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Journal of Infectious Diseases & Preventive Medicine

Mini Review

Antimicrobial Photodynamic Action in Medical Materials: A Novel Thriving Area for Hospital Pneumonia Prevention

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ABSTRACT

Background: Endotracheal tubes, used for mechanical ventilation assistance for bedridden patients, are conducive to developing microbial biofilms due to the accumulation of body fluids. These systems are closely linked to hospital pneumonia by dispersing these cells from microbial biofilm from endotracheal tube to the lung.

Objective: Describe endotracheal tubes' functionalization with photosensitizers such as curcumin, the progress, and perspectives of this research.

Methods: An antimicrobial endotracheal tube was developed through the functionalization of its surface with a photosensitizer activated by light for the generation of reactive oxygen species, which inactivate microorganisms. Therefore, the prevention of pneumonia associated with mechanical ventilation was the object of a study to reach a future phase of clinical research tests.

Results: The mechanisms involved in a complete airway system (upper and lower), including microbial biofilm formation and its elimination, are being studied to prove the transition to clinical applications.

Conclusion: In this context, the main factors related to the development and use of functionalized endotracheal tube with photosensitizer to prevent hospital pneumonia will be described in this mini review.

Keywords: Endotracheal tubes; Photodynamic therapy; Curcumin

INTRODUCTION

Pathogenic microorganisms, including mainly multiresistant bacteria to known antimicrobials and untreated respiratory viruses, have been causing emerging diseases of worldwide importance and endotracheal intubation allows ventilatory assistance in these patients [1]. Hospital pneumonia are characterized by the inflammatory response resulting from penetration and microbial multiplication in the lower respiratory tract after 48 hours from endotracheal intubation [2].

The microorganisms that cause this pneumonia can originate from the patient's endogenous flora or even from nasal cavities with the non-filtration of the inhaled air in these conditions [3]. These microorganisms form biofilms in these materials through initial adhesion on the endotracheal tube (ETT) surface, which use body fluids such as saliva and mucus as a source of nutrients in their development, forming an extracellular polysaccharide resulting from the irreversible adhesion of the microorganisms to the tube [4]. The biofilm consists of microbial cells from one or more species and from 75 to 90% formed by the extracellular polysaccharide, which guarantees their dispersion as planktonic cells can reach the lung [4].

Aiming to address this issue, an photo-antimicrobial ETT was developed thought functionalization of ETT surface with Curcumin (a natural photosensitizer (PS)) and characterized by spectroscopy, microscopy, and mechanical traction methods [5]. This Curcumin functionalized ETT can be activated by light producing a photodynamic action that is able to Ventilator-Associated Pneumonia (VAP). The photo-antimicrobial action is based on formation of oxygen-reactive species (ROS) by Curcumin in the medium and the restructuring of the bacterial biofilm due to the electrostatic repulsions between the photosensitizer molecules and the biofilm polysaccharides [5].

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Received: December 14; **Accepted**: December 28, 2020; **Published**: January 04, 2021

Citation: Blanco KC, Dias LD, Zangirolami AC, Bagnato VS (2020) Antimicrobial Photodynamic Action in Medical materials: A Novel Thriving Area for Hospital Pneumonia Prevention. J Infect Dis Prev Med. 9: 211.

Herein, we described the classification of infectious diseases of the respiratory tract, current treatments, functionalization of medical devices with PS, photodynamic inactivation (PDI), and PDI perspectives for the prevention of hospital pneumonia.

RESPIRATORY TRACT INFECTIONS

Respiratory infections, including those of the upper and lower airways, are among the most common and relevant public health problems worldwide [6]. Most antibiotic prescriptions, which account for 20% of all medical consultations in hospital emergencies, come from respiratory infections. Problems such as absences from work and infant mortality are observed in 30% and 20% (in children under five years old), respectively [7]. Hospital pneumonia and VAP, characterized by being developed within 48 hours after admission to outpatient settings, have high mortality rates of patients bedridden in the intensive care unit, often associated with infection nosocomial [8]. Figure 1 shows a radiographic image of a picture of VAP of bacterial etiology.

Figure 1: Chest radiograph of an adult patient with community-acquired pneumonia. Patchy infiltrates are seen in both lungs and are especially prominent in the lower lobes [9].

ENDOTRACHEAL TUBE AND ITS COMPLICATIONS AND RISKS

VAP presents ETT as one of the main risk factors for its development, which is considered a surface for developing pathogenic microorganisms, being a channel between the oropharynx and the lung that keeps the epiglottis open, allowing secretions to pass beyond to change the cleaning of secretions by coughing [10]. A microbial biofilm is developed with the presence of these secretions containing microorganisms that begin with adhesion on the ETT surface [11]. VAP development results from the displacement of microorganisms to the sterile lung by micro-aspiration, with the transfer of microorganisms from secretions from the ETT cuff, as seen in Figure 2. Preventions directed at this problem are related to limiting the passage of secretions through the cuff of the ETT, either by removing secretions by aspiration, inflating the cuff, or preventing or destroying biofilms [12]. The reduction of biofilm formation through the mechanisms mentioned above in intubation has effectively helped prevent VAP, such as changes in the ETT cuff, in pressure monitoring, or by coating the ETT with silver, removing mucus, or by photodynamic therapy.

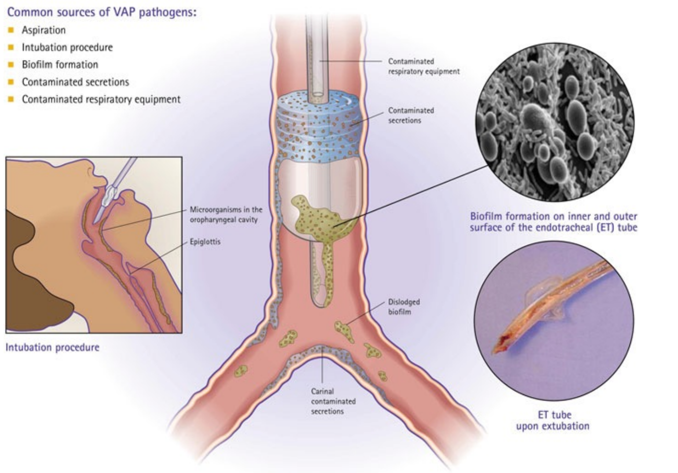

Figure 2: Pathogenesis of ventilator-associated pneumonia [13].

ANTIMICROBIAL PHOTODYNAMIC THERAPY AND ITS MECHANISM

APDT has been showed as an alternative and effective tool against a wide family of pathogenic microorganisms [14]. Moreover, due to its multi-targeting mechanism, the development of resistance microorganisms is minimal [15].

Regarding its mechanism, a combined action of three fundamental components is needed to produce a photodynamic action: i) light with a specific wavelength (depending on absorption spectrum of PS); ii) molecular oxygen (O2); and iii) a photosensitizing molecule. Its mechanism (photochemical and photo physical processes) is explained by Jablonski diagram (Figure 3) [16].

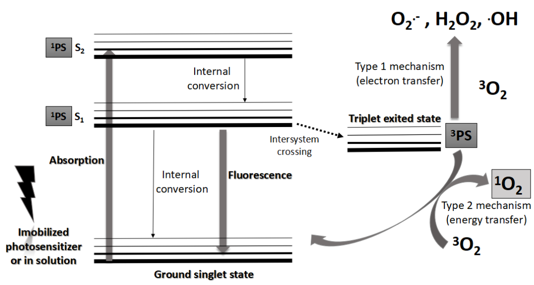

Figure 3: General mechanism of photodynamic therapy explained by the simplified Jablonski diagram [16].

As described in Figure 3, when a PS (0PS) is irradiated by a light source with a specific wavelength. It undergo an electronic transition from a low energy ground state (S0) to an excited singlet state (S1). Then, this PS may decay to S0 state by emission of fluorescence or may undergo a transition to a triplet state via intersystem crossing process (Figure 3). In this step, the triplet state photosensitizing molecule (3PS) can react with O2 via two pathways: i) type 1 mechanism - through electron transfer and/or proton abstraction producing reactive oxidative species (ROS) e.g. superoxide ion (O_2), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH). On the other hand, via type 2 mechanism through energy transfer to O_2 resulting on formation of singlet oxygen ($1O_2$), a highly reactive oxidative species. Those of these oxidative species are able to promote oxidation reactions in a wide family of microorganisms including multi-resistance bacteria and viruses [17].

FUNCTIONALIZATION OF MEDICAL DEVICES WITH PHOTOSENSITIZERS

Medical devices are indispensable components for human healthcare system. In general, these medical materials are made by low cost and high available polymers such as polystyrene, polypropylene and polyethylene [18] which do not present significant antimicrobial properties. Along the years, many researches have been done aiming to attached molecules with antimicrobial properties (e.g. peptides, antibiotics, photosensitizers) [19,20] on medical devices surfaces to avoid biofilm formation and future infectious diseases (Figure 4). However, the development of antimicrobial coatings for medical devices is still a challenge.

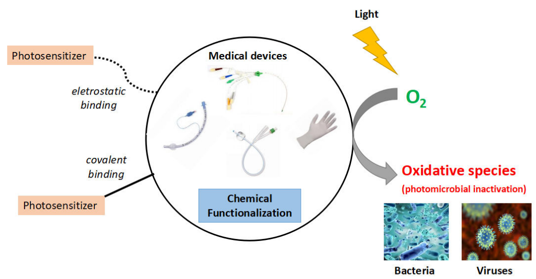

Figure 4: General approaches for functionalization of medical devices (endotracheal tube, catheters, hospital gloves) with antimicrobial molecules.

Among the antimicrobial molecules used, photosensitizing chemical entities have attracted much attention due to their high photo antimicrobial properties resulting by photodynamic action.

In this regard, different types of photosensitizers have been immobilized on medical devices and materials (inorganic and organic) by covalent and/or electrostatic binding for photo-antimicrobial proposals. An immobilized photosensitizer shows many advantages and applications compared to non-immobilized photosensitizers e.g. i) higher stability; ii) complete PS removal from the treated medium; and iii) reuse of PS [21].

In a hospital environment, this immobilization strategy can be applied for the development of different types of photosensitizer-functionalized medical devices (such as endotracheal tubes, catheter and others) with photo antimicrobial applications. Moreover, the use of these photo activable materials is considered an alternative to use of high amount of commercial antibiotics avoiding the development of resistance microorganisms.

ANTIMICROBIAL PHOTODYNAMIC THERAPY FOR PREVENTION OF HOSPITAL PNEUMONIA

The development of commercial Curcumin-functionalized endotracheal tube has been studied to inhibit the formation of microbial biofilms or even through its disruption after lighting to perform the photodynamic action, showing to be efficient in vitro to prevent infections [5]. Zangirolami et al. (2020) investigated microbial inactivation in biofilms on the surface of these functionalized ETTs, proving their antimicrobial efficiency in the different strain P. *aeruginosa*, *E. coli* and *S. aureus*. The spectroscopic characterizations and mechanical properties of the Curcumin-functionalized-ETT showed the maintenance of all its functional properties, thus guaranteeing its intended use.

The ETT lighting performed at 450 nm penetrates the microbial biofilm and not the polyvinyl chloride; thus, it does not reach the trachea, ensuring this treatments safety.

PERSPECTIVES AND FUTURE DEVELOPMENTS

The proof of principles made in this work must now proceed so that it can arrive at the clinic very soon. As the contamination occurs largely in contact with the internal surface, and the fact that the inside of the tube is directly connected with the lungs, increases the chances of contamination. In this sense, from the inner surface, the functionalization of the tube is extraordinarily efficient and closer to the illumination provided by the fiber. The remaining infection that occurs through the external contact surface, must overcome the contact with the balloon, and in this case, the narrow space between the surface of the plastic and the trachea wall promote an even more efficient microbial elimination. So, from both internal and external surface the system may work quite well. Little or nothing should affect the tracheal walls, because there will be no molecules of photosensitizer in close contact to the wall, and light without photosensitizer cause no effect. In order to better understand all the mechanisms involved, including the necessary equilibrium between the growing of microorganism colonies and their elimination, an experiment with artificial tracheas is underway, in order to prove relevant facts for the final transition to the clinical world. Those experiments must be concluded as soon as possible in order to create subsides for the final clinical experiments.

If successful, the attempt to avoiding infections arising from mechanical ventilation should greatly reduce the need for increasing uses of antibiotics, and consequently avoid the rapid evolution of bacterial resistance to antibiotics. In special the pneumonia acquired from hospital may be improved with respect to resistance.

CONCLUSION

Finally, among the future perspectives, this technique can be extended to other catheters, of constant use in modern medicine, and subject to several types of infection. Both endo-gastro catheters and patients with gastrostomy can be severely benefited by such functionalization.

The main factors related to the development of ETT-curcumin, such as the absence of significant changes in its properties and the antimicrobial effect in preventing hospital pneumonia, were described in this mini-review.

ACKNOWLEDGEMENT

FUNDING

The authors thank Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) for CEPOF 2013/07276-1, and INCT "Basic Optics and Applied to Life Sciences" (FAPESP 2014/50857-8, CNPq 465360/2014-9). L.D.D. and K.C.B thanks FAPESP for the Post-doc grants 2019/13569-8 and 2019/12694-3, respectively.

AUTHORS' CONTRIBUTION

KCB, LDD, VSB conceptualized the manuscript, KCB, LDD, ACZ, VSB drafted the manuscript, KCB, LDD, VSB critically reviewed manuscript and validated resource material.

COMPETING INTEREST

All authors have declared that there are no conflicts of interest.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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