fixation is needed[10][4][5].
- Prolonged inter-stage duration may be beneficial, allowing for sustained antifungal exposure[5].

CONCLUSION

The use of amphotericin B deoxycholate loaded bone cement in staged management of osteoarticular infections offers a highly effective, organ-sparing strategy for chronic fungal infections, with high infection-free survival and minimal systemic toxicity. Ongoing research is needed to further optimize cement formulations and define best practices for various clinical scenarios.

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