QUESTION 9: Is there evidence that interference with bacterial communication by blocking quorum sensing molecules can minimize biofilm formation *in vivo*?

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Response:

In vivo animal studies have demonstrated that interference with quorum sensing signals/molecules in some infections leads to decreased biofilm formation. There are contradictory results in *Staphylococcus* species. However, there are no clinical studies demonstrating this phenomenon.

Level of Evidence: Limited

Delegate Vote: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

Post Meeting Rationale:

In Feb 2018 NCBI, EMBASE and SCOPUS databases were searched for English language publications during the previous 5 years in which the abstract contained the following terms: "biofilm" and "quorum" and "*in vivo*". These papers were reviewed to identify data specifically related to interference of quorum sensing the caused alteration in biofilm formation. All *in vitro* basic science studies were excluded and there were no clinical studies. There were 7 *in vivo* investigations reported during the last five years [1–7] (Table 1). In addition, there have been reports of quorum sensing inhibitor and quorum quenching studies presented at scientific meetings utilizing multiple *in vivo* models [8].

The experimental strategy varies. *In vitro* data are relied upon to identify the molecular mechanism leading to interference with quorum sensing that causes decreased biofilm formation, whether it be blocking the signaling peptide production, blocking receptors, or active initiation an antagonist signals by the agent. *In vivo* studies are then done to confirm that the agent decreases biofilm formation.

While there is extensive *in vitro* and *in silica* work being done and reported on quorum sensing and anti-quorum sensing molecules, otherwise known as quorum quenching, there are limited *in vivo* data and none of the anti-quorum sensing strategies are ready for widespread clinical application.

Table 1: In vivo investigation during the last 5 years

Study	Animal Model	Agent	Mechanism	Clinical effect
[1]	Medaka fish peritoneal catheter infection	3-Phenyllactic Acid (PLA)	Antagonistically binds to quorum sensing receptors RhlIR and RqsR, blocking initial attachment of Pseudomonas aeruginosa (PA01) thereby delaying biofilm formation	Decreased biofilm formation
[2]	Mouse gingivitis	Quorum Sensing Inhibitors (furane compunds, d-ribose)	Interfere with AutoInducer-2	decreased colony counts and alveolar bone loss
[3]	Round worm survival (Caenorhabditis elegans)	Pyrrolo[1,2-a]pyrazine-1,4-dione, hexahydro-3-(2-methylpropyl) from Alcaligenes faecalis	Modulate expression of quorum sensing (QS) regulators luxT and lafK	Increased survival from *V. alginolyticus* infection
[4]	Round worm survival (Caenorhabditis elegans)	Sub-inhibitory concentration of ceftazidime	inhibition of QS regulated virulence traits and biofilm formation; binds to the las and pqs QS receptors in P. aeruginosa	Increased survival
[5]		Acylase	Degrades Quorum sensing peptides	Delay biofilm formation for S. aureus and P. aeruginosa for up to 7 days
[6]	larval oyster mortality	Phaeobacter gallaeciensis S4Sm	Down regulate pathogen virulence genes	Decreased mortality from V. tubiashii infection
[7]	Wistar rat pyelonephritis	Phytol	down regulate offimA, fimC, flhC, flhD, bsmB, pigP shlA genes in S Marcescens leading to decreased biofilm formation and virulence factor production	Decreased bacterial counts and virulence enzymes (lipase and protease) decreased inflammatory markers (MDA, NO, MPO) and histologically no acute inflammation

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