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The Biofilm Resistance: Many Responses but Still Many Questions

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ABSTRACT

Microbial biofilms (i.e., bacterial and fungal) are often very deleterious due to their exceptional tolerance to treatments, in particular to conventional antimicrobials therapy. The processes involved in this low efficacy of antimicrobials on adherent cells have been widely studied in the last decades. It is now accepted that this tolerance of sessile cells is multiparametric. It involves different mechanisms, physico-chemical and biological. A major characteristic of biofilm microorganisms is that they are subjected to very deleterious environmental conditions which induce in them a large number of stress response mechanisms, some of which are obviously involved in this tolerance. On the other hand, few resistance systems, specifically expressed by sessile cells, have been described so far. Moreover, the fact that most natural and clinical biofilms are polymicrobial raises questions about the relevance of some observations obtained on monocultures.

Keywords: Biofilm; Resistance; Antimicrobials; Antibiotics

Abbreviations: EPS: ExoPolymers; eDNA: Extracellular DNA ; MIC: minimum inhibitory concentration; SCVs: small colony variants; QS: Quorum sensing; TCS: Two Component System

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It is well known that biofilm infections are difficult to eradicate, adherent cells (bacteria and yeasts) exhibiting antimicrobial resistance increases of up to 200 times, as compared with planktonic counterparts [1,2]. These biofilms are thus the primary cause of failures in the implantation of medical devices, which generate high morbidity and mortality [3]. This resistance is actually more of a tolerance than a real resistance; indeed, it is essentially induced by an adaptation of the microorganisms, a reversible phenotype which switches back in the planktonic mode [4,5]. Resistance, on the other hand, generally involves an increase in the minimum inhibitory concentration (MIC) of the antimicrobial, due to an irreversible change in the microorganism through a mutation, or resistance acquired via horizontal gene transfer. The low efficacy of antimicrobials on biofilms is clearly multiparametric [6] and implies both tolerance and resistance of adherent cells, in particular due to the high heterogeneity of the sessile cell physiology [7] due to gradients instauration within these structures [8].

Tolerance of Biofilms to Inhibitors

The mechanisms involved in the tolerance of biofilms are multiple [9-11] and include a low diffusivity of antimicrobials within the polymer matrix [12], a lower sensitivity to phagocytosis and other mechanisms put in place by the immune system of the host [13], a low growth rate of the microorganisms (dormancy), metabolic alterations, environmental gradients within the biofilm, and the presence of persister cells (Table 1).

Table 1: Main mechanisms involved in the tolerance of fungal and bacterial biofilms.

Mechanism Involved	Effect	References
Low penetration of the antimicrobial	Decrease of the local concentration of the antimicrobial	[15,16]
Low growth rate	Decrease of the efficacy of some antimicrobials (dormancy)	[19-21]
Metabolism alterations	Accumulation of proteins involved in adaptation, target modifications	[25,26]
Oxygen gradient	Decrease of the efficacy of some antimicrobials (intracellular penetration, dormancy)	[33-35]
Presence of persisters	Decrease of the efficacy of some antimicrobials (dormancy)	[37-38]
Quorum sensing	Activation of efflux pumps	[43]
Stress responses	Cross-resistance against antimicrobials	[50]

A Diffusional Resistance to Inhibitors

Due to its structural and mechanical properties, the polymer matrix constitutes the first defense against antimicrobial agents. It consists mainly of water, ions and ExoPolymers (EPS) in both fungal [11] and bacterial [14] biofilms. These EPS are essentially exopolysaccharides, protein lipids, but also extracellular DNA (eDNA). Due to their physico-chemical properties, EPS act as a filtering barrier, either by interaction with the compound (due to the presence of negative charges), or by trapping. Positively charged antibiotics, such as aminoglycosides, will thus bind to a negatively charged matrix, which will limit their diffusion within the biofilm [15]. Chlorine, commonly used as a disinfectant, penetrates weakly into a mixed biofilm of *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* [16]. Nevertheless, the limitation of the inhibitor diffusion in this gangue cannot alone explain the extraordinary resistance of biofilms. Thus, for example, an antibiotic such as the vancomycin, which diffuses correctly within the biofilm, is just as ineffective on sessile bacteria [17]. Likewise, fluoroquinolone antibiotics efficiently penetrate within *P. aeruginosa* biofilms [18,19].

A Low Growth Rate

Within biofilms, it exists heterogenous microenvironments corresponding to areas deficient in nutrients, oxygen or with extremely low local pH values [8,20]. Many studies show that microorganisms (yeasts [21] and bacteria [22]) display, within biofilms, a low growth rate and a phenotype close to, but different [23], from cells in the stationary phase of growth. This dormancy partially explains the ineffectiveness of antifungals [21] and antibiotics [22,24] on biofilm cells.

An Alteration of the Cellular Metabolism

It is now well recognized that the "biofilm" phenotype reflects alterations in the gene expression of adherent cells, leading to the activation of some metabolic pathways, in particular in the deeper zones of the biofilm, whereas these alterations are weaker in the more peripheral regions [24,25]. These changes in metabolism reflect adaptations of the microorganisms to the environmental conditions they encounter and explain some tolerances to inhibitors. Thus, local deficiencies in amino acids, such as leucine, cysteine and lysine, have been shown to be responsible for the tolerance of *Escherichia coli* biofilms to ofloxacin [26]. The development of so-called "post-genomic" approaches, such as transcriptomic (consisting of identifying and quantifying the mRNAs expressed) and proteomic (consisting of identifying and quantifying the proteins expressed by a cell at a given time), allowed, in the recent decades, to draw up an inventory of the differences in gene expression in bacteria [27,28] and fungi [29-31] organized in biofilm and in suspension. However, significant differences were observed at the quantitative level between the proteomic and transcriptomic approaches. Thus, while proteomics suggests that a large number of proteins are expressed differently in bacteria in biofilms, i.e. between 15 and 50% proteome modifications, the results obtained by transcriptomic suggest that a small proportion of the genome (between 1 and 15%) shows significant changes in expression. These differences can of course be explained by the weak correlation between the quantity of mRNA and protein, but could also indicate the existence of key proteins which would not yet be identified because modified qualitatively and not quantitatively, via post-translational modifications such as phosphorylations and/or acetylations, for example [32]. Thus, Massier, et al. [33] reported significant differences in the phosphorylation rates of extracellular proteins in planktonic and sessile *Acinetobacter baumannii cells*. These authors also demonstrated that some phosphosites were located in key regions of proteins involved in antibiotic resistance, such as in betalactamases [33].

Oxygen Gradients

The oxygen tension is low in deep zones of the biofilms. This property has been demonstrated by using microelectrodes a little 20 years ago [34]. Thus, it has been shown that oxygen penetrates the first 50 microns of biofilms [35]. These oxygen-deficient areas contribute to the ineffectiveness of some antibiotics on bacterial biofilm [36-38]. For example, these anaerobic microenvironments directly impact the efficacy of aminoglycosides, including intracellular transport, which requires the presence of a protomotive force [39].

A Presence of Persisters

Within biofilms, there is also a high proportion of persistent cells called persisters, corresponding to a subpopulation of dormant cells,

which do not divide, and that are highly adapted to resist against various stresses. These persisters are found in both bacterial [40] and fungal [41] biofilms. These cells represent less than 1% of the original population and their genome is identical to that of their congeners. Different mechanisms are involved in their formation [9 and cited references]. The slow metabolism of these cells makes them less sensitive to antibiotics compared to cells in the exponential or even stationary growth phase [42]. Persisters contribute significantly to the difficulty encountered in eradicating biofilm infections such as chronic urinary and pulmonary infections. The biofilm is in fact a very favorable protective niche for persisters [43]. When the antimicrobial treatment is stopped, the emergence of these bacteria from dormancy leads to the reformation of the biofilm and the recurrence of the infection [44]. These "persisters" differ from "small colony variants" (SCVs) which are found in high proportion within bacterial biofilms [40]. SCVs are adapted variants that grow poorly on standard culture media and therefore produce very small colonies. SCVs have been involved in the recurrence and persistence of chronic infections [43,44] and show a greater ability to adhere compared to "wild" bacteria in *Staphylococcus aureus* [40].

A Role of the Quorum Sensing

The Quorum sensing (QS) is a communication system between microorganisms, linked to cell density. It is based on the synthesis and accumulation in the extracellular medium of small molecules, called auto-inductors, playing the role of pheromones. QS is strongly involved in the formation and dispersion of bacterial [[45] and cited references] and fungal [[46] and cited references] biofilms, but less so in their resistance. However, it has been shown to play a role in the biofilm tolerance of *P. aeruginosa* through the activation of efflux pumps [47].

A Response to Stress

Many environmental stresses are known to induce resistance to antimicrobials in microorganisms [48]. The unfavorable environmental conditions prevailing within the biofilms will obviously cause significant stress on the sessile microorganisms. It has thus been shown that many genes involved in the stress response were strongly over-expressed in sessile bacteria [49] and yeasts [50]. In *Candida glabrata*, for example, the resistance of biofilms to oxidative stress has been correlated with the accumulation of proteins involved in the response to oxidative stress [51].

An Overexpression of Efflux Pumps

Efflux pumps allow cells to expel inhibitors from their cytoplasm [50]. The involvement of efflux pumps in the tolerance of sessile microorganisms is relatively controversial. Thus, some studies have shown no correlation between the tolerance of biofilms of *P. aeruginosa* and the expression of efflux pumps [52,53]. By contrast, Liao et al. suggested a possible correlation between the expression of efflux pumps and the decreased sensitivity of *P. aeruginosa* biofilms [54]. Similarly, overexpression of efflux pumps has been described as involved in the tolerance of *C. albicans* biofilms [[9] and references cited]. However, this involvement could be temporary and not concern mature biofilms [10], suggesting the role of other mechanisms such as genes and operons specifically involved in biofilm resistance. Few resistance mechanisms specifically set up by adherent bacteria have been described until now. Among these, it has been demonstrated in *P. aeruginosa* the production and accumulation in the periplasm of biofilm bacteria, of small cyclic sugar polymers able to trap aminoglycosides [55]. The production of these polymers is under the control of the *ndvB* gene which encodes a glucosyltransferase. This gene is specifically over-expressed from the first minutes following the bacterial adhesion. The PA0756-PA0757 proteins are the two elements of the first two component system (TCS) described as specifically involved in the biofilm resistance to antibiotics, in particular to ciprofloxacin [56] while these TCS were already strongly known to be involved in the biofilm formation [[57] and references cited] Similarly, still in *P. aeruginosa*, a cluster of 4 genes, called bac for *biofilm associated cluster*, has been identified, coding for proteins with unknown functions. This proteic system seems involved in the biofilm formation, in the sessile bacteria virulence but also in the resistance to tobramycin [58].

Polymicrobial Biofilms

In nature, biofilms are often polymicrobial [59]. In the medical field, chronic infections are also frequently caused by multispecies biofilms, sitting in different sites [see [59] and references therein], Emerging evidence suggests that a lot of interspecies interactions occur in these complex communities, leading to therapeutic failures [60]. In all these communities, the biological interactions are complex and are most often defined according to the result of the interaction on each of the two participating species: they can be commensal type or, on the contrary, parasitic or even mutualistic. Regardless of the consequences for each species, these interactions can lead to an acceleration and aggravation of the disease [61,62]. We can then speak of synergy between bacterial species, which can result, for example, by an increase in the production of virulence factors or even by an increase in the tolerance of species to certain antibiotics [62]. This antimicrobial tolerance can be developed by different mechanisms [63], e.g., horizontal gene transfer [64], production of β-lactamases [65], of primary metabolites [66,67] and/or of QS molecules [68] which protect neighbors, even against environmental stresses [69]. In a contradictory way, it has been shown that *P. aeruginosa* became more susceptible to ampicillin when in the presence of a drug-sensitive anaerobic community than in monoculture [70], pointing out that polymicrobial interactions can produce different antibiotic sensitivity profiles. Though polymicrobial biofilms may associate eukariotic and procaryotic organisms, it is clear that most studies are still today performed on bacterial pathogens. Nethertheless, it has been reported

that the biofilm matrix produced by *C. albicans* modify the structure of polymicrobial biofilms and lead to altered sensitivity of bacterial species to antibiotics [71,72]. The farnesol, a quorum sensing molecule produced by *C. albicans,* has also been shown to be able to protect *S. aureus* from vancomycin within a polymicrobial biofilm [73].

Conclusion

The resistance of microorganisms in biofilms is obviously complex and multiparametric, even if one can consider the existence of different stresses encountered by sessile cells as a common denominator. The massive doses of antimicrobial agents that would be required to eradicate them are incompatible with environmental requirements and medical reality. The fight against biofilms therefore requires new antibacterial control strategies. Among these, we can cite the search for new molecules that are more effective on adherent bacteria. This approach requires upstream a better knowledge of the molecular mechanisms specifically mobilized in this resistance, which would constitute new therapeutic targets. It is also clear that interspecies interactions modulate the sensitivity of polymicrobial communities in unpredictable ways, data obtained on monospecies cultures being not able to be extrapolated to polymicrobial structures. Better understanding these interactions is obviously an important challenge in the near future in order to better fight against polymicrobial biofilm infections.

References

1. Naparstek L, Carmeli Y, Navon Venezia S (2014) Biofilm formation and susceptibility to gentamycin and colistin of extremely drug-resistant KPC-producing Klebsiella pneumoniae. J Antimicrob Chemother 69(4): 1027-1034.
2. Pereira R, Dos Santos Fontenelle RO, de Brito EHS, de Morais SM (2021) Biofilm of Candida albicans: formation, regulation and resistance. J Appl Microbiol131(1): 11-22.
3. Singh A, Amod, A Pandey, P Pranay B, M Shivapriya Pingali, et al. (2022) Bacterial biofilm infections, their resistance to antibiotics therapy and current treatment strategies. Biomed Mater 17(2).
4. Lebeaux D, Ghigo JM (2012) Infections associées aux biofilms. Quelles perspectives thérapeutiques issues de la recherche fondamentale? Med/scie 28(8-9): 727-739.
5. Mah TF (2012) Biofilm-specific antibiotic resistance. Future Microbiol 7(9): 1061-1072.
6. Stewart PS, Costerton JW (2001) Antibiotic resistance of bacteria in biofilms. Lancet 358(9276): 135-138.
7. Mah TF (2012) Regulating antibiotic tolerance within biofilm microcolonies. J Bacteriol 194(18): 4791-4792.
8. Jeanyoung J, Price-Whelan A, Dietrich LEP (2022) Nat Rev Microbiol 20: 593-607.
9. Ohlsen I (2015) Biofilm-specific antibiotic tolerance and resistance. Eur J Clin Microbiol Infect Dis 34(5): 877-886.
10. Mathé L, Van Dijck P (2013) Recent insights into Candida albicans biofilm resistance mechanisms. Curr Genet 59(64): 251-264.
11. Kaur J, Nobile CJ (2023) Antifungal drug-resistance mechanisms in Candida biofilms. Curr Opin Microbiol 71: 102237.
12. Nickel JC, Ruseska I, Wright JB, Costerton JW (1985) Tobramycin resistance of Pseudomonas aeruginosa cells growing as a biofilm on urinary tract catheter. Antimicrob. Agents Chemother 27(4): 619-624.
13. Hänsch GM (2012) Host defence against bacterial biofilms: "Mission impossible"? ISRN Immunol.
14. Branda SS, Vik A, Friedman L, Kolter R (2005) Biofilms: the matrix revisited. Trends Microbiol 13(1): 20-26.
15. Meers P, Neville M, Malinin V, Scotto AW, Sardaryan G, et al. (2008) Biofilm penetration, triggered release and *in vivo* activity of inhaled liposomal amikacin in chronic Pseudomonas aeruginosa lung infection. J Antimicrob Chemother 61(4): 859-868.
16. Stewart PS, Rayner J, Roe F, Rees WM (2001) Biofilm penetration and disinfection efficacy of alkaline hypochlorite and chlorosulfamates. J Appl Microbiol 91(3): 525-532.
17. Dunne WM, Mason EO, Kaplan SL (1993) Diffusion of rifampin and vancomycin through a Staphylococcus epidermidis biofilm. Antimicrob. Agents Chemother 37(12): 2522-2526.
18. Suci PAK, Mittelman MW, Yu FP, Geesey GG (1994) Investigation of ciprofloxacin penetration into Pseudomonas aeruginosa biofilms. Antimicrob. Agents Chemother 38(9): 21252133.
19. Vrany JD, Stewart PS, Suci PA (1997) Comparison of recalcitrance to cirpfloxacin and levofloxacin exhibited by Pseudomonas aeruginosa biofilms displaying rapid-transport characteristics. Antimicrob. Agents Chemother 41(6): 1352-1358.
20. De Beer D, Stoodley P, Lewandowski Z (1997) Measurement of local diffusion coefficients in biofilms by microinjection and confocal microscopy. Biotechnol Bioeng 53(2): 151-158.
21. Baillie GS, Douglas LJ (1998) Effect of growth rate on resistance of Candida albicans biofilms to antifungal agents. Antimicrob Agents Chemother 42(8): 1900-1905.
22. Ander JF, Zahller J, Roe F, Stewart PS (2003) Role of nutrient limitation and stationary-phase existence in Klebsiella pneumoniae biofilm resistance to ampicillin and ciprofloxacin. Antimicrob Agents Chemother 47(4): 1251-1256.
23. Collet A, Cosette P, Beloin C, Ghigo, Christophe Rihouey, et al. (2008) Impact of rpoS deletion on the proteome of *Escherichia coli* grown as biofilm. J Prot Res 7(1): 4659-4669.
24. Walters MC 3rd, Roe F, Bugnicourt A, Franklin MJ (2003) Contribution of antibiotic penetration, oxygen limitation and low metabolic activity to tolerance of Pseudomonas aeruginosa biofilms to ciprofloxacin and tobramycin. Antimicrob. Agents Chemother 47(1): 317-323.
25. Werner E, Roe F, Bugnicourt A, Franklin M, Arne Heydorn, et al. (2004) Stratified growth in Pseudomonas aeruginosa biofilms. Appl Environ Microbiol 70(10): 6188-6196.
26. Bernier SP, Lebeaux D, DeFrancesco AS, Valomon A, Guillaume Soubigou, et al. (2013) Starvation, together with the SOS response mediates high biofilm-specific tolerance to the fluoroquinolone ofloxacin. Plos Genet 9(1): e1003144.
27. Folsom JP, Richards L, Pitts B, Roe F, Garth D Ehrlich, et al. (2010) Physiology of Pseudomonas aeruginosa in biofilms as revealed by transcriptome analysis. BMC Microbiology 10: 294.
28. Khemiri A, Jouenne T, Cosette P (2016) Biofilmology and proteomics approaches : what have we learned from a decade of research. Med. Microbi-

ol. Immuno 205(1): 1-19.

29. Seneviratne CJ, Wang Y, Jin L, Abiko Y (2010) Proteomics of drug resistance in Candida glabrata biofilms. Proteomics 10(7): 1444-1454.
30. Abdulghani M, Iram R, Chidrawar P, Bhosle K, Kajal Bhosle, et al. (2022) Proteomic profile of Candida albicans biofilm. J Prot 265: 104661.
31. Zarnowski R, Sanchez H, Jaromin A, Zarnowska U, Aaron P Mitchell, et al. (2022) A common vesicule proteome drives fungal biofilm development. Proc Natl Acad Sci USA 119(38): 2211424119.
32. Gaviard C, Jouenne T, Hardouin J (2018) Proteomics of Pseudomonas aeruginosa: the increasing role of post-translational modification. Exp Rev Proteomics 15(9): 757-772.
33. Massier S, Robin B, Mégroz M, Wright A, John D Boyce, et al. (2021) Phosphorylation of Extracellular Proteins in Acinetobacter baumannii in Sessile Mode of Growth. Frsont Microbiol 12: 738780.
34. Xu KD, Stewart PS, Xia F, Huang CT (1998) Spatial physiological heterogeneity in Pseudomonas aeruginosa biofilm is determined by oxygen availability. Appl Environ Microbiol 64(10): 4035-4039.
35. Stewart PS, Zhang T, Xu R, Pitts B, Frank Roe, et al. (2016) Reaction-diffusion theory explains hypoxia and heterogeneous growth within microbial biofilms associated with chronic infections. Npj Biofilms and Microbiomes 2: 16012.
36. Tresse O, Jouenne T, Junter GA (1995) The role of oxygen limitation in the resistance of agar-entrapped, sessile-like *Escherichia coli* to aminoglycoside and β-lactam antibiotics. J Antimicrob Chemother 36(3): 521-526.
37. Borriello G, Werner E, Roe F, Kim AM, Garth D Ehrlich, et al. (2004) Oxygen limitation contributes to antibiotic tolerance of Pseudomonas aeruginosa in biofilms. Antimicrob Agents Chemother 48: 2659-2664.
38. Webster CM, Shepherd M (2022) A mini-review: environmental and metabolic factors affecting aminoglycoside efficacy. World J Microbiol Biotechnol 39(1): 7.
39. Taylor P, Yeung ATY, Hancock REW (2014) Antibiotic resistance in Pseudomonas aeruginosa biofilms: Towards the development of novel anti-biofilm therapies. J Biotechnol 191: 121-130.
40. Singh R, Ray P, Das A, Sharma M (2009) Role of persisters and small-colony variants in antibiotic resistance of planktonic and biofilm-associated Staphylococcus aureus: an *in vitro* study. J Med Microbiol 58(pt 8): 1067-1073.
41. LaFleur MD Kumamoto CA, Lewis K (2006) Candida albicans biofilms produce antifungal-tolerant persister cells. Antimicrob Agents Chemother 50(11): 3839-3846.
42. Miyaue S, Suzuki E, Komiyama Y, Kondo Y, Miki Morikawa, et al. (2018) Bacterial memory of persisters bacterial persister cells can retain their phenotype for days or weeks after withdrawal from colony-biofilm culture. Front Microbiol 26: 1396.
43. Lewis K (2007) Persister cells, dormancy and infectious disease. Nat Rev Microbiol, p. 48-56.
44. Neut D, Van der Mei HC, Bulstra SK, Bussher HJ (2007) The role of small-colony variants in failer to diagnose and treat biofilm infections in orthopedics. ACTA Orthop 78(3): 299-308.
45. Zhou L, Zhang Y, Ge Y, Zu X (2020) Regulatory mechanisms and promising applications of quorum sensing-inhibiting agents in control of bacterial biofilm formation. Front Microbiol 15: 589640.
46. Zhao X, Yu, Ding T (2020) Quorum sensing regulation of antimicrobial resistance in bacteria. Microorganisms 8(3): 425.
47. Bjarnsholt T, Jensen PØ, Burmølle M, Morten Hentzer, Janus AJ Haagense, et al. (2005) Pseudomonas aeruginosa tolerance to tobramycin, hydrogen peroxide and polymorphonuclear leukocytes is quorum sensing dependent. Microbiology 151(2): 373-383.
48. Dawan J, Ahn J (2022) Bacterial resistance responses as potential targets in overcoming antibiotic resistance. Microorganisms 10(17): 1385.
49. Rahman MA, Amirkhani A, Chowdhury D, Mempin M, Karen Vickery, et al. (2022) Proteome of Staphylococcus aureus biofilm changes significantly with aging. Int J Mol Sci 23(12): 6415.
50. Seneviratne CJ, Wang Y, Jin L, Abiko Y (2008) Candida albicans biofilm formation is associated with increased anti-oxidative capacities. Proteomics 8(14): 2936-2947.
51. Van Acker H, Coenye T (2016) The role of efflux and physiological adaptation in biofilm tolerance. J Biol Chem 291(24): 12565-12572.
52. Pitts L, Roe B, Ehrlich F, Parker GD (2010) Physiology of Pseudomonas aeruginosa in biofilms as revealed by transcriptome analysis. BMC Microbiol 10: 294.
53. Stewart PS, Franklin MJ, Williamson K S, Folsom J P, Boegli L, et al. (2015) Contribution of stress responses to antibiotic tolerance in Pseudomonas aeruginosa biofilms. Antimicrob. Agents Chemother 59(7): 3838 -3847.
54. Liao J, Schurr MJ, Sauer K (2013) The MerR-like regulator BrlR confers buiofilm tolerance by activating multidrug efflux pumps in Pseudomonas aeruginosa biofilms. J Bacteriol 195(15): 3352-3363.
55. Mah TF, Pitts B, Pellock B (2003) A genetic basis for Pseudomonas aeruginosa biofilm antibiotic resistance. Nature 426(6964): 306-310.
56. Zhang L, Fritsch M, Hammond L, Landreville R (2013) Identification of genes involved in Pseudomonas aeruginosa biofilm-specific resistance to antibiotics. Plos One 8: e61625.
57. Sultan M, Arya R, Kim KK (2021) Role of Two-Component Systems in Pseudomonas aeruginosa virulence. Int J Mol Sci 22(22): 12152.
58. Macé C, Seyer D, Chemani C (2008) Identification of biofilm-associated cluster (bac) in Pseudomonas aeruginosa involved in biofilm formation and virulence. Plos One 3(12): 110 e3897.
59. Exton B, Hassard F, Vaya AM, Grabowski RC (2023) Polybacterial shift in benthic river biofilms attributed to organic pollution – a prospect of a new biosentinel? Hydrol Res 54(3): 348-359.
60. Anju VT Busi S, Imchen M, Kuavath R (2022) Polymicrobial infections and biofilms: clinical significance and eradication strategies. Antibiotics 11(12): 1731.
61. Marchaim D, Perez F, Lee J, Bheemreddy S (2012) "Swimming in resistance": Cocolonization with carbapenem-resistant Enterobacteriaceae and Acinetobacter baumannii or Pseudomonas aeruginosa. Am J Infect Control 40(9): 830-835.
62. Nguyen AT, Oglesby Sherrouse AG (2016) Interactions between Pseudomonas aeruginosa and Staphylococcus aureus during co-cultivations and polymicrobial infections. Appl Microbiol Biotechnol 100(14): 6141-6148.
63. Orazi G, OToole GA (2020) "It takes a village": mechanisms underlying antimicrobial recalcitrance of polymicrobial biofilms. J Bacteriol 202(1): e00530-19.
64. Tanner WD, Atkinson RM, Goel RK, Toleman MA (2017) Horizontal transfer of the blaNDM-1 gene to Pseudomonas aeruginosa and Acinetobacter baumannii in biofilms. FEMS Microbiol Lett 364(8): fnx048.
65. Liao YT, Kuo SC, Lee YT, Chen CP (2014) Sheltering effect and indirect pathogenesis of carbapenem-resistant Acinetobacter baumannii in poly-

microbial infection. Antimicrob Agents Chemother 58(7): 3983-3990.

66. Hirakawa H, Inazumi Y, Masaki T Hirata T (2005) Indole induces the expression of multidrug exporter genes in Escherichia coli. Mol Microbiol 55(4): 1113-1126.
67. Kim KS, Lee S, Ryu CM (2013) Intersepcific bacterial sensing through airborne signals modulates locomotion and drug resistance. Nat Commun 4: 1809.
68. Ryan RP, Fouhy Y, Garcia BF, Watt SA (2008) Interspecies signalling via the Stenotrophomonas maltophilia diffusible signal factor influences biofilm formation and polymyxin tolerance in Pseudomonas aeruginosa. Mol Microbiol 68(1): 75-86.
69. Demenec L, Cain AK, Dawson CJ, Liu Q (2023) Cross-protection and cross-feeding between Klebsiella pneumoniae and Acinetobacter baumannii promotes their coexistense. Nat Commun 14(1): 702.
70. Adamowicz EM, Flynn J Hunter RC, Harcombe WR (2018) Cross-feeding modulates antibiotic tolerance in bacterial communities ISME J 12(11): 2723-2735.
71. Harriott MM, Noverr MC (2009) Candida albicans and Staphylococcus aureus from polymicrobial biofilms: effects on antimicrobial resistance. Antimicrob. Agents Chemother 53(9): 3914-3922.
72. Kong E, Tsui C, Kucharikova S, Andes D (2016) Commensal protection of Staphylococcus aureus against antimicrobials by Candida albicans biofilm matrix. mBio 7(5): e0165-16.
73. Kong EF, Tsui C, Kucharikova S, Van Dijck P (2017) Modulation of Staphylococcus aureus response to antimicrobials by the Candida albicans quorum sensing molecule farnesol. Antimicrob Agents Chemother 61(12): e1573-17.

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