A Microbiological Epilogue—Nosocomial Infections

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Abstract This chapter shortly presents our 5 years researching experience within the field nosocomial infections. We present a few research directions that we developed the last years, consisting in: microorganisms' adaptations characterization, testing the antimicrobial activity of different classes of active molecules and finding new and efficient methods for medical devices disinfections. All these studies are gathered by a final purpose to prevent, control and eradicate the nosocomial infections.

Keywords Nosocomial infections · New active molecules · Medical devices disinfection

Abbreviations

MDRO	Multidrug-resistant organisms
PAW	Plasma activated water
EPS	Exopolysaccharides
LAB	Lactic acid bacteria

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1 Introduction

Who are we? Where are we coming from? Where are we going? How is it possible that after so many years of evolution, and after reaching more than 7.8 billion, the human species, the top of the trophic niches, the most evolved soul of earth, to be so sensitive to microorganisms? How is it possible for the microorganism so small and apparently not evolved to be so harmful to the human kind? When our symbiosis changed so much? It's been a long, long way from the origins, the beginnings, where things came from, where we came from, where life came from. We are constantly evolving, but during the last two decades it has been noted a major increase in the proportion of severe microbial infections paradoxically due to the excessive use of broad-spectrum antibiotics, catheters, and a growing number of immunocompromised patients.

Nosocomial infections or healthcare associated infections occur in patients under medical care, these infections occurring worldwide and being produced by bacteria (*Acinetobacter* sp., *Clostridium difficile*, *Klebsiella* sp., *Escherichia coli*, methicillin-resistant *Staphylococcus aureus*—MRSA), viruses (hepatitis B and C, influenza, HIV, rotavirus and herpes-simplex virus) and fungal strains (*Candida albicans*, *Cryptococcus neoformans*, *Aspergillus* sp) (Vincent 2003; Rosenthal *et al.* 2012; Haque *et al.* 2018). Some of them belong to the natural flora of the patient and may cause infection only when the immune system becomes prone to infections, being called opportunistic pathogens. The most common infections are those of the urinary tract, followed by pneumonias, surgical site infections, and primary bloodstream infections (Emori and Gaynes 1993). Regarding the mortality caused by nosocomial infections, this area is quite controversial since the patients developing these infections are in general sicker and have a greater risk of death compared with other patients (Vincent 2003).

2 Where Are We Now?

Due to the alarming level of nosocomial infections, a phenomenon that has grown and aroused globally, the interest of the researchers on this theme increased proportionally. Within this context, since 2012, in the IntelCentru—Advanced Research Center for Bionanoconjugates and Biopolymers department, within the "Petru Poni" Institute of Macromolecular Chemistry in Iași, we set up a dedicated laboratory, intended to (bio) synthesize and test biologically active molecules with applicability in fighting against nosocomial infections. In this laboratory, a multidisciplinary team tested the antimicrobial activity (antibacterial and antifungal) of various classes of active molecules (bio) synthesized.

2.1 Microorganisms Environmental Adaptations

Our studies started with the estimation of the characteristics of the opportunistic pathogens, which give them resistance to current antibiotics/antifungals. For instance, *Candida albicans* is a member of the normal human microbiome, usually being commensal and harmless, but under certain circumstances, if the defence mechanisms of the host are damaged, it becomes an opportunistic pathogen and produces candidiasis (Kabir *et al.* 2012). *C. albicans* is known to produce two major types of infections: superficial infections, such as oral or vaginal candidiasis, and deep-seated life-threatening systemic infections (such as endocarditis and acute invasive candidiasis as causes of sepsis) (Sanita *et al.* 2013).

Within this context first of our investigations was on the correlation between the infection site and the characteristics of *C. albicans* strains isolated from Romanian patients, in order to quantify the yeas strains evolution. Therefore a total number of 301 isolates from different clinical sites were investigated and clustered in terms of genotype determination, resistogram, phospholipase activity, haemolysis, proteinase activity, and biofilm formation. Biofilm formation is clearly one of the main strategies for microorganisms survival in a variety of sites, the different stages in biofilm formation including initial attachment to the surface, formation of a monolayer along the surface with formation of micro-colonies, biofilm maturation with formation of a three-dimensional structure, and cell dispersion (Fig. 1).

We proved that all the isolated and analysed strains of *C. albicans* had strain-dependent variable levels of enzymatic activity, and there were not all biofilm producers. Although much progress has been made in understanding the phenotypic and genotypic profile of *C. albicans*, still much less is known regarding their interaction with the host. *C. albicans* is a diploid organism and its pathogenicity is linked to a series of inherent and environmental factors and it is mostly related to the host immunological status. No significant correlation was found between the genotype and the infection site (Rosca *et al.* 2018a), but a significant correlation was found between genotype C and isolates from HIV-infected patients proving once

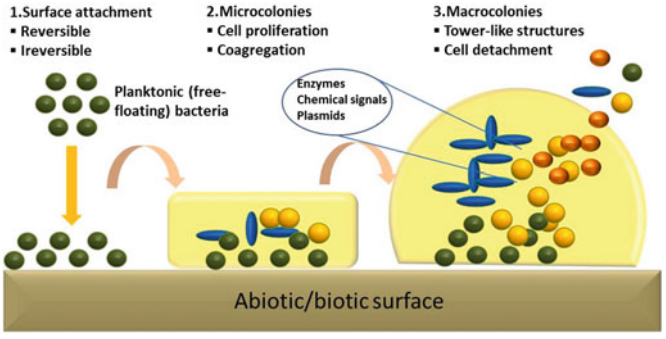

Fig. 1 Scheme of bacterial biofilm and antimicrobial resistance formation

again that *C. albicans* pathogenicity probably relies on factors related to the host (Bostanaru *et al.* 2019).

In the same time the resistance rates to the antifungal agents are increasing because of the selective pressure produced by antifungal treatment. In another study we described the *in vitro* inhibitory and fungicidal activity of the three echinocandins currently use in antifungal therapy such as caspofungin, micafungin, and anidulafungin against a large multicenter derived collection of pathogenic yeasts from Romania. Echinocandins are semisynthetic lipopeptides that block an enzyme complex from the fungal cell membrane, which is responsible for the synthesis of β-glucan, a major component of the cell wall of certain groups of fungi. Although they have a relatively narrow activity spectrum compared with other classes of antifungal agents (Rogers and Frost 2009), echinocandins are very effective against *Candida* and *Aspergillus* strains, the most prevalent invasive fungal pathogens (Meersseman and Wijngaerden 2007; Arendrup *et al.* 2014). This first survey of the susceptibility to echinocandins of pathogenic yeasts from Romania revealed alarming rates of resistance to echinocandins and significant multiple drug resistance to echinocandins and azoles (Mares *et al*. 2018).

2.2 Medical Devices Contamination

On the other hand, the numerous outbreaks of nosocomial infections caused by multidrug-resistant organisms (MDRO) in digestive endoscopy are one of the most worrying effects of recent years (Kovaleva *et al.* 2013). Most nosocomial pathogens exhibit adhesion phenomena at endoscopes in general and duodenoscopes in particular, their persistence at inert surfaces being difficult to access for reprocessing (Schaefer *et al.* 2010). In this regard, the microbiological safety of duodenoscopes has become an ardent topic, constantly on the panel of professional discussions and debates at global level. Duodenoscopes are distinguished by their technological design and the recent data abounds in cases related to nosocomial infections with the most commonly encountered pathogens, such as *Staphylococcus aureus* and *Klebsiella pneumoniae* (Muscarella 2014; Humphries and McDonnell 2015), species that are known due to their ability to form a MDRO, adhering to surfaces and spaces that are difficult to access for reprocessing. Recent data support the fact that inert surfaces at the endoscopes are becoming more susceptible to contamination, and thus to reprocessing, due to the simple repeated use of endoscopes in commonly working cycles, which generate alterations of the interface polymers thus facilitating contamination and subsequently the growth and development of MDRO (Petersen *et al.* 2016).

Within this framework our research described the impact of routine procedural use and reprocessing cycles on the duodenoscope, underling alterations of both coating and working channel polymers due to usage (Balan *et al.* 2019) (Fig. 2). The present study brought new evidences regarding the assessment of duodenoscope reliability concerning the coating materials in both direct and indirect contact with living tissues,

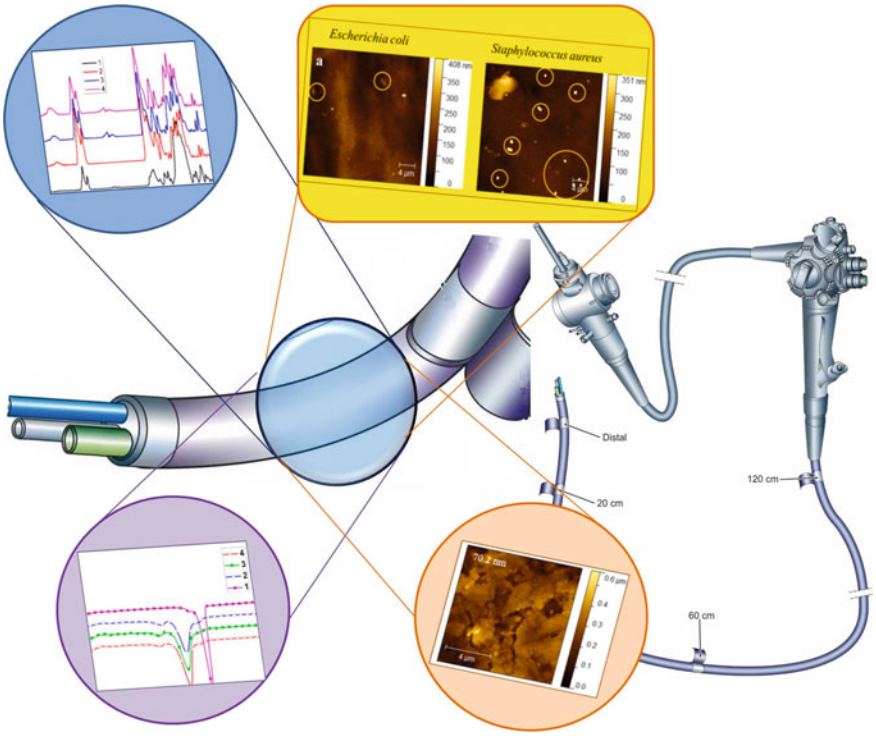

Fig. 2 Scheme of the study of reprocessing cycles on the duodenoscope

via devices manipulated through the working channel. We noticed alterations of both the coating and working channel polymers due to usage, even for a relatively small number of cases. External alterations increased progressively from the distal to the proximal samples, up to the elevator sample. However, the coating surface was proven to still be efficient against bacterial adhesion. All this physical evidences showed that the impact of routine procedural use and reprocessing on the dupodenoscope possibly made it susceptible to bacterial contamination and MDRO biofilm formation due to difficult reprocessing of altered surfaces.

3 Where Are We Going Now?

We know so far that we are dealing with menacingly microorganisms adapted to live in all the conditions regardless the organism and environmental characteristics. These microorganisms are quite adapted to all kind of environmental conditions, can elude the drug's effects and populate different hidden places of medical devices producing resistant biofilms. *What can we do to confute them?* In the last decade

studies focused on finding active molecules that can act as new and improved antimicrobial agents, since, generally, nanosystems can interact with microbial cells directly by disrupting/penetrating the cell envelope (Wang *et al*. 2017). Usually, most antifungal drugs possess low water solubility or are unstable in physiological conditions consisting in the decrease of the therapeutic efficiency and leading to the increase of the dosages. Within this context there is a meaningful searching for alternatives in order to improve the antifungal properties of new and effective drugs.

3.1 New Active Molecules for Nosocomial Infections Control

While looking for new natural and efficient active molecules in order to fight against fungal infections, another important stop was in exploiting microorganisms in fighting against their own kind. Due to numerous industrial applications such as pharmaceutical, medical and food products and to numerous health benefits, exopolysaccharides (EPS), which are extracellular bio-macromolecules, have received special attention and were selected to be tested as new and efficient antifungal agents. EPS produced by lactic acid bacteria (LAB) have been proved to possess immunemodulatory, antitumor and anti-inflammatory effects, acting as oxidizing agents, their biological activity and technological applications being determinate by their structural properties (Kavitake *et al.* 2016).

We analysed the biosynthesis conditions, structure and the biological applications of an exopolysaccharides (EPS) producing strain, isolated from yogurt, and identified as *Weissella confusa* by 16sDNA gene sequencing. The strain was shown to produce a high amount of EPS (25.2 g/L of freeze-dried EPS/L culture medium) in De Man, Rogosa and Sharpe agar (MRS) culture medium improved with sucrose (80 g/l) and dissolved in UHT milk. EPS are important both from a technological as well as from a medical point of view and both aspects will be taken into account in any envisaged biotechnological applications. The extracted and purified EPS were characterized by FTIR and ^{13}C-NMR spectroscopic methods, GPC investigation and thermal analysis (DSC and TGA) showing that the EPS extracted from fermentative culture medium have a dextran structure, with 100% glucose composition.

Dextran is a very complex glycan composed of chains of α-D-glucose with α-(1 → 6) linear links and different percentages of α-(1 → 4), α-(1 → 3) and α-(1 → 2) bonds, which depend on the nature of dextransucrase biosynthesized by the microbial strain (Shukla and Goyal 2013). Beside food applications, especially for bakeries (Kajala *et al.* 2015), the biopolymer has various applications in pharmaceutical and light industries (Gloria Hernandez *et al.* 2011), being used in medicine as antithrombotic agent (Naessens *et al.* 2005). Dextran-based nanoparticles have applications in targeted drug therapy, where dextran is used in coating and it can be functionalized (McBain *et al.* 2008). Dextran is also used as coating for protection against oxidation of metal nanoparticles (Bautista *et al.* 2005).

We conducted several studies revealing that the obtained EPS amount after the fermentative processes is strongly influenced by the culture medium composition

and by the fermentation conditions (Petrovici *et al.* 2018a). These EPS had a dextran structure, with 100% glucose composition and high molecular weight. These characteristics classified the pure EPS produced by *W. confusa* as a suitable ecological candidate product for the pharmaceutical and alimentary field (Petrovici *et al.* 2018b). In the end a concentration up to 3 mg/mL of dextran proved to have no cytotoxic effect on normal human dermal fibroblasts (NHDF) and, moreover, at this concentration, dextran broken up to 70% of the biofilms formed by the *C. albicans* SC5314 strain, in the same time having no antimicrobial activity against standard bacterial strains. We concluded also that, due to their characteristics, these EPS are suitable as hydrophilic matrix for controlled release of drugs in pharmaceutical industry (Rosca *et al.* 2018b).

Knowing that biofilm formation is one of the most challenging problems of nowadays, being associated with severs nosocomial infections, we managed to improve the EPS antifungal activity in order to completely destroy the yeast biofilms. One of the handy solutions was the use of nanostructures which interact directly with the microorganism's cell envelope. We engineered dextran coated iron oxide nanoparticles, loaded with propiconazole, in order to test the hypothesis of a combined effect of the polymer and drug, both known for their antifungal activities. Magnetic nanoparticles were coated with the biosynthesized dextran of 1% and 2% concentrations (Fig. 3), followed by the embedding of propiconazole onto the dextran shell. It was proved that while the 2% formulation nanoparticles revealed an activity on *C. albicans* strain, breaking 77% of biofilm, the improved version of the system (loaded with propiconazole) showed a maximum antifungal activity on *C. albicans*, in both planktonic and biofilm phase (Lungoci *et al.* 2018).

Other classes of molecules that our group had studied in terms of microbiological activity during the last years included organic ligands (Bahrin *et al.* 2019), cyclodextrins (Fifere *et al.* 2018), metal oxide nanoparticles (Turin-Moleavin *et al.* 2019) and natural and synthetic epoxy resins (Rosu *et al.* 2018, 2019, 2020).

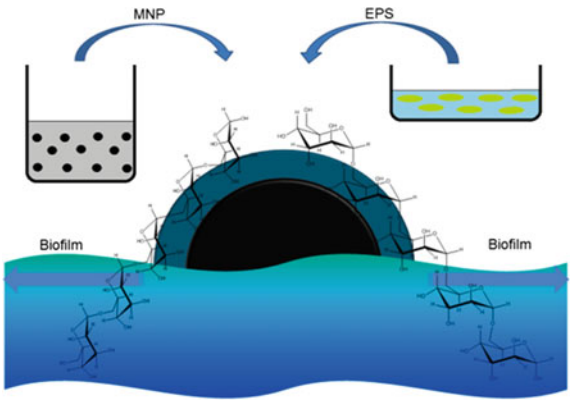

Fig. 3 Concept illustration of coated magnetic nanoparticles (MNP) with exopolysaccharides (EPS) with antifungal activity

3.2 New Methods for Medical Devices Disinfection

Thus we studied the microorganisms responsible for nosocomial infections properties, we tested several types of active molecules in order to better eradicate the opportunistic pathogens, what else could be done? Resistant multi-drug and pan-drug strains have the ability to form biofilms resistant to both physical and chemical cleaning agents in high-grade disinfection reprocessing (Otter *et al.* 2015). The formation of such biofilm is catalysed not only by the difficulties or defects of reprocessing but also by the alterations of the surfaces subjected to reprocessing. Other sources of contamination are either manufacturing defects or secondary to the processes of physical destruction by friction phenomena, abrasion with maximum expression in daily practice in areas of maximum angulation, in areas of post-use handling, or at the level of working channels subject to repeated passage of medical devices (Kovaleva *et al.* 2013).

Plasma activated water (PAW) has been recognized as an effective non-thermal method in decontaminating, disinfecting, and even sterilizing a variety of devices and surfaces for medical and sanitary use (Farin and Grund 1994; Fridman *et al.* 2006; Deng *et al.* 2007; Deilmann *et al.* 2008). The application of non-thermal liquid plasma has proven to be an innovative method of reprocessing surfaces by the lithic activity it exhibits at the level of microorganisms at the same time without causing physical or chemical damage or alteration to treated surfaces or materials (Lerouge *et al.* 2001; Sladek and Stoffels 2005). PAW is a highly active resource against a wide range of microorganisms and is required over other alternative methods of reprocessing by the fact that it is easy to produce and use. It has non-thermal and non-aggressive cytotoxic and cytolytic properties with exposed inert surfaces and last but not least has capacity of penetration and early activity at the level of hard to reach spaces conferred by its fluid character (Sladek and Stoffels 2005).

Within this context our goal was to evaluate if the duodenoscope and it surface components are suited for repeated use of PAW in reprocessing cycles. We also aimed to evaluate the efficacy of PAW in high-level disinfection of endoscopy unit in order to consider PAW as a possible new alternative for duodenoscope reprocessing. Our preliminary study showed that PAW reprocessing is characterized by a significant decrease of bacterial populations, doubled by no surface and composition damage of the duodenoscope polymer coatings. PAW allows also skipping the water-rinsing stage of disinfection and minimizes biofilm formation. Therefore, it could be considered as a new and effective alternative method of disinfection for duodenoscope reprocessing, to be used after current-standard manual cleaning (Balan *et al.* 2018, 2019).

Being still at the road threshold, the conclusions are far from being generally valid, we have the assuredness of fighting on a multi-level way to eradicate the nosocomial infections and promising results are emerging, but we have a long way to go in order to reach the final achievement. Within this context our studies will continue to focus on finding new and efficient biomolecules with antimicrobial effects and able to improve the medical devices disinfection at a high level.

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