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ORIGINAL ARTICLE

The impact of biofilms on intravascular catheter-related bloodstream infection and antimicrobial resistance

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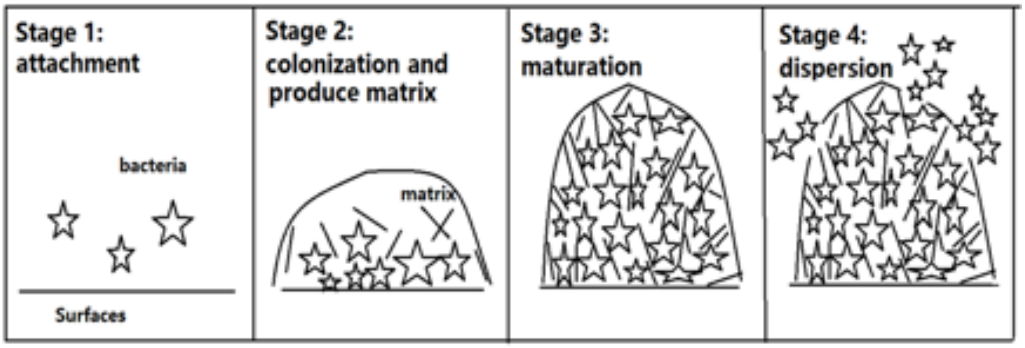
INTRAVASCULAR CATHETERS AND BLOODSTREAM INFECTIONS

Intravascular catheters (IVCs) are one of the most common medical devices used in hospitals. IVCs have various purposes, including haemodynamic monitoring, nutrition supplements, and medicine administration. It is estimated that nearly 300 million IVCs are used annually in the USA[1]. IVCs are, however, often associated with serious IVC-related bloodstream infection (IVC-BSI), which leads to high morbidity and mortality[2]. Over 40,000 IVC-BSIs occur annually in Australia[3], and over 250,000 in the USA, with reported costs up to US$2.68 billion annually[4].

The microorganisms that cause IVC-BSI attach on the catheter surfaces, form a biofilm, and then enter the sterile bloodstream to cause infection. Catheter hubs and insertion sites are the two main entrances for contamination. For short-term catheters, skin contamination at the insertion site is the likely entrance for pathogens, while catheter hub contamination is more likely for long-term catheters[5]. Biofilm formation on catheters is characterised by four stages (see Figure 1). Firstly, bacteria adhere to the external and internal surfaces of catheters[6], which are the two principal niches for bacterial colonisation in IVC-BSI[7]. Secondly, bacteria aggregate to form microcolonies and produce a matrix to form the skeleton of biofilm[8]. Bacteria will colonise sustainably until biofilm has maturated, and the microbes inside have high resistance to antimicrobial agents and traditional therapy becomes ineffective[9,10]. Finally, microbes are released from maturated biofilm by either shedding or biofilm dispersal and enter into the bloodstream, potentially leading to serious infections[11].

Figure 1: Biofilm formation process



Biofilm dispersal allows bacteria from the biofilm to spread throughout the bloodstream and colonise in other parts of the body to establish new biofilms, which eventually can lead to systemic bloodstream infection (BSI)[12]. After biofilms have been established on a catheter, pathogens inside will exhibit tolerance to antimicrobial agents and will not respond consistently to therapeutically achievable concentrations of antimicrobial agents[6]. More importantly, biofilm infections on intravascular catheters are usually polymicrobial, which can cause worse clinical conditions than mono-biofilm[13], and mortality due to polymicrobial infections is higher than that of mono-specie infections[14]. Polymicrobial biofilm infections are generally more difficult to treat, as they can exhibit increased antimicrobial resistance to antibiotics compared to mono-biofilm[15]. Conventional treatment of systemic IVC-BSI usually requires catheter salvage, exchange or removal, and antibiotic therapy,

based on empiric therapy and culture reports of removed catheters[5]. Traditional therapy turns out to be inconvenient, costly, and often ineffective, thus in-depth investigations on biofilm and new strategies to control biofilm formation and development are needed.

BIOFILM CHARACTERISTICS

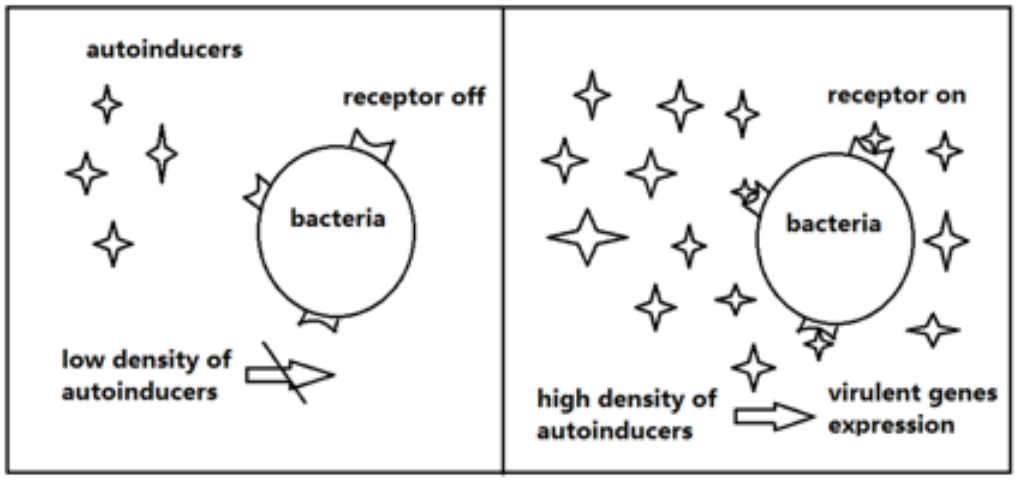
Biofilms are a three-dimensional multicellular community, consisting of an extracellular polymeric matrix and adherent bacteria[16]. The raw material of the extracellular polymer matrix is extracellular DNA, which is mainly produced by bacterial genomic DNA through cell lysis[17]. Microorganisms embedded in biofilms often present different phenotypic and genotypic characteristics compared with those in the planktonic (free-living) state. Firstly, biofilms make use of the nutrient concentrative effect[18] to facilitate nutrition. The biofilm matrix is also negatively charged and hydrophobic, which enables biofilm to concentrate ions and organic carbon agents as an energy source[19]. Additionally, there are nutrient gradients of various growth factors in a biofilm system, including oxygen, sulfide and carbon[19]. For example, moving from the outside surface to the interior of the biofilm, the oxygen level decreases dramatically from the aerobic zone to the anaerobic zone. Oxygen gradients provide a broader range of habitats available for different bacteria colonisation and protect the inner bacteria by decreasing the efficacy of antimicrobial agents[20]. More importantly, gene expression of bacteria grown in biofilm exhibit huge differences compared with their planktonic counterparts. In a study conducted in 2002[21], more than 800 proteins (over 50% of the proteome) of *Pseudomonas aeruginosa* maturated biofilm cells were shown to have a six-fold or larger change in expression level compared with that of *P. aeruginosa* planktonic cells.

MICROBIAL RESISTANCE AND QUORUM SENSING

Microorganisms within biofilm exhibit tolerance to various antimicrobial agents, including antibiotics, disinfectants and germicides[22]. In addition, a biofilm can show tolerance to phagocytosis and other aspects of the immune system[23]. Biofilm resistance is usually multifactorial. In one biofilm system, slow antibiotic penetration, low metabolic rate, steep gradients, enhanced gene expression and persister cells cooperate to establish a multi-layered resistance[24]. For example, biofilm is too compact to be penetrated by antimicrobial agents. At the same time, slow penetration gives bacteria extra time to initiate stress responses, including slowing down their own metabolism. As previously described, the oxygen gradient, which alters the environment in biofilm, also decreases the efficacy of antibiotics[20]. Different microbial species may cooperate to reduce the susceptibility to antimicrobial agents. This can be seen when *Staphylococcus epidermidis* and *Candida albicans* grow in a biofilm together; the staphylococcal matrix can protect the yeast cells from azoles (antifungal drugs), while the matrix produced by the yeast also reduces the activity of vancomycin against the bacteria[25].

When bacteria live in biofilm, their colonisation and most of the virulent activities are regulated by a central system called quorum sensing (QS). Quorum sensing is the regulation of gene expression by chemical signal molecules called autoinducers, and this process responds to the concentration of environmental bacteria[23]. Once the concentration reaches a critical value, QS receptors can receive the autoinducer and initialise the gene expression (see Figure 2).

Figure 2: Mechanism of quorum sensing



FREQUENTLY IVC ISOLATED PATHOGENS

Most IVC-BSIs are caused by *Staphylococci*, especially *S. epidermidis* and *S. aureus*, followed by Enterococci, aerobic Gram-negative bacilli and yeast[4]. *S. epidermidis* is the most common isolated pathogen in IVC-BSI[2]. The virulence of *S. epidermidis* is mostly due to its ability to readily colonise and form biofilm on catheters[26], leading to BSI and associated bacteremia. Approximately 80–90% of *S. epidermidis* isolated from patients with BSI carry the methicillin-resistant gene *mecA*, which can provide *S. epidermidis* with multi-resistance to a number of antimicrobial agents[27,28]. Additionally, the *mecA* gene seems to be over-expressed when grown in a biofilm, leading to strong multi-resistance[28].

Compared with *S. epidermidis, S. aureus* is a more virulent pathogen, with higher rates of bacteremia and mortality[29]. At the same time, *S. aureus* biofilm-associated infections are more difficult to treat and catheters need to be replaced more frequently than with *S. epidermidis* infections[26]. The virulence of *S. aureus* is due to its production of adhesions, pathogenic enzymes, and exotoxins, while *S. epidermidis* does not encode for these virulence factors[30]. Methicillin-resistant *S. aureus* (MRSA), the most virulent and highly antimicrobial resistant strain of *S. aureus*, is highly prevalent in hospitals worldwide. The isolated rate of MRSA varies dramatically ($P < 0.0001$) from 22.5% in Western Australia to 43.4% in New South Wales/Australian Capital Territory[31]. The strong resistance of MRSA is mainly due to *mecA* gene, making it highly resistant to most common antibiotics[32,33].

C. albicans is the most frequently isolated fungal pathogen in IVC-BSI. *C. albicans* is the fourth leading cause of BSI overall and is associated with the highest mortality[34,35]. In addition, nearly 25% of patients with candidaemia also have an associated bacteraemia[36]. The strong virulence of *C. albicans* in IVC-BSI is largely due to the ability of *C. albicans* to readily form biofilms on IVCs[37]. Furthermore, the hyphae of *C. albicans* show a strong propensity to invade the human tissues, probably facilitating the invasion of other bacteria and leading to more serious infection[38]. *C. albicans* biofilm is highly resistant to most antifungal drugs, especially azoles[39]. One study shows nearly one-third of the oral *C. albicans* strains isolated from HIV patients possess strong azole resistance[39]. Compared with planktonic fungal cells, the minimum inhibitory concentrations (MICs) of biofilm-forming *C. albicans* increased 30 to 20,000-fold[40].

Polymicrobial infections can cause worse clinical conditions than monomicrobial infections[13], and it is estimated that mortality due to polymicrobial infections is twice that of monomicrobial infections[14]. Bacteria-fungal infection has become a serious clinical problem in recent years. The most prevalent fungal biofilm-forming pathogen is *C. albicans*, and it is estimated that 27–56% of *C. albicans* BSIs are polymicrobial[37]. In a survey of 372 patients with candidaemia, the three most commonly co-isolated bacterial species were *S. epidermidis, Enterococcus spp*., and *S. aureus,* and their combination usually causes more serious clinical conditions[13]. *S. aureus* is the third most common organism isolated in conjunction with *C. albicans*[29], and its resistance to vancomycin is significantly enhanced by coating the matrix of *C. albicans*[29]. At the same time, the invasive properties of yeast hyphae also help the invasion of both *C. albicans* and *S. aureus,* leading to more serious bacteria-fungal infection.

CONCLUSION

Polymicrobial biofilms are often involved in IVC-BSI. Polymicrobial biofilms are more virulent and difficult to treat, compared to mono-biofilms or their planktonic states. Biofilm infections are characterised by chronic infections, as they are difficult to treat completely, which is why IVCs must be removed when patients are suspected of BSI. While many studies have described biofilms, there are still deficits in our understanding of the mechanism of biofilm formation and multifactorial antimicrobial resistance. Therefore, it is urgent to increase our understanding of microbial biofilm on IVCs and develop new therapies to treat and prevent IVC-BSI. Preventative strategies might include phage therapy, impregnating catheters with antibiotics, and antibiotic lock therapy. Furthermore, exploring new biomaterials might also have the potential to inhibit early stages of biofilm formation and prevent IVC-BSI without increasing antimicrobial resistance.

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