Question B9: Can bacteria survive in the intracellular space of osteoblasts?

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RESPONSE/RECOMMENDATION: Yes, there is a substantial body of *in vitro* and *in vivo* evidence that PJI pathogens are capable of infecting and residing in the intracellular space of osteoblastic cells, although the duration of this intracellular infection is variable with studies estimating persistence ranging from 24 hours to weeks. Much of the available current evidence is of *S. aureus,* but a diverse array of other pathogens has also been identified as infecting osteoblasts.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: [% vote], Disagree: [%], Abstain: [%]

RATIONALE: Osteoblast lineage cells, including osteoblast progenitors, bone lining cells, mature osteoblasts, and osteocytes, constitute the vast majority of cells in hard bone tissue, with osteocytes alone comprising 90-95% of these[1]. Intracellular infection of this lineage is an important potential mechanism whereby pathogens may escape antimicrobial treatments, as recently summarized for the most prevalent pathogen in human osteomyelitis, *Staphylococcus aureus*[2]. The long-lived nature of osteocytes in particular, also lends a potentially long-term niche for bacteria that phenotypically adapt to low-growth phenotypes, such as small colony variants (SCV). These bacteria may also escape detection during diagnosis if the infected tissue is not suitably sampled and processed, and thus may present as culture-negative infections. The ability of bacteria to survive in viable 'deep bone' cells (potentially in otherwise 'healthy' bone) also informs the need for appropriate bony debridement during surgical management or other treatment modality to address these bacteria, with the risk of chronic infection if this is not achieved.

A comprehensive literature search was conducted of PubMed and Embase, initially identifying 1358 potentially relevant unique studies, screened by two independent reviewers, of which 200 were selected for full-text review and 89 included for evaluation. We defined 'persistence' as a period of at least 24 hours post-infection where there was evidence of both viable host cells containing viable intracellular bacteria. We included peer-reviewed, original research studies of all osteoblast lineage cells, as well as informative case reports and systematic reviews. Several cases of chronic osteomyelitis detailed osteoblastic infection from bone biopsy: 1) in a 53 year old (y.o.) female with the obligate anaerobe *Prevotella melanginoganica* visible in osteocytes[3]; 2) a case of Gram-positive cocci in viable osteoblasts and osteocytes established by histochemistry and transmission electron microscopy (TEM) in a 73 y.o. male[4]; 3) *S. aureus* was present in osteoblasts from a 14 y.o. boy[5].

The majority of *in vitro* studies demonstrated viable intracellular bacteria in host cells following a short infection period of 45-180 min, followed by removal of extracellular bacteria, and then assessment of colony forming unit (CFU) formation following plating of host cell lysates after at least 24 hours. An indication of host cell viability following infection was also a requirement for inclusion. Of the included studies, 68 (76%) examined intracellular *S. aureus*, well known to be a facultative intracellular pathogen, with a multitude of both methicillin resistant (MRSA) and sensitive (MSSA) strains, clinical isolates, and standard laboratory strains. Seven studies examined *S. aureus* infection of the well-characterized mouse osteoblast cell line MC3T3-E1[6-12], with intracellular persistence shown for up to 28 days[7]. Other mouse cell line infection studies were performed in osteoblast-like NRG[13] and OBβ1 cell lines[14]. A single rat mature osteoblast cell line, UMR-106, was

utilized to demonstrate *S. aureus* intracellular persistence for up to 8 days[15], while rat primary calvarial osteoblasts were used to show persistence for 21 days[16]. Four studies examined *S. aureus* infection of mouse primary (calvaria-derived) osteoblasts[17-20], with persistence demonstrated between 24-48 hours. The majority of human cell line studies were performed in MG-63 osteosarcoma cells, an immature osteoblast model, which undergoes limited, if any, osteogenic differentiation. In total, 25 studies examined *S. aureus* infection of MG-63, most presenting evidence for a 24-48 hours post-infection period [9; 21-40] with several extending observations for 7-8 days[41-43]. Five further studies were performed in the human mature osteoblast cell line, SaOS-2, which has strong osteogenic potential, with persistence demonstrated between 24-72 hours[44-48]. A single group used SV-40 transformed human osteoblasts[49; 50] to study infection. Fifteen studies utilized human primary osteoblasts, derived from trabecular bone explant cultures, as the host cell type to examine *S. aureus* intracellular persistence. This was most commonly demonstrated between 24-48 hours[39; 51-60], while some studies extended observations to a week or more[11; 61-63], and up to 21 days in a study by Tuchscherr *et al.*[64]. This group also demonstrated the phenotypic switch of *S. aureus* to an SCV phenotype, linked to chronic infections[53].

Osteocyte cell models have also been used to demonstrate *S. aureus* persistence. Yang *et al.*[65] demonstrated *S. aureus* infection and persistence in human primary osteoblast-derived osteocytes, associated with a phenotypic switch to SCVs over a 6 day infection period. More recently, SaOS-2 cells differentiated to an osteocyte-like phenotype have also been utilized, showing *S. aureus* persistence for up to 21 days[48; 66-69]. Mouse MLO-Y4 osteocyte-like cells also supported *S. aureus* infection [12]. Viable osteocyte infection by *S. aureus* was also shown in a human *ex vivo* bone model and in PJI patient bone specimens[65]. de Mesy Bentley and colleagues showed by TEM that *S. aureus* invades the osteocyte lacunocanalicular network (OCLN), appearing to deform in order to enter canaliculi in a mouse PJI model[70] and in a human case study of diabetic foot infection[71]. This process was shown in an *ex vivo* mouse bone model[72], and OCLN immunostaining of *S. aureus* was reported in several other, both paediatric and adult, cases of osteomyelitis[73]. Although infection of living osteoblasts/osteocytes in these latter studies was not reported, they are supportive of *S. aureus* accessing these cell types.

In addition to *S. aureus*, staphylococcal species *S. argenteus* and coagulase-negative *S. pseudintermedius* were shown to infect MG-63 cells for up to 7-10 days[37; 43], and *S. epidermidis* was shown to infect human primary osteoblasts[11; 58] and MC3T3-E1 cells for up to 10 days[11; 74]. Another common periprosthetic joint infection isolate, *Cutibacterium acnes* was also shown to persist in MG-63 cells for up to 96 hours, becoming undetectable after this time point[75]. Gram-negative species *Streptococcus gordonii* (in MG-63)[36], *Salmonella Dublin*[19] and *P. melanginoganica*[3] have also been shown to persist in osteoblastic cells. Pathogens associated with periodontitis have also been demonstrated as tropic for osteoblasts, including *Aggregatibacter actinomycetemcomitans* (in MG-63)[76], and *Porphyromonas gingivalis*, shown in mouse primary osteoblast models[77-79] and *in situ* in osteoblasts and osteocytes of alveolar bone in a mouse model [80]. Several Mycobacterium species have been shown to persist in osteoblasts *in vitro*: *Mycobacterium tuberculosis* in MG-63[38], SaOS-2 cells[81] and human primary osteoblasts[82], and *M. bovis* in MC3T3-E1 cells (up to 7 days)[83]. Arguably most directly supportive of the affirmative to this question is the demonstration of the *obligate* intracellular pathogen *Chlamydia pneumoniae* infection and persistence in the human osteoblastic hFOB 1.19 cell line[84] and in SaOS-2 cells[85]. Finally, intra-osteoblastic (SaOS-2, MG-63[86]; MC3T3-E1[87; 88]; mouse primary osteoblast[87]) and intra-osteocyte (MLO-Y4[89; 90]) infection was demonstrated with the causative pathogen of osteoarticular brucellosis, *Brucella abortus,* as well as other species *B. suis*, *B. melitensis* and *B. canis* [86].

Conclusion: The ability of pathogens to invade and reside in host cells is widespread and this also occurs in the context of bone infection. There is overwhelming evidence that pathogens including *S. aureus*, coagulase-negative staphylococci, *Brucella* species, *Chlamydia,* and a number of other pathogenic species are capable of infecting osteoblast lineage cells.

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