Beads vs Bugs?

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_Chest_ 2012;141;1136-1137
DOI 10.1378/chest.11-2637

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ISSN: 0012-3692
REFERENCES


3. Horvath G, Lieb T, Conner GE, Salathe M, Wanner A. Steady-state bronchodilation with formoterol and fluticasone alone and in combination, delivery method, or duration of administration. Thoracic empyema remains a primarily surgical disease; antibiotics penetrate empyemata poorly, allowing for the largely undisturbed accumulation and organization of damaging fibropurulence. Guidelines for treatment focus heavily on invasive maneuvers such as drainage and fibrinolysis, mentioning antibiotics only as adjuvant therapy. What is universally agreed upon is that antibiotic recommendations are not evidence-based. Instead, research efforts have understandably focused on optimizing invasive methods of reducing and removing purulence and scarring. In recent years, studies have established the merits of video-assisted thoracoscopic surgery with pleural debridement as opposed to open thoracotomy, the superiority of small- over large-bore chest tubes, and the role of imaging guidance in drainage. Although we have learned a few things about the best surgical and fibrinolytic approaches to thoracic empyema, its optimal antibiotic therapy remains opaque.

It is against this backdrop that Liu and colleagues in this issue of CHEST (see page 1197), offer a new approach. Because of its elegant structure and bioavailability, poly(D,L)-lactide-co-glycolide (PLGA) is a copolymer currently enjoying immense success in a host of US Food and Drug Administration-approved therapeutic devices. During polymerization of PLGA, successive monomeric units of glycolic or lactic acid are linked together; in vivo, the copolymer degrades by hydrolysis back to its monomers, both of which are by-products of the body’s usual metabolic pathways. As one of the first truly biodegradable medication delivery systems, PLGAs have spurred an explosion of research in the past decade. PLGAs are currently being tested in nanoparticle and microparticle delivery of antibiotics to hard-to-reach intracellular pathogens such as *Mycobacterium tuberculosis* and *Brucella* species, chemotherapeutic agents to cancer cells, and anti-Parkinsonian drugs to neurons.

Most of this research is still at the in vitro level. The medical field most advancing the study of biodegradable antibiotic delivery—with experiments now at the level of animal models—is orthopedics. This is not surprising, given its heavy burden of osteomyelitis and prosthetic joint infections. Until now, in the realm of thoracic empyema, only one study, to our knowledge, examining the placement of antibiotic beads in the pleural cavity in vivo has ever been published. In 1988, Mavroudis et al inserted tobramycin-impregnated polymethylmethacrylate beads into the chest cavities of 57 guinea pigs infected with *Staphylococcus aureus*. Polymethylmethacrylate beads are not biodegradable, and in the decades since, no discernible attempts were made to follow this thread of research.

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Novel strategies for thoracic empyema have been few and far between. Our therapeutic approach today is almost identical to Hippocrates’ roughly 2,400 years ago, apart from the injection of warm wine before withdrawal of the chest tube. The few variations since his time have been either misbegotten (at the turn of the 20th century, physicians were routinely removing their patients’ entire chest walls) or of uncertain value (intrathoracic streptokinase alone does not affect morbidity or mortality, but tissue plasminogen activator with DNase might). Surprisingly, it remains unclear whether the single most effective development in humanity’s fight against bacterial infection—the antibiotic—has helped to decrease either the morbidity or mortality of thoracic empyema. In the nearly 70 years since antibiotics became widely available, no serious, large-scale trials have been conducted to explore their optimal combination, delivery method, or duration of administration.

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Now, however, Liu and colleagues\(^9\) revisit intrathoracic antibiotic beads in vivo, but with a biodegradable substance. In a straightforward study, antibiotic beads were created from PLGA copolymers and penicillin \(G\) and placed in phosphate-buffered saline as well as the pleural cavities of uninfected New Zealand white rabbits. In the in vitro experiment, a significant release surge was seen; 40% of the penicillin was discharged from the beads on day 1, and the rest gradually in the subsequent 30 days. In the in vivo study, a smaller release surge was seen initially. Drug concentrations in the in vitro experiment remained above the minimum inhibitory concentration for pneumococcal susceptibility to penicillin for 30 days (14 days in the in vivo study).

This research is embryonic. The authors readily admit the preliminary nature of their findings; much more benchwork in the form of tinkering, titrating, and retesting is needed. The lack of release surge and the early dips in antimicrobial activity in the in vivo experiment are worrisome: will these lead to selective pressure on intrapleural bacteria, thereby favoring the growth of resistant strains that the later-released antibiotic cannot match?\(^{2,13}\) Other questions persist: Is it unclear what stability other antibiotics will exhibit in bead form, and whether antimicrobial activity will be sufficient against harder-to-treat pathogens such as \(S\) \(aureus\). Should the beads make it to clinical trials, might they be subject to paradoxically negative findings—as demonstrated in the human trials of gentamicin sponges for surgical site infections despite consistently positive experimental data?\(^{2,13,14}\) Finally, while PLGA copolymers should not intuitively carry risk to humans, the side-effect profile of biodegradable antibiotic beads remains unknown.

And yet new avenues of research in the treatment of this frustrating entity are sorely needed, and the implications here could be far-reaching. If, adjuvant to standard systemic antibiotic therapy, PLGA-based antibiotic beads could be placed early in the course of pleural infection, the fibropurulent and organizing phases of empyema might be slowed or even halted, and the need for repeated invasive maneuvers either decreased or obviated entirely. Seventy years after the advent of antibiotics, we may at least be closer to a viable method of truly introducing them to their targets.

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**Financial/nonfinancial disclosures:** The authors have reported to CHEST that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

**Funding/Support:** Dr Harbarth received funding from the European Commission [FP7-HEALTH-2009-SINGLE STAGE-SATURN contract No. 241796].

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DOI: 10.1378/chest.11-2637

**REFERENCES**
