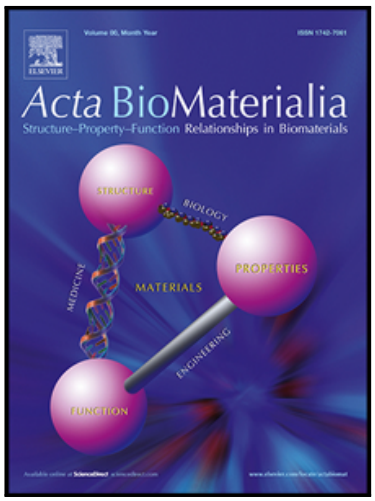


Antimicrobial materials for endotracheal tubes: A review on the last two decades of technological progress

Diana Alves , Tânia Grainha , Maria Olívia Pereira , Susana Patrícia Lopes

PII: S1742-7061(23)00002-8
DOI: https://doi.org/10.1016/j.actbio.2023.01.001
Reference: ACTBIO 8532

To appear in: *Acta Biomaterialia*

Received date: 17 October 2022
Revised date: 21 December 2022
Accepted date: 3 January 2023

Please cite this article as: Diana Alves , Tânia Grainha , Maria Olívia Pereira , Susana Patrícia Lopes , Antimicrobial materials for endotracheal tubes: A review on the last two decades of technological progress, *Acta Biomaterialia* (2023), doi: https://doi.org/10.1016/j.actbio.2023.01.001

Antimicrobial materials for endotracheal tubes: a review on the last two decades of technological progress

Diana Alves[a,b,i], Tânia Grainha[a,b], Maria Olívia Pereira[a,b], Susana Patrícia Lopes[a,b,*]

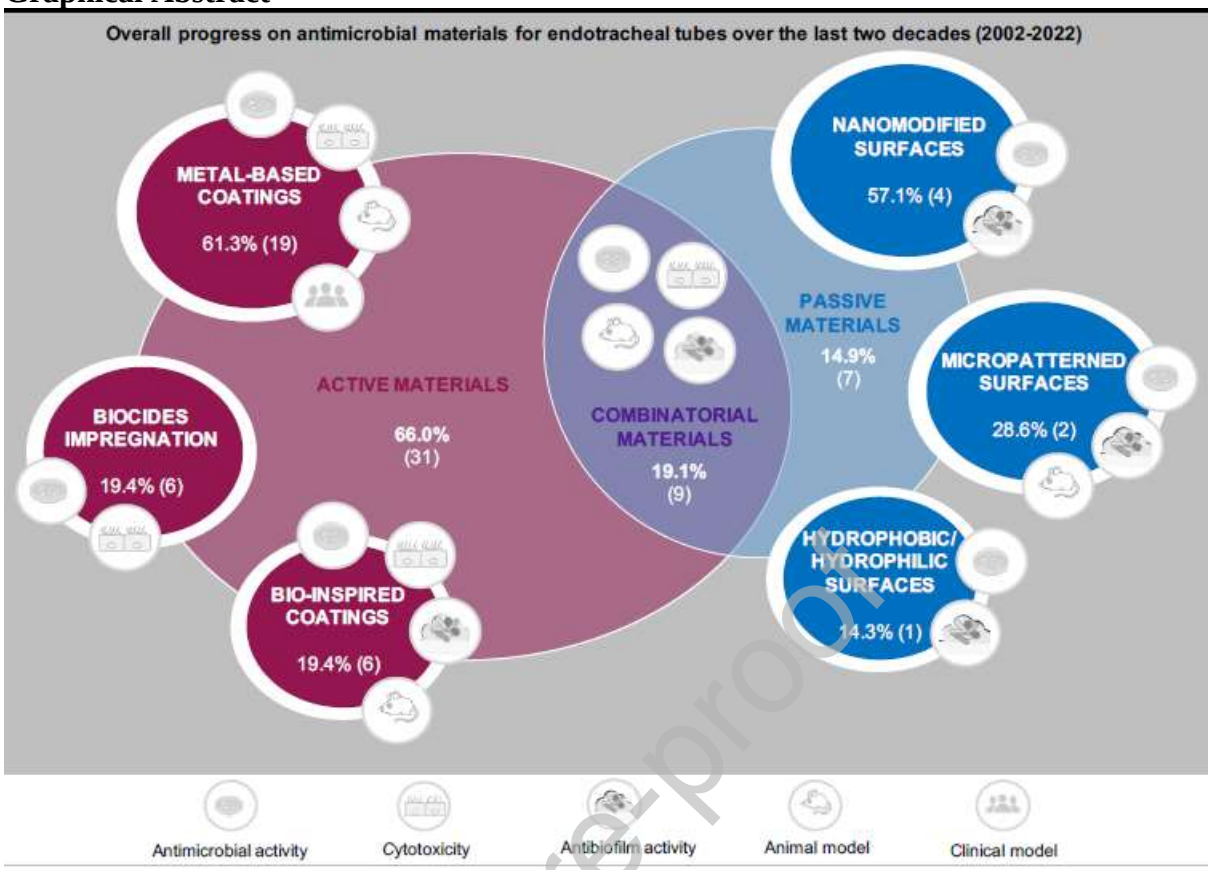
[a] CEB - Centre of Biological Engineering, University of Minho, 4710-057 Braga, Portugal
[b] LABBELS – Associate Laboratory, Braga/Guimarães, Portugal

Diana Alves: dianalves@ceb.uminho.pt
Tânia Grainha: taniagrainha@ceb.uminho.pt
Maria Olívia Pereira: mopereira@deb.uminho.pt
Susana Patrícia Lopes: supat@deb.uminho.pt

Corresponding author at: CEB - Centre of Biological Engineering, University of Minho, 4710-057 Braga, Portugal; LABBELS – Associate Laboratory, Braga/Guimarães, Portugal
Tel. No. (+351) 253 601 968 (office)
E-mail address: supat@deb.uminho.pt

[I] Current affiliation: INL - International Iberian Nanotechnology Laboratory, Av. Mestre José Veiga, 4715-330 Braga, Portugal

Graphical Abstract



Abstract

Ventilator-associated pneumonia (VAP) is an unresolved problem in nosocomial settings, remaining consistently associated with a lack of treatment, high mortality, and prolonged hospital stay in mechanically ventilated patients. The endotracheal tube (ETT) is the major culprit for VAP development owing to its early surface microbial colonization and biofilm formation by multiple pathogens, both critical events for VAP pathogenesis and relapses. To combat this matter, gradual research on antimicrobial ETT surface coating/modification approaches has been made.

This review provides an overview of the relevance and implications of the ETT bioburden for VAP pathogenesis and how technological research on antimicrobial materials for ETTs has evolved. Firstly, certain main VAP attributes (definition/categorization; outcomes; economic impact) were outlined, highlighting the issues in defining/diagnosing VAP that often difficult VAP early- and late-onset differentiation, and that generate misinterpretations in VAP surveillance and discrepant outcomes. The central role of the ETT microbial colonization and subsequent biofilm formation as fundamental contributors to VAP pathogenesis was then underscored, in parallel with the uncovering of the polymicrobial ecosystem of VAP-related infections. Secondly, the latest technological developments (reported since 2002) on materials able to endow the ETT surface with active antimicrobial and/or passive antifouling properties were annotated, being further subject to critical scrutiny concerning their potentialities and/or constraints in reducing ETT bioburden and the risk of VAP while retaining/improving the safety of use. Taking those gaps/challenges into consideration, we discussed potential avenues that may assist upcoming advances in the field to tackle VAP rampant rates and improve patient care.

Keywords: antimicrobial coating; biofilm; endotracheal tube; pathogenesis; ventilator-associated pneumonia

1. Introduction

1.1 VAP definition and differentiation between early- and late-onset VAP

Ventilator-associated pneumonia (VAP) is a common complication that occurs in critically ill individuals undergoing invasive tracheal intubation and prolonged mechanical ventilation (MV) [1,2]. It remains the second most frequent hospital-acquired infection (HAI) [3] and one of the most reported biomaterial-associated infections (BAIs). VAP, but also catheter-associated urinary tract infection, surgical site infection, or central line-associated bloodstream infection, are well-known for being associated with the use of indwelling devices, that are critical to patient care and which have grown dramatically over the past 2-3 decades [4].

There is currently no gold standard, valid, reliable definition for VAP. It has been defined as an infection of the pulmonary parenchyma, which develops at least 48h or longer after using a ventilator [5]. Its primary symptoms overlap with those of a plethora of other medical conditions, which difficult and makes diagnosis delayed or even missed [6–9]. Despite the advances in microbiological technologies, the epidemiology and diagnostic criteria for VAP are still controversial topics, often raising concerns regarding the interpretation of treatment, prevention, diagnosis, and outcome studies.

VAP has been categorized into early- and late-onset VAP, according to the timing of MV onset. However, there is widespread variation in defining the exact time that differentiates both types of VAPs. The cut-off points of a range of 4–7 days onset have greatly varied [10–12], even though international guidelines recently have recommended the cut-off of 5 days after hospitalization [5,13,14]. Dissimilar outcomes on the main attributes of each type of VAP are often found across the studies (Table 1).

Table 1. Comparative overview of the main attributes of early- vs. late-onset VAP

	Early-onset VAP	Late-onset VAP	Ref(s).
Time of occurrence	2-4 days post intubation/MV	≥ 5 days post intubation/MV	[5,13,14]
MV days	14	23	[15–17]
ICU/Hospital length of stay	13-20/26.5 days	20-26.5/35.5 days	[15–17]
Incidence	11-16%	81-84%	[16,18]
Hospital mortality rate	16-23%	31-44%	[15–17]
Microbial etiology	Antibiotic sensitive bacteria: ● MSSA ● *Streptococcus pneumoniae* ● *Haemophilus influenzae* ● *Klebsiella pneumoniae* ● *Escherichia coli*	Antibiotic-resistant or MDR bacteria: ● *Pseudomonas aeruginosa* ● MRSA ● *Acinetobacter* spp. ● *Enterobacter* spp. ● VRE	[10,15,19]

	• *Proteus* spp. • *Serratia* spp.		

Legend: MDR - multidrug-resistant; MRSA - methicillin-resistant *S. aureus*; MSSA - methicillin-sensitive *S. aureus*; VRE - Vancomycin-resistant *Enterococcus*

Overall, late-onset VAP has been commonly associated with the worst prognosis and is essentially caused by antibiotic- or multidrug-resistant (MDR) pathogens. It has also a significantly longer duration of MV, length of stay in intensive care units (ICU), and higher mortality than the early-onset VAP. The large discrepancies in VAP surveillance data observed among different reports demonstrate how VAP criteria and definitions are poorly or inconsistently documented [20,21]. VAP definition criteria have opportunely evolute, with the National Healthcare Safety Network (NHSN) changing the way that VAP surveillance is done [20,22]. The new NHSN surveillance algorithm for the ventilator-associated event (VAE) was proposed in 2013 and several initiatives have provided effective strategies in promoting adherence to these international recommendations. VAE embeds the following definition tiers: ventilator-associated condition (VAC); infection-related ventilator-associated complication (IVAC; a subset of VAC with infectious symptoms); and, possible and probable VAP (PVAP; IVAC added to microbiological evidence of pneumonia). VAE was designed to address the limitations of the subjective and variable longstanding VAP definitions, constituting a useful tool in surveillance reports, but still restricted to public reporting, benchmarking, and/or internal quality improvement, thus not addressing patient management [23].

1.2 VAP variable outcomes

Studies have reported discrepant VAP incidence rates, potentially related to the different interpretations of the VAP definition, limitations regarding the diagnostic methods, and use of non-standardized microbiological sampling methodologies [24]. VAP incidence greatly varies from 5 to 40%, based on the diagnostic criteria, type of healthcare unit, and studied patient population [7,25]. In 2009, a report from the International Nosocomial Infection Control Consortium presented a pooled density of 13.6 cases per 1000 ventilator days, which included data from Latin America, Asia, Africa, and Europe [26]. In Northern US hospitals, VAP rates are referred to as low as 1 to 2.5 episodes per 1000 ventilator days [27]. In turn, much higher VAP rates are reported by the European centers. In a more recent study, which enrolled patients from 27 ICUs in 9 European countries, VAP rates have been reported to be 18.3/1000 ventilator days [28]. On average, the incidence rate of VAP varies from 2.8 in the United States (US) [27], 14.5 in Europe [29], and 22 episodes per 1000 ventilator days in developing countries [30]. Contrary to the patient's age, which is not related to a high risk of VAP, intubated patients with underlying clinical conditions (e.g., comorbidities; severity of illness) are more likely to acquire VAP. For example, high incidence rates are reported in cancer patients (24.5 cases per 1000 ventilator days) [31] or patients with traumatic injuries (at a rate of 17.8%) [32]. Specific risk factors such as prolonged invasive MV, high incidence of microaspiration and airway bacterial colonization, defective mucociliary clearance, and altered local and general host immune defenses, all account for the increased VAP incidences in intubated chronic obstructive pulmonary disease (COPD) patients. VAP incidence in COPD patients ranges widely from 6.2% to 56% [33–37]. Also, a recent study has suggested a higher risk of VAP occurring among coronavirus disease 2019 (COVID-19) patients compared with the general ICU population (25.5 vs 15.4 cases per 1000 ventilator-days), with a similar microbiological ecology and resistance pattern. VAP all-cause mortality has been reported to be as high as 50%, and patients admitted to ICU are generally at increased risk for

VAP, even though there is still considerable controversy regarding the attributable mortality of VAP in ICU patients [38]. However, VAP in ICU remains a major unresolved clinical issue, causing a longer duration of MV, prolonged stays in the ICU and hospital; increased risk of disability and mortality (at a rate varying from 25% to 45%) [39,40], and increased healthcare costs.

1.3 VAP economic burden

VAP imposes a significant worldwide economic impact, accounting for increased direct healthcare costs in the US, ranging from $28-$33 billion per year [41], which represents about 32% of the total HAI annual cost [42]. A study conducted by Kollef et al. reported average costs of $99,598 for patients with VAP, against $59,770 for patients without VAP [43]. Less costly is the economic impact of VAP in the European healthcare system, which is estimated between €13 and 24 billion per year [44–46]. Recently, a detailed epidemiological observational study of VAE involving about twenty thousand mechanically ventilated patients has estimated hospitalization costs totaling $25,073 for VAEs, which corresponds to more than twice those for non-VAE patients with at least 1 ventilator-day ($11,840), and nearly to 1.5 times than those for non-VAE with at least 4 ventilator-days ($25,073 vs. $18,298).

1.4 Endotracheal tube: a life-saving device vs. a conduit for VAP

The endotracheal tube (ETT) has become an indispensable medical device to support airway patency (that is, an unobstructed or open airway) and deliver oxygen and inhaled gasses to the lungs of mechanically ventilated patients. Endotracheal intubation is a life-saving procedure, still potentially hazardous in critically ill patients needing artificial ventilation for a prolonged time. The process is invasive, and consists of placing the ETT through the nose (nasotracheal intubation), but essentially through the mouth (orotracheal intubation) into the trachea [47]. Though the duration of MV; bed positioning; enteral feeding; witnessed aspiration; prior antibiotic therapy; and multiple comorbidities, may all contribute to VAP [48], the ETT alone has been affirmed as an independent risk factor and the major culprit for its development, contributing for up to 25-56% of the intubated patients to contract VAP [40,49]. In other words, the risk of acquiring VAP increases by 6 to 20 folds every time an ETT is placed in a patient [50,51].

The role of the ETT in VAP pathogenesis has become very prominent in the last decades due to extensive research devoted to medical device-related infections and biofilms [52–54]. Generally made of flexible materials such as polyvinyl chloride (PVC) or silicone, the ETT provides an ideal source for microbial colonization and biofilm proliferation on the ETT surface [55], thereby increasing the patient's opportunity of getting pneumonia. In healthy individuals, lung protection is typically assured by the mucociliary clearance mechanism, which is composed of a mucous layer, the airway surface liquid, and the cilia on the surface of ciliated cells [56,57]. The presence of the ETT bypasses these clearance airway mechanisms and, as consequence, microorganisms from the oropharynx can reach the distal airways and colonize the ETT, only a few hours after its insertion [58,59]. This process may occur at varying degrees in all intubated patients, ending with the deposition of mucus and microbial secretions, a decline in airway patency, and sometimes with the ETT undergoing complete occlusion after long-term intubation [60]. Contaminated secretions can, therefore, reach the lungs via two major routes: around the ETT (microaspiration) and through the ETT surface (microbial colonization followed by biofilm formation) [61]. Microaspiration comprises the distal migration of microorganisms from secretions accumulated above the ETT cuff. Specifically, the hydrophobic surface of PVC-ETTs provides ideal conditions for

microbial attachment and proliferation, ultimately resulting in persistent microbial colonization over the entire external and internal ETT surfaces [62–64].

1.5 ETT biofilms

Biofilms have long been considered the dominant microbial lifestyle in nature. They are well-organized, three-dimensional structured microbial communities adhered to surfaces, in which microbial cells are surrounded by a self-produced polymeric matrix [65]. Biofilms are of hard eradication, owing to their inherent tolerance to antimicrobial therapy and the immune system responses, often resulting in persistent and recurrent infections [66]. About 80% of human infections are biofilm-related [67]. They represent one of the greatest current challenges in nosocomial settings, paying for 1.7 million HAIs in the US and an annual economic burden of approximately 11 billion US dollars [68]. Microorganisms can reach the surface and establish biofilms on biomaterial surfaces of indwelling medical devices, jeopardizing their clinical applicability and limiting the advancement of these systems [69]. This frequently implies the need for device withdrawal to achieve microbiological and clinical healing.

Typically, the development of a biofilm is a multi-step and dynamic process that involves several stages: initial cell attachment; aggregation; maturation, and dispersion. Following initial attachment, and as biofilm formation progresses, the microbial cells inside the consortia can produce an extracellular matrix of polymeric substances until achieving a mature biofilm architecture. The cells within this mature biofilm can subsequently disperse, leading to the colonization and infection of other sites. During biofilm formation, attachment of different species may occur, resulting in a multi-layered multispecies biofilm [70].

The ETT acts as a reservoir for infecting microorganisms, providing them with an optimal surface to adhere to and develop biofilm, which may occur in both its inner luminal and outer surfaces [71]. The accumulation of tracheobronchial secretions at its distal end creates a favorable environment, so that microorganisms coming from the surroundings, from the upper airway, and eventually from the gastrointestinal tract, can migrate and undergo multilayer aggregation along the ETT [72]. Microcolonies formation on the ETT surface, combined with an injured host-defense system caused by the invasive endotracheal intubation, significantly contribute to the development of the ETT biofilm and the consequent spread of the infection [73]. Indeed, biofilm formation is an early and frequent phenomenon occurring on ETT surfaces. Vandecandelaere and Coenye (2015) have proposed a model elucidating how bacteria propagate and develop a multi-species biofilm at the distal end of the ETT. In their model, the earliest stage of biofilm formation results from the leakage of nasopharyngeal secretions enriched with non-pathogenic oral bacteria (mostly *Streptococcus* spp.) around the cuff of the ETT. Following bacterial initial attachment and accumulation, the next stage comprises streptococci coaggregation with several other commensal members of the subgingival flora such as *Veilonella* spp. and *Actinomyces* spp., followed by the recruitment of a variety of opportunistic oral species (e.g., *Fusobacterium nucleatum*; *Prevotella* spp.). This may allow further nosocomial pathogens such as *P. aeruginosa* or *S. aureus*, to persistently join to and interact with oral bacterial species within the pre-formed biofilm, with harmful consequences leading to VAP development [73].

Additional factors such as the supine patient positioning, but also the shape, thickness, and great permeability of the ETT cuff wall, alongside variations in the cuff pressure level inside the trachea, are sufficient to allow deposited contaminated secretions to leak through the folds formed by the cuff in contact with the trachea, migrating to the lower airways and easily triggering pneumonia [74–76]. The ETT poses, therefore, a central role in VAP pathogenesis, thus becoming a new ecosystem, while allowing microorganisms to colonize

and form resilient biofilms on its surface, and likely shaping lung ecology during invasive MV at a microbiome scale [77]. Biofilm forms quickly along the ETT, which may start within a few hours after the ETT insertion, despite it particularly lining the internal distal third of the ETT [63,78]. Portions of the biofilm can be easily dislodged during suctioning, bronchoscopy, or simply by gravity, spreading into the lower airways, and invading the lungs [79]. The ETT biofilm colonization was early evidenced, first by culture [80] and later, through advanced assessment methods (e.g., scanning microscopy; quantitative polymerase chain) [54,81]. Since then, increasing research has shown that ETT biofilm is an early and recurrent event in intubated patients, and a great contributor to the pathogenesis, lack of treatment, and relapses of VAP [52,53,73,78,82–84]. When settled on a surface such as the one of the ETT, the biofilm becomes hard to treat by oral or systemic antibiotic therapy, a consequence of its inherent recalcitrance nature [78]. These microorganisms have proved significantly greater antibiotic resistance compared to their tracheal counterparts [85]. Overall, 10-5000 times more antibiotic doses are necessary to eliminate biofilm-associated infections, compared with "free-living" bacteria [86,87].

1.6 Polymicrobial ETT biofilms

The original concept that the lower respiratory tract is considered sterile has been refuted by mounting evidence, which has supported the presence of a distinct microbiome, either in healthy subjects or in various respiratory disorders [88–90]. Data have demonstrated that ETT biofilms generally harbor multiple microbial pathogens, which makes VAP a polymicrobial infection, with considerable inter-patient and intra-patient diversity [55]. Several prospective studies have allowed a broad look at the diverse microbial communities in VAP, reporting distinct polymicrobial profiles and varied microbial causes [19,73,78,90].

Bacteria from the ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.) group are frequently found in nosocomial environments. Of those, *P. aeruginosa*, *A. baumannii*, *K. pneumoniae*, or *S. aureus*, play a dominant role in VAP etiology. Gram-negative bacterial species generally account for 80% of the total isolates [91], and Gram-positive bacteria represent 20-30% of VAP cases [92]. Typically, 25-40% of VAP episodes tend to be polymicrobial [93–95], with a dominance of MDR *P. aeruginosa*, *S. aureus*, and *K. pneumoniae* [96,97]. Taking into account that the ETT facilitates the straight communication from the stomach and oropharyngeal cavities to the tracheobronchial area, it is not surprising the presence of other microbial pathogens that can reach the lungs either after aspiration or by direct inoculation into the airways [89–91]. Some authors showed that most VAP patients had identical pathogens isolated from both the ETT biofilm and secretions from the lower respiratory tract [54,85]. However, this does not imply that all microorganisms that reside in the ETT biofilm may be directly involved in VAP [73]. In turn, an enrichment of pathogen strains [27] and a fluctuation in the prevalence of detectable organisms within ETT biofilm have served as strong indicators of VAP [71,98]. A link between the major pathogens isolated from the ETT biofilms and the development of VAP has been demonstrated [54]. Hotterbeekx et al. examined the composition of ETT biofilms, stating that the highest chance of survival was for VAP patients with a relative abundance of *Pseudomonadaceae* and *Staphylococcaceae* were <4.6 % and <70.8 %, respectively. In its turn, in patients infected with *Pseudomonadaceae* at rates greater than 4.6 %, the age of the patient (<66.5 years) became the most relevant predictor of patient survival [99].

Alongside bacterial pathogens, viruses (e.g., Influenza and Cytomegalovirus) and fungi (e.g., *Candida* spp. and *Aspergillus* spp.) also have been implicated as major causes of VAP, however at lower incidences, playing a more important role in immunocompromised patients

[92,100]. Polymicrobial communities, in which multi-kingdom species often appear, are another worrying feature of biofilm-associated infections, by playing extensive ecological roles in nosocomial infections, and substantially increasing the resistance and the burden of VAP infections [95,101].

Unfortunately, there are still many hurdles that frequently limit and challenge VAP diagnosis. There is often an unclear relationship between the dynamics of the microbiome and the onset of the infection; the difficulty in differentiating colonization and infection in clinical practice; the uncertainty about the ETT biofilm flora as the primary source of VAP or just a concomitant infection; and the unawareness of the causative agent at the time of VAP suspicion [102,103] are concerns that make VAP diagnosis complex. Besides, the gold standard assessment methods used to identify VAP-associated pathogens rely on culture analysis, which may misrepresent the real composition of ETT biofilms, generally encompassing microorganisms difficult to culture or even unculturable (e.g., members of the oral cavity) [71,104].

1.7 Aim of the Review

This review has a dual aim. First, it intends to outline the central role of ETT biofilm (mostly polymicrobial) on VAP pathogenesis but also addresses the main attributes of and the hurdles in defining and diagnosing VAP, which often leads to unfortunate misinterpretations in VAP surveillance that result in variable clinical outcomes.

The second aim is to provide knowledge on how technological research on antimicrobial materials designed for ETTs has evolved in the last years. Following up on a preceding report reviewing biomaterial approaches to help prevent the ETT bioburden [2], this review intended to give a more complete picture of the technological improvements in the design of ETTs over the last two decades. We hereby gathered the most recent developments (reported since 2002) on materials (that mean, coating or modification) able to endow the ETT surface with active antimicrobial and/or passive antifouling properties, highlighting their potentialities and/or constraints in reducing ETT bioburden and the risk of VAP while retaining/improving the safety of use. Finally, we elucidate potential avenues that may assist upcoming advances in the field to tackle VAP rampant rates and improve patient care.

2. Recent technological advances in antimicrobial materials for ETTs

Studies have reported that inadequate and excessive use of antibiotic (essentially of broad-spectrum) therapy in ICU is associated with an increase in antibiotic resistance, biofilm formation, and patient mortality [7,105,106]. The hurdles with diagnosing VAP coupled with the urgent need of getting an effective treatment to combat VAP infections make prevention of ETT microbial colonization the most reliable approach for staving off biofilm proliferation and preventing VAP occurrence. Some useful interventions to prevent VAP have included subglottic secretions aspiration (SSA) [107,108], control of ETT cuff pressure [109], or change of the ETT surface material and/or shape [107,110] to provide a better seal and avoid lung injury. However, their benefit in terms of diminishing the outcomes associated with VAP (e.g., MV duration; mortality; cost-benefit ratio) remains unclear, limiting its widespread use [111].

Antimicrobial coating materials are believed to offer new ideas to solve the problem of microbial adhesion on device surfaces. Improvements in the design of the ETT have been achieved in recent years [2] with many active (i.e., directly killing microbes on device surfaces), passive (i.e., altering the surface composition and pattern to produce a

contamination-resistant surface) and combinatorial approaches being developed to render ETT with either active antimicrobial and/or passive antifouling properties. We hereby propose to review the latest technological advances in the field, by gathering, sorting, and annotating studies on ETT surface coatings/modifications published in the last two decades (2002-2022) (Table 2). Reports covering active approaches: i) metal-based coatings; ii) impregnation with antiseptics/antibiotics; iii) coatings based on bio-inspired antimicrobials; passive approaches: iv) hydrophobic surfaces; v) micropatterned surfaces; vi) nano rough surfaces; and finally combinatorial approaches involving both active and passive technologies, were the further subject of critical scrutiny, in respect to their potentialities and/or constraints in reducing ETT surface colonization/biofilm formation, safety, and ability to reduce the risk of VAP. A summary of the findings is described next.

2.1 Active Materials

2.1.1 Metal-based antimicrobial materials

Among the wide variety of metals and metallic nanoparticles (NPs) with proven antimicrobial properties, silver, zinc, selenium, and titanium oxide have been extensively studied, in particular as antimicrobial coatings for ETTs.

2.1.1.1 Silver-based antimicrobial coatings

Silver is the noble metal that has been most extensively studied (for at least 30 years), being the only one that has been put through multiple clinical trials and that has reached commercialization [112,113]. After its successful application on urinary catheters back in 1990, its potential has been also investigated for ETTs [114]. Silver establishes an ionic binding with cell components in bacteria, allowing to alteration of many fundamental bacterial processes [115,116] which include increased cell permeability; membrane penetration; oxidative damage due to disruption of cell respiration; and changed protein activity [2]. A wide variety of silver-related compounds, alloys, NPs, and materials have been investigated as antimicrobial coatings for ETTs by their broad-spectrum mechanisms, either actively incorporated in the biomaterial for combinatorial applications or the synthesis of silver nanomaterials.

Hartmann et al. were the first to demonstrate that silver-coated ETTs were able to significantly inhibit the growth of *P. aeruginosa* (a 2-log reduction after 50 h of incubation) in a continuously ventilated oropharynx lung model [117]. In this approach, silver deposition was used to modify the ETT. In a similar approach, but using an animal model, Olson et al. challenged silver-coated ETTs for 3 days with *P. aeruginosa*, resulting in delayed bacterial colonization on the inner lumen of the ETT, as compared to the unmodified ETT [118]. In the latter case, silver ions were incorporated in a hydrogel covering the surface of the ETT. Chemical modification of ETTs by a radio frequency-oxygen glow discharge plasma, enhanced its reactivity towards the incorporation of sodium hydroxide and silver nitrate, thus creating an ultra-hydrophobic surface. The modified ETT was able to completely inhibit the adhesion of four strains of *P. aeruginosa* and prevented biofilm formation up to 72 h [119]. Despite these promising antimicrobial effects, the reaction times required for chemical modification were too long (several weeks). Ramstedt et al. presented, then, a faster and simpler method to attach silver ions to the ETT surface, applying silver nitrate instead of sodium hydroxide, as has been previously reported [120]. Modified tubes inhibiting the growth of *P. aeruginosa* and silver ions leaching were observed.

Most of the aforementioned studies relied on the release of silver ions, which generally present a high level of cytotoxicity and remain active for short periods. Silver nanoparticles (AgNPs) have increasingly emerged as a promising safe approach addressing such limitations, by displaying enhanced antimicrobial efficacy against bacteria, viruses, and fungi when incorporated into ETTs. The transformation of metals into nanoparticles (NPs) may be advantageous over the use of bulky metals by its i) small sizes but enlarged surface area; ii) altered morphology permitting intimate microbial-surface interaction; iii) precise application when preparing medical devices, and iv) cost-effective synthesis procedures [2,121]. An antimicrobial hydrogel obtained through the loading of AgNPs on polyvinyl alcohol (PVA) was proposed to be used on the ETT [122]. Results showed that prepared coatings were effective in reducing colonization of *P. aeruginosa* and *S. aureus*, compared to PVA alone. Additionally, it showed no toxicity against human bronchial epithelial cells. More recently, a green and facile fabrication technique to coat the surface of ETTs with AgNPs has been reported in a polyelectrolyte multi-layered film, obtained using layer-by-layer deposition [123]. The modified ETT exhibited a better antimicrobial activity towards *P. aeruginosa* and *S. aureus*, as compared to a commercially available silver-coated ETT, and it showed no toxicity against human lung epithelial cells. The antimicrobial activity of polyamide/AgNP composite-coated ETTs was performed against single and polymicrobial cultures of both VAP-related Gram-negative and Gram-positive bacteria, but also fungi. The results revealed that coated ETTs demonstrated considerable antimicrobial outcomes on the growth of planktonic *P. aeruginosa* and *S. aureus* populations, retaining their antimicrobial activity for 4 weeks. Also, biofilm formation by both bacteria was inhibited (4-6 log) after 72 h [64]. No indication of toxicity assessment was reported in this study.

The aforementioned studies evidence the antimicrobial properties of silver biomaterials *in vitro* and *in vivo*, but there is still controversy concerning silver-related toxicity, which has been limitedly addressed. In regards to AgNPs, when rabbits were orally exposed to silver nanoformulations for 28 days, nanosized granules were found in the basal lamina, macrophages, and connective tissue of submucosa [124]. It has also been demonstrated that when different-sized AgNPs were intravenously injected into rats, these were redistributed to the liver, lung, heart, and all other organs, showing a systemic distribution [125]. By contrast, Jiang *et al.* reported no cytotoxic effect by dip-coated polyethylene ETTs with a solution of silver-silicon dioxide using rabbits and a gold hamster in vivo model, no pyrogenic effect was observed and hemolysis test showed biocompatibility with red blood cells [126]. Despite the effort made to study these aspects, data regarding silver toxicity and effectiveness is still limited and/or discrepant, which hinders drawing definitive conclusions about their safety and clinical use.

In addition, scant data is reporting the effective reduction of secondary VAP outcomes such as mortality rates, and ICU length of stay [112,127] by silver-coated ETTs. In 2015, an ETT coating based on a combinatorial approach with a sub-micron layer of a noble metal alloy (NMA) composed of silver-gold-palladium (“Bactiguard®” Infection Protection, BIP) was reported by its clinical tolerability, safety, and performance during short-term intubation (3-8 h) in a small sample size (29 patients) [128]. Later, a pilot study enrolled 300 ventilated patients from different ICUs and hospital centers (n=9, Belgium), to test the impact of BIP ETT in reducing VAP incidence, antibiotic consumption days, and tracheal colonization by pathogenic bacteria [129]. Even though the length of ICU stays, MV duration, tracheostomy rate, and hospital mortality were not significantly different among both NMA-coated and non-coated groups, this study still provided evidence of the benefit of mixed noble metal coating in preventing VAP, by reducing its incidence by 5.1%, the number of antibiotic days

by 6.6% and tracheal pathogen colonization by 3.7% in the NMA-coated compared with non-coated subglottic suctioning ETTs in the ICU patients. Another subsequent study that involved a shorter number of ICU patients showed to reduce in the ventilation days from 5.03 ± 1.88 in the control group to 3.2 ± 0.78 in the intervention (NMA-coated) group, in addition to a decreased incidence of VAP and ICU stays for ventilated patients [130]. The BIP ETT is currently seeking FDA approval.

2.1.1.2 Zinc-based antimicrobial coatings

Zinc oxide (ZnO), a common antimicrobial metal agent applied in personal care products (e.g., sunscreen or anti-dandruff shampoo) has been widely included in the design of novel ETT coatings. NPs of zinc oxide (ZnO-NPs) have attracted interest specifically over the last decade, likely due to their appealing properties, including high surface-to-volume ratio, stability under diverse environmental conditions, and low costs associated with its production [131]. Even though the complex and fully understood exact mechanism of antimicrobial activity of ZnO-NPs, these nanostructures have proved enhanced broad-spectrum activity, mostly against Gram-positive (e.g., *Bacillus subtilis* and *S. aureus*), but also Gram-negative bacteria (e.g., *P. aeruginosa* and *E. coli*) [132,133], while non-toxic to human cells (Colon et al., 2006). Despite the many studies evaluating the potential of surfaces incorporating ZnO-NPs [134–136], only a few have examined its effect in particular for ETTs.

Films of PVC, in which ZnO-NPs with about 60 nm diameter were incorporated at increasing weight percentages (2%, 10%, 25%, and 50%), were further challenged with *S. aureus*. Results showed that the highest concentration of ZnO-NPs in the PVC composite surfaces led to 28% and 55% reductions in bacterial growth and biofilm formation after 24 h and 72 h, respectively [137]. In a similar study, the incorporation of ZnO-NPs on PVC taken from commercially available ETTs resulted in an 87% reduction in the biofilm formation of *S. aureus* within 24 h [138]. Besides the clinical application in reducing the bioburden on surfaces, the potential of ZnO-NPs has been also exploited for their antimicrobial properties against foodborne contamination and food packaging [139,140]. Despite their widespread use in a variety of settings, their adverse effects have been increasingly reported in both *in vitro* and *in vivo*, requiring caution in their use. For instance, it has been shown that long-term exposure of mice to a diet based on lower doses of ZnO-NPs caused minimal toxicological effects, while higher doses resulted in developmental toxicity and alteration in the zinc metabolism and biodistribution in these animals [141]. Also, ZnO-NPs may induce pulmonary inflammation in endotracheally exposed mice [142].

2.1.1.3 Selenium-based antimicrobial coatings

Selenium, a nutrient element playing crucial roles in biological systems, has also been pointed out for its antimicrobial properties. More specifically, selenium nanoparticles (SeNPs) have proved anticancer [143], antioxidant [144], antibacterial and anti-biofilm attributes [145,146], combined with low acute toxicity [146]. The potential of this strategy for ETTs was evidenced by Tran and Webster [147]. The authors showed that PVC medical grade coated with SeNPs resulted in a better reduction in *S. aureus* colonization as compared to a silver coating on PVC. It should be mentioned, however, that colonization was only investigated for a period of 8 h [147]. Further research is required, therefore, to conclude its application in the context of VAP.

2.1.1.4 Titanium-based antimicrobial coatings - Photodynamic therapy

Photo-based antimicrobial coatings have been applied in the design of novel ETT coatings. This kind of approach uses a photosensitizer that is activated by a specific wavelength of light to create an active component that will induce antimicrobial effects [148]. Titanium dioxide (TiO_2) is widely known for its photocatalytic properties, providing excellent electronic configuration, stability, chemical inertness, commercial availability, reduced cost, and biocompatibility [149]. Its use is based on its ability to cause oxidative stress through the generation of reactive oxygen species (ROS), after being exposed to light with wavelengths lower than 385 nm [150]. TiO_2 nanoparticles (TiO_2-NPs) have proved to be antimicrobial against both Gram-positive (e.g., *S. aureus* and *Listeria monocytogenes*) and Gram-negative bacteria (e.g., *P. aeruginosa, E. coli*, and *Pseudomonas fluorescens*) [151,152]. Recently, modified forms of TiO_2-NPs have been explored to enhance TiO_2 photocatalytic activity for antimicrobial applications under visible light [153]. Only a study could be found applied directly for ETTs, using two types of NPs, standard anatase commercially available TiO_2, and N-doped TiO_2, placed on the internal surface of segments from commercially available ETTs [154]. Authors challenged these two approaches for 24 h with *P. aeruginosa* and *S. aureus*. In the absence of light, no antimicrobial activity could be found for both species. Under fluorescent light irradiation, on the other hand, bacterial inactivation was observed. N-doped NPs were more effective against *S. aureus*, as compared to commercial NPs and no differences were found for the inactivation obtained against *P. aeruginosa*. Although TiO_2 exhibits photocatalytic antibacterial activity under ultraviolet (UV) and visible light, the use of potentially harmful UV light is not comprehensively recommendable in hospital environments. Recently, modified forms of TiO_2-NPs capable of showing photocatalytic antibacterial activity in the spectrum of visible light [155] are under investigation. Unfortunately, adverse pulmonary effects in animals caused by TiO_2 have been reported, which, along with allegations regarding its carcinogenic risk for humans, make conclusions unclear for its NPs [156].

2.1.2 Coatings based on the impregnation of biocides

One of the first reported antimicrobial coating approaches comprised the straightforward incorporation of biocidal compounds such as antibiotics or antiseptics into the bulk material of the device, before injection molding or extrusion [157]. Of these, antibiotic impregnation has been mostly applied in orthopedic practice, namely in antibiotic-loaded cement [158] and the development of central venous catheters [159]. Although these strategies had the advantage of using already approved compounds, which enhanced their commercialization for some applications, concerns regarding the development of antimicrobial resistance (AMR) resulted in the search for alternative compounds, such as antiseptics. Impregnation of antiseptics has been mostly applied to the development of central venous catheters, but there are also some *in vitro* studies on ETTs. Antiseptics used in the impregnation of ETTs include gendine, which is a combination of Gentian Violet with chlorhexidine, [160] alone or combined with gardine, this latter resulting from a combination of brilliant green (antiseptic dye) with chlorhexidine [127]; chlorhexidine alone [161]; and, hexetidine [162]. For instance, gendine- and gardine/gendine-coated ETTs proved to prevent adhesion of methicillin-resistant *Staphylococcus aureus* (MRSA), MDR Gram-negative bacteria and even fungal species such as *Candida albicans* or *Candida parapsilosis* [127,160]. Furthermore, they proved to be more efficient than the silver-coated ETTs, which were used for comparison purposes. Of these, only gendine was inspected for its biocompatibility, showing no toxicity against fibroblasts.

The design of antimicrobial materials based on soaking nature-based bactericidal substances produced by living organisms such as essential oils (e.g., eugenol) to repel

bacteria from medical device surfaces has also been investigated. Venkateswaran and others have produced and trapped poly(lauryl acrylate) nanocapsules containing clove oil or its major ingredient eugenol within 1 cm-pieces of a commercially available PVC-ETT, thus creating an interpenetrating polymer network, which resulted in the slow-release of eugenol driving to notable reductions in surface-bound *K. pneumoniae* and MRSA [163].

One suitable ETT coating approach results from mimicking human defense mechanisms. Homeyer and colleagues employed nitric oxide (NO) to develop a NO-releasing PVC coating (NORel-ETT) [164]. NO is an endogenous gas consistently released from the natural endothelium, with potent antimicrobial activity [165,166] due to its adverse reactions on microbial cell components. Incorporation of *S*-nitroso-*N*-acetylpenicillamine (SNAP), a synthetic NO donor with promising antimicrobial properties [167,168], into an ETT, resulted in a decreased build-up of the secretion on the ETT lumen and increased alveolar macrophage activity. Also, bacterial proliferation was inhibited and the risk of infection decreased. The impregnation of SNAP forms a hydrophobic polymer effectively releasing NO over 7 days while keeping natural mechanical ETT properties preserved. Besides, the NORel-ETT could significantly reduce *P. aeruginosa* infection over a 24 h period. Studies have shown that sustained NO-releasing materials can support both active and passive approaches, as they can be used combined with hydrophilic polymer topcoats, forming suitable and highly efficient antifouling and antibacterial polymers for biomedical applications [169].

2.1.3 Coatings based on bio-inspired antimicrobials

2.1.3.1 Antimicrobial peptides-based antimicrobial coatings

Antimicrobial peptides (AMPs) play a significant protective role in the innate immune system of most living organisms against invading pathogens [170]. As the first line of defense, AMPs display important features appealing for their use as antimicrobials alternative to antibiotics, including their immobilization on medical devices [171], cell selectivity (that is, discrimination between host and microbial cells), prompt action mechanisms; wide-spectrum antimicrobial activity, even against resistant and MDR strains, and low propensity for AMR development [172]. In the past few years, certain AMPs (asioglossin-III) have been applied in ETT coatings, with promise in preventing bacterial adhesion without *in vitro* cytotoxicity against mammalian cells [173].

To overcome some limitations associated with AMPs, including proteolytic degradation, concerns with hemolysis and cytotoxicity, *de novo* designed peptide sequences have been developed [174,175], among which ceragenins have aroused a growing interest in the last few years [176]. Ceragenins comprise a group of cholic acid derivatives with amine groups, chemically modified to mimic the amphiphilic properties of AMPs [177]. Unlike AMPs, ceragenins are not peptide-based, so insensitive to proteolytic activity and with ability to exhibit a longer half-life in the body. Other advantages include the fact that ceragenins can be readily synthesized on a large scale, making their preparation more cost-effective [178]. Of particular interest is their antimicrobial activity against a wide range of microorganisms, including MRSA [179], colistin-resistant *Klebsiella pneumoniae* [180], MDR *P. aeruginosa* [181] and fluconazole-resistant *C. albicans* [182]. The great potential of ceragenins has been recently explored for application in ETTs. The authors have proposed the incorporation of a lead ceragenin, CSA-131, into a polyurethane-based hydrogel that was then dip-coated onto a PVC-based ETT. The hydrogel provided a reservoir for the ceragenin and allowed its sustained release. The eluting ceragenin prevented ETT microbial colonization by *P. aeruginosa*, MRSA, *K. pneumoniae*, *C. albicans*, and *Candida auris*, and biofilm formation

for several days. The duration of its antimicrobial activity was species-dependent, ranging from 4 days for *P. aeruginosa* until a maximum of 16 days when challenged with *C. albicans*. The modified ETT was also challenged against mixed-species biofilms of *P. aeruginosa* with MRSA and with *C. auris*, being able to prevent their formation for up to 2 and 3 days, respectively. This study, also comprised a pre-clinical porcine model to investigate the safety of modified ETT under MV for 24 h. No abnormalities in the oropharyngeal area, trachea, or lungs were observed, as well as no inflammation was shown by histological examination, as compared to the unmodified ETT. The great potential of this study has led to seeking FDA approval.

2.1.3.2 Biosurfactants-based antimicrobial coatings

Other bio-inspired compounds investigated to prevent ETT microbial colonization have been the biosurfactants (e.g., cholesterol, lecithin, sphingosine), which are microbial compounds displaying pronounced surface and emulsifying activities [183]. Regarding their potential for ETT functionalization, coating of PVC-ETTs with solutions of surfactants containing different ratios of cholesterol and lecithin, resulted in more than 90% reduction of *S. aureus* and *P. aeruginosa* adhesion, up to 8 h [184]. More recently, sphingosine coatings of ETTs were reported to prevent the adhesion and biofilm formation by *P. aeruginosa*, *A. baumannii*, and *S. aureus* up to 24 h [185]. This antimicrobial activity was similarly exhibited in an *in vivo* model while no side effects on tracheal epithelial cells or inflammation could be observed.

2.1.3.3 Bacteriophages-based antimicrobial coatings

Although still in its infancy, bacteriophages represent a novel, promising, and challenging alternative to deal with the microbial invasion of device surfaces, namely on ETTs. Among the main advantages of phage therapy, its low risk for host-microbiota injury, its self-replication inside host cells, specificity for the host, and low expenditure [186] are highlighted. A recent study reported a cocktail of two phages previously selected by anti-biofilm screen testing, able to prevent *P. aeruginosa* settlement of the surface of ETTs using a dynamic biofilm model [187]. Being challenged with different *P. aeruginosa* strains, the phage cocktail-coated tubes promoted strain-dependent differences in bacterial colonization. Scanning electron microscopy revealed alterations in biofilm structure, with consortia forming tower-like structures, in addition to a reduction in biofilm cells (phage-coated vs. non-coated tubes). A newer report showed considerable prevention (up to 3.2 log inhibition) and even significant removal of biofilm to a maximum of 2.4 log by MDR *P. aeruginosa* strains in 12 mm-long ETT segments exposed for pre- and post-treatments, respectively, with lysates of two *P. aeruginosa*-specific designated ΦJHS-PA1139 and ΦSMK-PA1139 [188].

2.2 Passive Materials

Microbial adhesion to a surface is strongly dependent on its physicochemical properties, including surface energy, wettability, charge, chemistry, roughness, and topography [189]. Alteration of any of these factors may stimulate or repress microbial adhesion, biofilm formation, or biofouling. For instance, surfaces with mild wettability are more prone to cell adhesion, as compared to extremely hydrophobic or hydrophilic surfaces [190]. The surface free energy of the material plays a role in the reversibility of adhesion. When this parameter is positive, unfavorable adhesion occurs according to the thermodynamic principle [191]. This notion has steered researchers to engineer anti-biofouling materials for different applications, encompassing medical devices, the food industry, or marine transportation [119,192–197]. A few passive approaches proposing changes on the surface composition and

pattern of ETT surfaces to prevent microbial establishment or absorption to ETT material surfaces have included designing hydrophobic/hydrophilic, nanomodified, and micropatterned surfaces. Some examples are described next.

2.2.1 Hydrophobic/hydrophilic surfaces

Understanding the relationship between the surface charge/hydrophobic attributes for both microorganisms and materials is critical to recognize the potential for developing biofouling on a material surface. The adhesion of bacteria to inert materials varies widely owing to several physicochemical features that are known to influence cell attachment [198]. For instance, two studies relied on treating chemically PVC with oxygen plasma, yielding hydrophilic surfaces that reduced *P. aeruginosa* adhesion by 70%, compared with the non-treated control [195]. Also, a combination of solvent and non-solvent approach was used to impart PVC surfaces with varied hydrophobicity, with water contact angles ranging from 80° to 150° [199]. Surfaces with higher hydrophobicity, challenged with *P. aeruginosa*, prevented its adhesion for 6 h, which resulted in a delayed biofilm formation, as compared to unmodified PVC.

2.2.2 Nanomodified surfaces

The influence of surface topography on microbial adhesion and biofilm development has been extensively investigated by engineering surfaces with geometries of ordered features, and designed with unique roughness. Initial approaches reported were carried out by mechanical roughness and polishing techniques, generating random texturized roughness surfaces. Surface topography manipulation around nano-scale generates surfaces with features <100 nm in one direction (referred to as nanomodified surfaces) [200] with the potential to control bioburden on abiotic surfaces. Nanomaterials offer ideal surface energetics owing to their considerably larger surface area when compared with conventional nano-smooth surfaces, thereby promoting initial protein binding, crucial for mediating bacterial primary attachment [201]. Therefore, these nanomodified surfaces´ unique properties still provide a solution to the persistent problems of VAP.

Nanoscale features have been created on PVC-based ETTs, through enzymatic degradation by a lipase from the fungus *Rhizopus arrhizus*. Such modifications proved to reduce the adhesion and biofilm formation by *S. aureus* [202,203] and *P. aeruginosa* [199,204,205], but concerns over AMR, coating stability, and biocompatibility, have limited the widespread use of these nanorough ETTs.

Nano-rough surface topographies have also been used to create surfaces with enhanced hydrophobicity - superhydrophobic surfaces -, thereby providing a unique water-repellent and antifouling resistance attribute [2]. This kind of surface can be achieved by altering the surface chemistry of the polymer by adding functional groups with low energy through specific techniques [206–208]. Regarding an example referred to in section 2.2.1, Loo et al. developed a combination of solvent (ethanol/methanol) and non-solvent approaches to impart PVC surface with altered hydrophobicity, and improve the surface roughness and porous network [199,209]. Surfaces with higher hydrophobicity (water contact angles varying from 80° to 150°) could prevent *P. aeruginosa* adhesion for 6 h, resulting in a delayed biofilm formation (compared to unmodified PVC), indicating the suitability of this strategy to delay the onset of VAP when applied to short-term ventilated patients.

2.2.3 Micropatterned surfaces

Recently, micropatterning has been used to fabricate well-defined and reproducible dimensioned and shaped microstructures [209]. Concerning alterations in the surface patterning of ETTs, only two studies have been reported. Inspired by the topography of shark skin, the Sharklet™ patterning creates a micropatterned surface mimicking the topography of shark placoid scales to prevent microbial adhesion, with its potential being investigated for several applications [210,211], including the modification of ETTs. As reported, a modified ETT with this technology was challenged by members of the ESKAPE bacterial group, including the top-five pathogens commonly associated with VAP: MRSA, *P. aeruginosa*, *K. pneumoniae*, *A. baumannii*, and *E. coli*. Results showed that adhesion was inhibited for all bacteria and that biofilm formation was impaired for MRSA and *P. aeruginosa* [212]. In another study, it was demonstrated the ability of the Sharklet™ textured surface to reduce the mucus occlusion of a PVC-ETT, when using a preclinical airway patency sheep model [213]. This technology is currently seeking FDA approval.

2.3 Combinatorial Active/Antibacterial and Passive/Anti-biofouling Materials

In clinical practice, a key weapon to cope with AMR has been antimicrobial combination therapy. Combinatorial strategies applied in the design of novel ETT materials have been advantageous to produce collective multifaceted attributes, including lowering antimicrobial doses, preventing the emergence of resistance and antibacterial attachment, and achieving biocompatibility [2,214]. Active and passive combinatorial strategies have been successfully introduced in the design of ETT surfaces, endowing them with both antibacterial and anti-biofouling properties and acting together to fight ETT bioburden and reduce the risk of VAP.

Inspired by the evidence that certain metabolites, such as fructose, may increase the efficacy of antibiotics [215], Durmus et al. combined the effect of nanoscale surface features created by a fungal lipase with sugar metabolites to prevent biofilm formation on ETTs [202]. When surfaces with only nanoscale features were challenged for 24 h with *S. aureus*, a 45% decrease in staphylococcal attachment was observed, while PVC soaked with a solution of fructose caused a 38% reduction. The combination of both strategies yielded a decrease of 60%, highlighting a synergistic effect of both.

Zeolites exhibiting well-defined channels and cavities able to host metal ions were also applied and combined with different materials such as copper [216] or silver [217]. In the latter example, composites incorporating silver, zeolites, and tyrosine coatings on ETTs were tested against MDR *A. baumannii* for 24 h and showed that silver zeolite coating led to a significant reduction of planktonic cells (74%) and also of immobilized cells (70%). Further combination with tyrosine yielded similar results against planktonic cells but caused a 100% reduction of immobilized cells [217].

As a bioactive polymer, chitosan (CS) possesses many active sites for complexation with metal ions to be applied for certain antibacterial applications (e.g., wound dressing) [218–220]. Likewise, CS-AgNPs have been exploited as promising nano-formulations for ETT surfaces. A recent study showed a complex CS-AgNPs@PAAm-Gelatin (PAAm = polyacrylamide) nanocomposite coating exhibiting excellent antibacterial and antifouling activities while achieving good biocompatibility. Using a porcine mechanical ventilation model, the strategy also allowed the prevention of occlusion and biofilm-related infection of conventional PVC-ETTs, holding great promise in the clinic.

Another combinatorial strategy consists of using a hydrogel entrapped with nebulized antimicrobial solutions to coat ETTs. Jones and co-workers reported copolymers of

hydroxyethyl methacrylate (HEMA): methacrylic acid (MAA) at varied ratios (100:0 to 70:30) and challenged with *S. aureu*s and *P. aeruginosa*. Findings showed reliance of antimicrobial persistence on the hydrogel composition, with the 70:30 HEMA: MAA copolymer displaying >20 successive days of persistence against both bacteria. Unlike gentamicin-treated HEMA PVC tubes, HEMA: MAA hydrogels-coated ETTs exposed for 20 min to a nebulized solution of gentamicin could prevent bacterial proliferation, therefore making HEMA: MAA copolymers potentially useful ETT coatings for use in combination with nebulized antibiotics and, hence, an auspicious strategy for VAP prevention [221].

Curcumin-functionalized ETTs and photodynamic action have been also used combined and further applied in ETTs. In a recent study, Zangirolami et al. reported *in vitro* ETT's functionalization with curcumin photosensitizer to avoid bacterial biofilm formation, resulting in substantial photoinactivation (up to 95%) against Gram-negative *(P. aeruginosa* and *E. coli*) and Gram-positive (*S. aureus*) bacteria when curcumin-functionalized ETTs were used. Curcumin-ETT remains active after six photodynamic sessions every 24 h up to 6 days with 23.76% of microbial reduction [222].

Other examples of reported combinatorial active and passive approaches are summarized in Table 2.

3. A critical appraisal of the technological progress on antimicrobial materials for ETTs

The overall frequencies of deadly biomaterial-associated HAIs, of which VAP is part, aggravated by the emergence and spread of microbial species no longer responding to common antimicrobial medicines, leading to AMR, has led researchers to move efforts toward alternative strategies to deal with the microbial contamination of indwelling medical devices. Pertinent antimicrobial materials have been developed to render the surfaces of such instruments with antimicrobial and antibiofilm activities, thereby aiming to reduce the risk of developing persistent and serious infections. Taking advantage of the technological progress over years and years of research, and having in mind the key role of ETT microbial colonization on VAP pathogenesis [53], the development of innovative and robust antimicrobial and/or anti-biofouling materials to improve ETT design is a promising way to combat this matter.

This review compiles the most recent developments in antimicrobial materials for ETTs (Table 2) (at the end of this document). A comprehensive picture of the findings can be found in Fig. 1, allowing for a better understanding of the overall technological progress in the field. A search on Pubmed allowed identifying 47 reports on materials for ETTs over the last twenty years (2002-2022). Intriguingly, about 70% (33 reports) of all developments have been published during the past decade (2012-). This eventually suggests that over the next years/decade, it is more likely to expect rapid and meaningful advancements to occur in the field. A general overview of Fig. 1A allows one to discern a consistent increase in the number of published studies on the subject that ranged from 0 (in 2009) and 5 (in 2020 and 2022) reports per year. This demonstrates that, even with significant technological change, the difficulty in overcoming the hurdles associated with VAP (e.g., persistent colonization and biofilm formation/MV duration/ICU length of stay/VAP occurrence) makes this an evolving, complex, and challenging matter. Active approaches, including materials exhibiting bactericidal nature, are by far the most reported ones, representing 31 (66%) of all annotated reports, followed by combinatorial active/passive (9/47, corresponding to 19.1%) and, lastly, passive approaches (7/47, corresponding to 14.9%) (Fig. 1B).

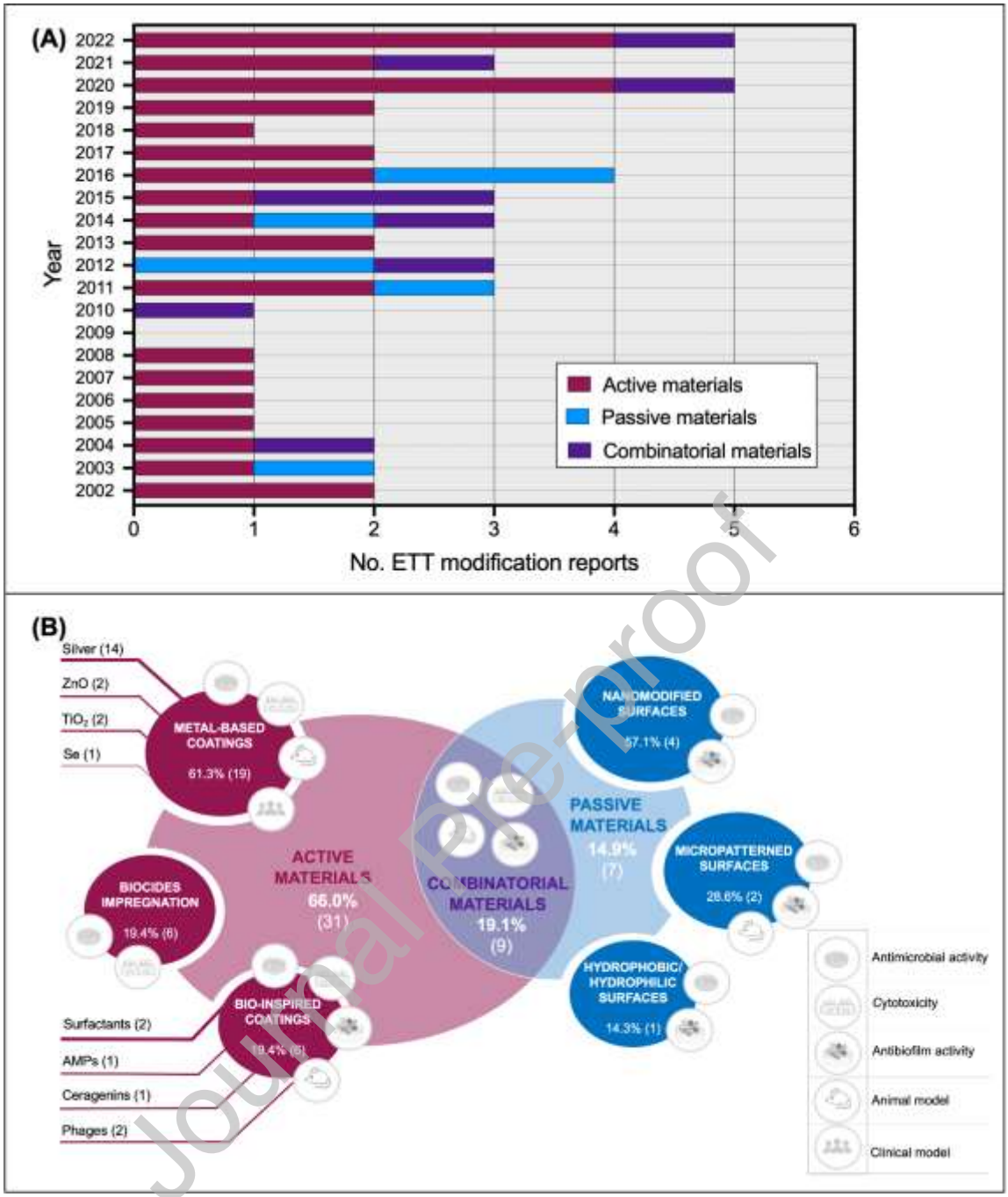


Fig.1. Overall progress on antimicrobial materials for ETTs over the last two decades (2002-2022). (A) A number of reports on active, passive, and combinatorial (active/antimicrobial plus passive/anti-biofouling) materials for ETTs annotated each year. **(B)** General overview on the type of reported material applied to ETTs, on the coating/modification approach, on the used testing, and the percentage allocated for each. Numbers in brackets refer to the no. of reports identified for each strategy.

Active strategies were ranked by metal-based ETT coatings (19 reports; 61.3%), where silver endured as the most well-documented metal, counting 14 reports. ETTs impregnated with biocidal agents and bio-inspired antimicrobials were reported to a lesser extent, both embodying 6 (19.4%) published works, respectively. Although less representative than active strategies, passive approaches encompassed nanomodified surfaces as the most reported ones (4 reports), followed by the micropatterned (2 reports) and hydrophobic/hydrophilic surfaces

(1 report), comparable to 57.1%, 28.6%, and 14.3%, respectively. Irrespective of combinatorial active/passive approaches, the number of published studies (9; 19.1%) particularly observed over the past few years highlights a notable growing interest by researchers in merging active antimicrobial and passive anti-biofouling strategies for biomaterial applications, namely for ETT modification surfaces. An overlook of these metrics can be discerned in Fig. 1B.

Designing and implementing antimicrobial materials for improving medical device surfaces [223,224] requires following safe-by-design criteria, including (but not limited to) antimicrobial performance, biocompatibility evaluation, potential to induce AMR, and long-term stability. The most likely strategy to attain these outcomes is by integrating multidisciplinary expertise into the full developmental processes, thus ensuring that reliable and robust testing or practice is efficiently employed [225]. A comprehensive analysis allowed us to discern many gaps/challenges in the studies found and annotated in this review.

Of all tested approaches, silver antibacterial materials for ETTs have received greater attention in the last decades, with the progress in their research reaching the clinical market in the US (BIP ETT). Its widespread use, however, has been hindered by the relatively high cost [226], in addition to the lack of a consensus about its safety, antimicrobial effectiveness, and long-term stability. Environmental and health concerns have been raised regarding the extensive application of silver [227], an important challenge that should be taken into consideration. For instance, bacterial clinical isolates resistant to silver have been found in sewage systems from healthcare facilities [228,229]. Furthermore, abundant leaching of silver can give rise to systemic side effects [2]. The limited studies developed *in vivo* have shown that toxicological issues found in silver-based products are extended to other metals (e.g., zinc; titanium) prepared into NPs, highlighting the need for monitoring selection and spread of metal-based resistant strains and more data to fully elucidate their resistance mechanisms and conclude about their safety and clinical usefulness.

Worthy of note, most of the reported approaches have to be determined about cytotoxicity. Only a few studies have evaluated *in vitro* biocompatibility of their ETT materials, mostly against human lung/tracheal epithelial cells [122,123,160,173,230] but also against mouse fibroblasts [160,230]. Toxicity remains an important factor when evaluating any antimicrobial coating strategy. Its assessment against relevant human cells should be part of any *in vitro* model to effectively predict the clinical outcome of these antimicrobial strategies. It should be the first step, before going further to *in vivo* assays. The limited studies on biocompatibility found suggest that the time and cost associated with such assays represent another challenge that may be likely addressed with standardized cytotoxic evaluation methods and conditions for the new materials, thus making comparisons possible and helping ensure the best safe approach [2].

In addition to silver, the antimicrobial properties of other noble metals such as copper, gold, titanium or zinc have long been recognized and applied [231]. With the recent research advances in nanotechnology, it was possible to address some limitations associated with bulky metals, namely their large size and the required high doses [232] by modifying them into NPs exhibiting a high ratio of surface area to mass, high reactivity and sizes in the nanometer range (1 to 100 nm), making them with unique physicochemical traits [233]. Metallic NPs have been the focus of interest for medical applications since they have been identified as promising alternatives to antibiotics in the fight against AMR [234]. Although the exact primary mechanisms that lead to the antimicrobial effects of metallic NPs are not yet fully elucidated, three major pathways are described: cell wall and membrane damage,

intracellular penetration, and oxidative stress [235]. Once inside the cell, metallic ions can act as a catalytic cofactor on a wide range of cell enzymes, either generating or catalyzing the production of ROS. If its production exceeds cell antioxidant capacity, oxidative stress will be harmful, causing damage to proteins, lipids, and DNA [236]. It has been proposed that these nonspecific mechanisms of antimicrobial activity hinder the development of resistance by microorganisms [237]. However, despite the promising antimicrobial performance demonstrated, the efficacy of nano-metal-based materials comes warranted with a varied number of challenges: 1) shortage of detailed and precise toxicity information to be further used in human treatment, therefore jeopardizing the rapid translation of the technology for the clinic; 2) risk of metal accumulation in the body leading to heavy metal toxicity; 3) propensity for inducing bacterial resistance 4) lack of antibiofilm testing or effectiveness in reducing biofilm formation; 5) lack of evidence on decreasing MV duration, ICU length of stay, thereby compromising its effectiveness in avoiding VAP occurrence.

An attractive and straightforward strategy to reduce the risk of VAP is impregnating ETTs with biocides, a strategy that has shown satisfactory results in inhibiting the adhesion of important VAP-associated pathogens while decreasing the risk of bacterial resistance by the extensive use of existing antibiotics. Some studies have reported ETTs anchoring varied antiseptics (e.g., chlorhexidine; gardine and gendine; hexetidine); however, the main challenges are related to controlled release kinetics and the ever-rising concerns about the development of AMR, which has led to the search for other antibiotic alternative compounds with less propensity to induce drug-resistant strains. Furthermore, the environmental and toxicity issues related to biocides, often in a dose-dependent manner, lead one to balance between their antimicrobial efficacy and impact on effectively reducing the spread of AMR among VAP pathogens and their related negative concerns [237].

The design of antimicrobial coatings based on natural compounds produced by living organisms such as essential oils (e.g., eugenol), surfactants, AMPs, and bacteriophages has developed effective strategies to prevent the colonization of their surfaces by pathogens [238]. Regarding surfactants, most of their applications have been essentially focused on their environmental applications, however, a few agents such as cholesterol, lecithin, or sphingosine gather some properties appealing for applications in the medical field, including lower toxicity, higher biodegradability, and efficacy at extreme temperatures and pH, in addition to their antibacterial, antifungal and antiviral activities [239]. To overcome the common contests associated with AMPs, regarding their expense and easy degradation by proteases [240], a novel class of small molecules mimicking the properties of AMPs, has been successfully proposed as a cost-effective solution for ETTs. Ceragenins have exhibited promising broad-spectrum antimicrobial (including bacterial and fungal species), antibiofilm activity, and low toxicological effect *in vivo* (pre-clinical porcine models) [241]. Also, an efficient and relatively cost-effective strategy recently reported is the immobilization of bacteriophages on surfaces [242–245], which has proved great potential for future avenues in the fight against BAIs. The use of phages, however, carries particular limitations, specifically its sensitivity to moisture, deactivation under certain conditions [246], or reliance on the application area [247]. Further investigations into ceragenins and bacteriophages would likely provide the necessary assets to prevent VAP.

Optimizing surface properties to reduce the attractive forces between the microorganisms and the surface material remains an alternative approach to the killing effect of the antimicrobials, by promoting an anti-biofouling surface while avoiding microbial adhesion and multiplication during the initial stage of contamination. This review showed that passive

approaches have been the least reported, which can be partly explained by the fact that manipulating surface chemistry is not as straightforward as thought, requiring specific technological methodologies and more complex protocols. Initially, approaches relied on applying mechanical roughness and polishing techniques to generate random texturized roughness surfaces. More recently, photolithographic etching of the Sharklet™ micropattern onto a silicone-made ETT resulted in anti-adhesive and antibiofilm properties against a variety of VAP-associated pathogens (e.g., *S. aureus, P. aeruginosa, K. pneumoniae, A. baumannii* and *E. coli*) [212], even decreasing the buildup of mucus inside the ETT, both *in vitro* and *in vivo* [213]. A few studies reporting nanomodified surfaces have displayed significant reductions in microbial growth [203–205] or even in biofilm development [199]. Despite the major developments in this field, the introduction of passive approaches in the market is still below expectations, with only Sharklet™ technology seeking FDA approval. Their widespread use has been hindered by concerns over structure stability and durability, biocompatibility, AMR, or even relatively high-cost issues, as well as health and environmental concerns due to the use of some chemicals such as fluorine [248].

A major cavity found in annotated ETT surface coating/modification approaches was related to the implementation of *in vivo* (animal) testing. ETT coating approaches implicating biocides impregnation, nanomodified, and hydrophobic/hydrophilic surfaces have not evolved for animal models, as discerned by Fig. 1B. An important aspect when designing antimicrobial materials is that the bridge from *in vitro* and *in vivo* (animal) testing to full-scale clinical trials may be as straightforward as possible. For better understanding, efforts should be undertaken to define, just in an early design stage, appropriate in *vivo-like* conditions (e.g., pathogens; environment) as well as the pertinent and representative testing models, so that any potential antimicrobial, health, and safety risks associated with the material may be eliminated when moving from *in vitro* to clinical testing. Otherwise, developed materials will debut or maybe never leave the workbench. Increased associated costs and complex constraints are challenging to models *in vivo*. Besides, there are specific difficulties associated with ETT placement and respective surrounding environments (enlarged surface area; constantly challenging environment; physiological altered conditions) that the novel materials were not designed to deal with. All these factors contribute to facilitating the clinical translation of most ETT materials.

Even though all approaches were anticipated to control the ETT microbial adhesion, an often-neglected point in most studies reporting ETT antimicrobial coatings is the VAP polymicrobial etiology, despite it having been increasingly recognized. The most frequently tested microorganism was *P. aeruginosa* (29 in 47 studies; 61.7%), followed by *S. aureus* (17 studies; 36.2%), MRSA and *A. baumannii* (8 studies for each; 17%), *K. pneumoniae* (5 studies; 10.6%), *C. albicans* (4 studies; 8.5%) and others with lesser frequencies. The first reported strategies, regardless of the type of approach used, only tested one microorganism, and the choice fell mainly between *P. aeruginosa* and *S. aureus*. More recently, proposed strategies have increased the number of organisms tested, including more bacterial species and even fungal species [64]. However, most of these strategies test these organisms individually, not truly reflecting the polymicrobial nature of VAP. Even having the awareness that VAP is often mediated by biofilms, only a very small number of studies addressing the effectiveness of ETT coatings towards biofilms (15 in 47 studies; around 32%) and in particular polymicrobial biofilms was uncovered. A unique study attending this latter matter was found in 2018, evaluating the performance of an immobilized ceragenin in a polyurethane-based hydrogel [241] against polymicrobial, including inter-kingdom (bacterial-fungal) biofilms. Though the antimicrobial efficacy of the coated tubes was reduced in

preventing mixed-species consortia for multiple days compared to their single-species biofilms, ceragenin films remain an attractive approach for the prevention of microbial colonization and subsequent biofilm formation on ETT surfaces, attaining significant reductions (to up 7 log CFU/mL). Future research should, therefore, venture into improving their ETT materials by providing a more holistic approach to the matter, taking into account a collective representation of VAP pathogens, thus reducing the number of barriers, shortening the path to proceed further to *in vivo* testing and ensuring success in patient care.

From the analysis of the main outcomes annotated in Table 2, it was also possible to discern that most of the strategies reported a delay in microbial colonization and/or biofilm formation, but they were not able to completely prevent these events. It is crucial, therefore, to determine if these remaining bacteria can grow into a mature biofilm, eventually reaching the lungs and thus leading to the establishment of VAP. It has been demonstrated that even a low number of bacteria (10^2 CFU/mL) can trigger an infection [249,250]. A promising solution to cope with this kind of result may contemplate the combination of such strategies with other approaches. For instance, the combination of a silver-coated ETT with periodic cleaning of mucus from the ETT´s internal surface in a sheep mechanically ventilated for 72 h, proved to reduce the accumulation of mucus and bacterial growth within the ETT [251]. However, when more recently, Pirrone et al. investigated a similar approach in a clinical trial, and results showed that the periodic cleaning procedure was not so efficient in avoiding bacterial colonization and lowering respiratory tract colonization, as compared to the standard suctioning [252]. Authors suggested that other pathways may have contributed to pneumonia establishment in addition to the inner surfaces of the ETT. Further research on this type of approach is needed to better understand their benefits in effectively preventing VAP.

4. Concluding Remarks and Future Perspectives

There is notable progress, yet in steady expansion, in the development of antimicrobial materials able to prevent microbial colonization on ETT surfaces, likely one of the most knowledgeable and reliable approaches in the prevention of VAP. In the last decades, a few passive approaches (surface composition and patterning alteration), but mostly active (antiseptic release, metal coatings, ceragenin, surfactants, photo-based therapy, and bacteriophages) and combinatorial approaches have been employed in the design of novel materials for ETTs. Despite the research progress in this field, VAP remains a frequent and deadly infection in patients admitted to ICU. Most of the reported studies present limitations, making challenging the interpretation of results reported, thus requiring additional rigorous randomized trials with larger population sizes to confirm those findings. Up until now, only silver-coated ETTs have reached the market and are subjected to multiple clinical trials, but concerns are raised by their cytotoxicity and stability. Most reported ETT antimicrobial strategies remain in the preclinical stage, failing to proceed into the clinic (lately, prospective trials have been the closest approach to testing the clinical application of ETT coatings). The absence of standards for preclinical research and/or the high cost of moving from in vitro/animal studies to clinical trials may impair achieving the leap from laboratory to clinical practice. Also challenging is the shortage of *in vitro* models that can effectively predict long-term *in vivo* antibacterial and antibiofilm performance. Suitable *in vitro* models are worth further investigation, now tackling VAP as a polymicrobial biofilm-associated infection, enlarging the studied microbial populations, however without dismissing the mostly representative VAP pathogens, as well as their intricate interactions and associated elements driving AMR in consortia. Taking the premise that biofilms are currently an emerging battleground in the fight against VAP, it is believed that shifting the focus of researchers to

this direction will assuredly help in the development and optimization of standard assessment methods and will broaden market perspective with newly effective strategies reducing VAP incidence and associated outcomes.

Still not dismissing the first aim of this review, the limitations of VAP diagnostic tools and criteria may also lead to the report of current misleading outcomes in VAP rates. Until the development of powerful tools to better diagnose VAP, more objective outcomes should be considered when evaluating the potential of proposed approaches, such as duration of MV, ICU length of stay, VAEs, antibiotic use, and mortality. For instance, although SSD has been associated with lower VAP rates, it does not appear to reduce the time to remove the ETT, ICU length of stay, prevent VAEs, or lower mortality rates.

Acknowledgments

This research was supported by the Portuguese Foundation for Science and Technology (FCT) under the scope of the strategic funding of UID/BIO/04469/2020 unit and BioTecNorte operation (NORTE-01-0145-FEDER-000004) funded by the European Regional Development Fund under the scope of Norte2020–Programa Operacional Regional do Norte. The authors also acknowledge the support, through the Programa Operacional Competitividade e Internacionalização (COMPETE2020) and by national funds, through FCT for the POLY-PrevEnTT project (PTDC/BTMSAL/29841/2017- POCI-01-0145-FEDER-029841) and the Ph.D. Grant of Tânia Grainha (SFRH/BD/136544/2018).

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] M.A. Biel, C. Sievert, M. Usacheva, M. Teichert, E. Wedell, N. Loebel, A. Rose, R. Zimmermann, Reduction of endotracheal tube biofilms using antimicrobial photodynamic therapy, Lasers Surg. Med. 43 (2011) 586–590.

[2] M. Barnes, C. Feit, T.A. Grant, E.J. Brisbois, Antimicrobial polymer modifications to reduce microbial bioburden on endotracheal tubes and ventilator-associated pneumonia, Acta Biomater. 91 (2019) 220–234.

[3] R.D. Scott, The Direct Medical costs of healthcare-associated infections in U.S. hospitals and the benefits of prevention, Division of Healthcare Quality Promotion National Center for Preparedness, Detection, and Control of Infectious Diseases Coordinating Center for Infectious Diseases Centers for Disease Control and Prevention, Atlanta 2009. https://stacks.cdc.gov/view/cdc/11550.

[4] S. Chen, M. O'Malley, V. Chopra, How common are indwelling devices in hospitalized adults? A contemporary point prevalence study in a tertiary care hospital, Am. J. Infect. Control. 49 (2021) 194–197.

[5] A.C. Kalil, M.L. Metersky, M. Klompas, J. Muscedere, D.A. Sweeney, L.B. Palmer, L.M. Napolitano, N.P. O'Grady, J.G. Bartlett, J. Carratalà, A.A. el Solh, S. Ewig, P.D. Fey, T.M. File, M.I. Restrepo, J.A. Roberts, G.W. Waterer, P. Cruse, S.L. Knight, J.L. Brozek, Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society, Clin. Infect. Dis. 63 (2016) e61–e111.

[6] J. Chastre, J.Y. Fagon, Ventilator-associated pneumonia, Am. J. Respir. Crit. Care Med. 165 (2002) 867–903.

[7] American Thoracic, Society, Infectious Diseases Society of Aerica, Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia, Am. J. Respir. Crit. Care Med. 171 (2005) 388–416.

[8] D.E. Craven, J. Hudcova, Y. Lei, Diagnosis of ventilator-associated respiratory infections (VARI): microbiologic clues for tracheobronchitis (VAT) and pneumonia (VAP), Clin. Chest. Med. 32 (2011) 547–557.
[9] C.P. Andrews, J.J. Coalson, J.D. Smith, W.G. Johanson, Diagnosis of nosocomial bacterial pneumonia in acute, diffuse lung injury, Chest. 80 (1981) 254–258.
[10] M.I. Restrepo, J. Peterson, J.F. Fernandez, Z. Qin, A.C. Fisher, S.C. Nicholson, Comparison of the bacterial etiology of early-onset and late-onset ventilator-associated pneumonia in subjects enrolled in 2 large clinical studies, Respir. Care. 58 (2013) 1220–1225.
[11] R. Jakribettu, R. Boloor, S. Suresh, Comparison of microbiological profile of pathogens isolated from early-onset and late-onset ventilator-associated pneumonia in a tertiary care center, Trop. J. Med. Res. 19 (2016) 14–14.
[12] P. Gastmeier, D. Sohr, C. Geffers, H. Rüden, R.P. Vonberg, T. Welte, Early- and Late-Onset Pneumonia: Is This Still a Useful Classification?, Antimicrob. Agents Chemother. 53 (2009) 2714.
[13] A. Torres, M.S. Niederman, J. Chastre, S. Ewig, P. Fernandez-Vandellos, H. Hanberger, M. Kollef, G.L. Bassi, C.M. Luna, I. Martin-Loeches, J.A. Paiva, R.C. Read, D. Rigau, J.F. Timsit, T. Welte, R. Wunderink, International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia, Eur. Respir. J. 50 (2017) 1700582.
[14] A. Torres, M.S. Niederman, J. Chastre, S. Ewig, P. Fernandez-Vandellos, H. Hanberger, M. Kollef, G.L. Bassi, C.M. Luna, I. Martin-Loeches, J.A. Paiva, R.C. Read, D. Rigau, J.F. Timsit, T. Welte, R. Wunderink, Summary of the international clinical guidelines for the management of hospital-acquired and ventilator-acquired pneumonia, ERJ Open Res. 4 (2018).
[15] P. Arayasukawat, A. So-ngern, W. Reechaipichitkul, W. Chumpangern, I. Arunsurat, P. Ratanawatkul, W. Chuennok, Microorganisms and clinical outcomes of early- and late-onset ventilator-associated pneumonia at Srinagarind Hospital, a tertiary center in Northeastern Thailand, BMC Pulm. Med. 21 (2021) 1–8.
[16] M. Dias, P. Marçal, P. Amaro, Ventilator-associated pneumonia (VAP) - Early and late-onset differences, Eur. Respir. J. 42 (2013).
[17] T.L. Hedrick, R.L. Smith, S.T. McElearney, H.L. Evans, P.W. Smith, T.L. Pruett, J.S. Young, R.G. Sawyer, Differences in early- and late-onset ventilator-associated pneumonia between surgical and trauma patients in a combined surgical or trauma intensive care unit, J. Trauma. 64 (2008) 714–720.
[18] R. Khan, H.M. Al-Dorzi, H.M. Tamim, A.H. Rishu, H. Balkhy, A. El-Saed, Y.M. Arabi, The impact of onset time on the isolated pathogens and outcomes in ventilator-associated pneumonia, J. Infect. Public Health. 9 (2016) 161–171.
[19] T. Zakharkina, I. Martin-Loeches, S. Matamoros, P. Povoa, A. Torres, J.B. Kastelijn, J.J. Hofstra, B. de Wever, M. de Jong, M.J. Schultz, P.J. Sterk, A. Artigas, L.D. Bos, The dynamics of the pulmonary microbiome during mechanical ventilation in the intensive care unit and the association with the occurrence of pneumonia, Thorax. (2017).
[20] S.S. Magill, M. Klompas, R. Balk, S.M. Burns, C.S. Deutschman, D. Diekema, S. Fridkin, L. Greene, A. Guh, D. Gutterman, B. Hammer, D. Henderson, D.R. Hess, N.S. Hill, T. Horan, M. Kollef, M. Levy, E. Septimus, C. VanAntwerpen, D. Wright, P. Lipsett, Developing a New, National Approach to Surveillance for Ventilator-Associated Events, Am. J. Crit. Care. 22 (2013) 469–473.
[21] T.C. Horan, M. Andrus, M.A. Dudeck, CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting, Am. J. Infect. Control. 36 (2008) 309–332.
[22] M. Klompas M. Ventilator-Associated Events: What They Are and What They Are Not Respir. Care. 64(2019) 953-961.
[23] Q. He, W. Wang, S. Zhu, M. Wang, Y. Kang, R. Zhang, K. Zou, Z. Zong, X. Sun, The epidemiology and clinical outcomes of ventilator-associated events among 20,769 mechanically ventilated patients at intensive care units: an observational study, Crit. Care. 25 (2021) 1–11.
[24] A. Ego, J.-C. Preiser, J.-L. Vincent, Impact of Diagnostic Criteria on the Incidence of Ventilator-Associated Pneumonia, Chest J. 47 (2015) 347-355.
[25] H.S. Ali, F.Y. Khan, S. George, N. Shaikh, J. Al-Ajmi, Epidemiology and outcome of ventilator-associated pneumonia in a heterogeneous ICU population in Qatar, Biomed. Res. Int. 2016 (2016). Article ID 8231787.
[26] V.D. Rosenthal, D.G. Maki, S. Jamulitrat, E.A. Medeiros, S.K. Todi, D.Y. Gomez, H. Leblebicioglu, I. Abu Khader, M.G. Miranda Novales, R. Berba, F.M. Ramírez Wong, A. Barkat, O.R. Pino, L. Dueñas, Z. Mitrev, H. Bijie, V. Gurskis, S.S. Kanj, T. Mapp, R.F. Hidalgo, N. ben Jaballah, L. Raka, A. Gikas, A. Ahmed, L.T.A. Thu, M.E. Guzmán Siritt, International Nosocomial Infection Control Consortium (INICC) report, data summary for 2003-2008, issued June 2009, Am. J. Infect. Control. 38 (2010) 95-104.

[27] M.A. Dudeck, T.C. Horan, K.D. Peterson, K. Allen-Bridson, G. Morrell, A. Anttila, D.A. Pollock, J.R. Edwards, National Healthcare Safety Network report, data summary for 2011, device-associated module, Am. J. Infect. Control. 41 (2013) 286–300.
[28] D. Koulenti, E. Tsigou, J. Rello, Nosocomial pneumonia in 27 ICUs in Europe: perspectives from the EU-VAP/CAP study, European Journal of Clinical Microbiology and Infectious Diseases. 36 (2017) 1999–2006.
[29] European Centre for Disease Prevention and Control, Annual epidemiological report 2011, Reporting on 2009 surveillance data and 2010 epidemic intelligence data. Stockholm: ECDC 2011. https://www.ecdc.europa.eu/en/publications-data/annual-epidemiological-report-2011-2009-data (accessed October 16, 2022).
[30] V.D. Rosenthal, C. Rodrigues, C. Álvarez-Moreno, N. Madani, Z. Mitrev, G. Ye, R. Salomao, F. Ulger, H. Guanche-Garcell, S.S. Kanj, L.E. Cuéllar, F. Higuera, T. Mapp, R. Fernández-Hidalgo, Effectiveness of a multidimensional approach for prevention of ventilator-associated pneumonia in adult intensive care units from 14 developing countries of four continents: Findings of the International Nosocomial Infection Control Consortium, Crit. Care Med. 40 (2012) 3121–3128.
[31] A. Stoclin, F. Rotolo, Y. Hicheri, M. Mons, E. Chachaty, B. Gachot, J.P. Pignon, M. Wartelle, F. Blot, Ventilator-associated pneumonia and bloodstream infections in intensive care unit cancer patients: a retrospective 12-year study on 3388 prospectively monitored patients, Support. Care Cancer. 28 (2020) 193–200.
[32] A. Cook, S. Norwood, J. Berne, Ventilator-associated pneumonia is more common and of less consequence in trauma patients compared with other critically ill patients, J. Trauma 69 (2010) 1083–1091.
[33] A. Torres, R. Aznar, J.M. Gatell, P. Jimenez, J. Gonzalez, A. Ferrer, R. Celis, R. Rodriguez-Roisin, Incidence, risk, and prognosis factors of nosocomial pneumonia in mechanically ventilated patients, Am Rev Respir Dis. 142 (1990) 523–528. https://doi.org/10.1164/AJRCCM/142.3.523.
[34] G. Gursel, Determinants of the length of mechanical ventilation in patients with COPD in the intensive care unit, Respiration 72 (2005) 61–67.
[35] S. Nseir, C. Di Pompeo, S. Soubrier, B. Cavestri, E. Jozefowicz, F. Saulnier, A. Durocher, Impact of ventilator-associated pneumonia on outcome in patients with COPD, Chest. 128 (2005) 1650–1656.
[36] E. Tejerina, F. Frutos-Vivar, M.I. Restrepo, A. Anzueto, F. Abroug, F. Palizas, M. González, G. D'Empaire, C. Apezteguía, A. Esteban, Incidence, risk factors, and outcome of ventilator-associated pneumonia, J. Crit. Care 21 (2006) 56–65.
[37] H.M. Al-Dorzi, A. El-Saed, A.H. Rishu, H.H. Balkhy, Z.A. Memish, Y.M. Arabi, The results of a 6-year epidemiologic surveillance for ventilator-associated pneumonia at a tertiary care intensive care unit in Saudi Arabia, Am. J. Infect. Control. 40 (2012) 794–799.
[38] L. Papazian, M. Klompas, C.E. Luyt, Ventilator-associated pneumonia in adults: a narrative review, Intensive Care Med. 46 (2020) 888–906.
[39] D. Nora, P. Póvoa, Antibiotic consumption and ventilator-associated pneumonia rates, some parallelism but some discrepancies, Ann. Transl. Med. 5 (2017) 450.
[40] A. Mehta, R. Bhagat, Preventing Ventilator-Associated Infections, Clin. Chest Med. 37 (2016) 683–692.
[41] J.A. Al-Tawfiq, P.A. Tambyah, Healthcare-associated infections (HAI) perspectives, J. Infect. Public Health 7 (2014) 339–344.
[42] E. Zimlichman, D. Henderson, O. Tamir, C. Franz, P. Song, C.K. Yamin, C. Keohane, C.R. Denham, D.W. Bates, Health care-associated infections: a meta-analysis of costs and financial impact on the US health care system, JAMA Intern. Med. 173 (2013) 2039–2046.
[43] M.H. Kollef, C.W. Hamilton, F.R. Ernst, Economic Impact of Ventilator-Associated Pneumonia in a Large Matched Cohort, Infect. Control Hosp. Epidemiol. 33 (2012) 250–256.
[44] D. Wyncoll, L. Camporota, Number needed to treat and cost-effectiveness in the prevention of ventilator-associated pneumonia, Crit. Care 16 (2012) 430.
[45] H. Arefian, S. Hagel, S. Heublein, F. Rissner, A. Scherag, F.M. Brunkhorst, R.J. Baldessarini, M. Hartmann, Extra length of stay and costs because of health care–associated infections at a German university hospital, Am. J. Infect. Control. 44 (2016) 160–166.
[46] H. Arefian, S. Hagel, D. Fischer, A. Scherag, F.M. Brunkhorst, J. Maschmann, M. Hartmann, Estimating extra length of stay due to healthcare-associated infections before and after implementation of a hospital-wide infection control program, PLoS One. 14 (2019) e0217159.
[47] C.F. Haas, R.M. Eakin, M.A. Konkle, R. Blank, Endotracheal tubes: old and new, Respir. Care 59 (2014) 933–955.
[48] D. Wu, C. Wu, S. Zhang, Y. Zhong, Risk factors of ventilator-associated pneumonia in critically III patients, Front. Pharmacol. 10 (2019) 482.

[49] C. Mietto, R. Pinciroli, N. Patel, L. Berra, Ventilator-associated pneumonia: evolving definitions and preventive strategies, Respir. Care. 58 (2013) 990–1007.
[50] M. Cavalcanti, M. Ferrer, R. Ferrer, R. Morforte, A. Garnacho, A. Torres, Risk and prognostic factors of ventilator-associated pneumonia in trauma patients, Crit. Care Med. 34 (2006) 1067–1072.
[51] R. Pinciroli, C. Mietto, L. Berra, Respiratory therapy device modifications to prevent ventilator-associated pneumonia, Curr. Opin. Infect. Dis. 26 (2013) 175–183.
[52] H.R. Thorarinsdottir, T. Kander, A. Holmberg, S. Petronis, B. Klarin, Biofilm formation on three different endotracheal tubes: A prospective clinical trial, Crit. Care 24 (2020) 1–12.
[53] O. Diaconu, I. Siriopol, L.I. Poloșanu, I. Grigoraș, Endotracheal Tube Biofilm and its Impact on the Pathogenesis of Ventilator-Associated Pneumonia, J. Crit. Care Med. 4 (2018) 50-55.
[54] S. Gil-Perotin, P. Ramirez, V. Marti, J.M. Sahuquillo, E. Gonzalez, I. Calleja, R. Menendez, J. Bonastre, Implications of endotracheal tube biofilm in ventilator-associated pneumonia response: A state of concept, Crit. Care. 16 (2012) 1–9.
[55] S. Cairns, J.G. Thomas, S.J. Hooper, M.P. Wise, P.J. Frost, M.J. Wilson, M.A.O. Lewis, D.W. Williams, Molecular analysis of microbial communities in endotracheal tube biofilms, PLoS One. 6 (2011).
[56] X.M. Bustamante-Marin, L.E. Ostrowski, Cilia and Mucociliary Clearance, Cold Spring Harb. Perspect. Biol. 9 (2017) a028241.
[57] B.M. Morrow, Airway clearance therapy in acute paediatric respiratory illness: A state-of-the-art review, S. Afr. J. Physiother. 75 (2019).
[58] B. Augustyn, Ventilator-Associated PneumoniaRisk Factors and Prevention, Crit. Care Nurse. 27 (2007) 32–39.
[59] T.J.J. Inglis, M.R. Millar, J.G. Jones, D.A. Robinson, Tracheal tube biofilm as a source of bacterial colonization of the lung, J. Clin. Microbiol. 27 (1989) 2014–2018.
[60] C. Mietto, R. Pinciroli, A. Piriyapatsom, J.G. Thomas, L. Bry, M.L. Delaney, A. du Bois, J. Truelove, J.B. Ackman, G.R. Wojtkiewicz, M. Nahrendorf, R.M. Kacmarek, L. Berra, Tracheal Tube Obstruction in Mechanically Ventilated Patients Assessed by High-resolution Computed Tomography, Anesthesiology. 121 (2014) 1226–1235.
[61] A. Coppadoro, L. Berra, L.M. Bigatello, Modifying endotracheal tubes to prevent ventilator-associated pneumonia, Curr. Opin. Infect. Dis. 24 (2011) 157–162.
[62] P.E. Danin, E. Girou, P. Legrand, B. Louis, R. Fodil, C. Christov, J. Devaquet, D. Isabey, L. Brochard, Description and Microbiology of Endotracheal Tube Biofilm in Mechanically Ventilated Subjects, Respir. Care 60 (2015) 21–29.
[63] I.A. Pneumatikos, C.K. Dragoumanis, D.E. Bouros, Ventilator-associated Pneumonia or Endotracheal Tube-associated Pneumonia?An Approach to the Pathogenesis and Preventive Strategies Emphasizing the Importance of Endotracheal Tube, Anesthesiology. 110 (2009) 673–680.
[64] S. Lethongkam, C. Daengngam, C. Tansakul, R. Siri, A. Chumpraman, M. Phengmak, S.P. Voravuthikunchai, Prolonged inhibitory effects against planktonic growth, adherence, and biofilm formation of pathogens causing ventilator-associated pneumonia using a novel polyamide/silver nanoparticle composite-coated endotracheal tube, Biofouling. 36 (2020) 292–307.
[65] H.C. Flemming, J. Wingender, The biofilm matrix, Nat. Rev. Microbiol. 8 (2010) 623–633.
[66] D. Lebeaux, J.-M.J.-M. Ghigo, C. Beloin, Biofilm-Related Infections: Bridging the Gap between Clinical Management and Fundamental Aspects of Recalcitrance toward Antibiotics, Microbiol. Mol. Biol. Rev. 78 (2014) 510–543.
[67] D. Sharma, L. Misba, A.U. Khan, Antibiotics versus biofilm: an emerging battleground in microbial communities, Antimicrob. Resist. Infect. Contro. 8 (2019) 76.
[68] O.A. Solis-Velazquez, M. Gutiérrez-Lomelí, P.J. Guerreo-Medina, M. de L. Rosas-García, M. Iñiguez-Moreno, M.G. Avila-Novoa, Nosocomial pathogen biofilms on biomaterials: Different growth medium conditions and components of biofilms produced in vitro, J. Microbiol. Immunol. Infect. 54 (2021) 1038–1047.
[69] K. BazakPneumonia Riska, M. V. Jacob, R.J. Crawford, E.P. Ivanova, Efficient surface modification of biomaterial to prevent biofilm formation and the attachment of microorganisms., Appl. Microbiol. Biotechnol. 95 (2012) 299–311.
[70] H.C. Flemming, J. Wingender, U. Szewzyk, P. Steinberg, S.A. Rice, S. Kjelleberg, Biofilms: an emergent form of bacterial life, Nat. Rev. Microbiol. 14 (2016) 563–575.
[71] H. Li, C. Song, D. Liu, Q. Ai, J. Yu, Molecular analysis of biofilms on the surface of neonatal endotracheal tubes based on 16S rRNA PCR-DGGE and species-specific PCR, Int. J. Clin. Exp. Med. 8 (2015) 11075.
[72] L. Berra, M. Panigada, L. de Marchi, G. Greco, Z.X. Yu, A. Baccarelli, J. Pohlmann, K.F. Costello, J. Appleton, R. Mahar, R.A. Lewandowski, L. Ravitz, T. Kolobow, New approaches for the prevention of

airway infection in ventilated patients. Lessons learned from laboratory animal studies at the National Institutes of Health., Minerva Anestesiol. 69 (2003) 342–347.
[73] I. Vandecandelaere, T. Coenye, Microbial composition and antibiotic resistance of biofilms recovered from endotracheal tubes of mechanically ventilated patients, Adv. Exp. Med. Biol. 830 (2015) 137–155.
[74] B. Maertens, K. Blot, S. Blot, Prevention of ventilator-Associated and early postoperative pneumonia through tapered endotracheal tube cuffs: A systematic review and meta-analysis of randomized controlled trials, Crit. Care Med. 46 (2018) 316–323.
[75] F. Philippart, S. Gaudry, L. Quinquis, N. Lau, I. Ouanes, S. Touati, J.C. Nguyen, C. Branger, F. Faibis, M. Mastouri, X. Forceville, F. Abroug, J.D. Ricard, S. Grabar, B. Misset, Randomized intubation with polyurethane or conical cuffs to prevent pneumonia in ventilated patients, Am. J. Respir. Crit. Care Med. 191 (2015) 637–645.
[76] R. Price, G. MacLennan, J. Glen, Selective digestive or oropharyngeal decontamination and topical oropharyngeal chlorhexidine for prevention of death in general intensive care: a systematic review and network meta-analysis, BMJ. 348 (2014) g2197.
[77] L. Fernández-Barat, R. López-Aladid, A. Torres, Reconsidering ventilator-associated pneumonia from a new dimension of the lung microbiome, EBioMedicine. 60 (2020) 102995.
[78] I. Vandecandelaere, N. Matthijs, F. van Nieuwerburgh, D. Deforce, P. Vosters, L. de Bus, H.J. Nelis, P. Depuydt, T. Coenye, Assessment of microbial diversity in biofilms recovered from endotracheal tubes using culture-dependent and independent approaches, PLoS One. 7 (2012) e38401.
[79] Y. Wang, B. Cai, D. Ni, Y. Sun, G. Wang, H. Jiang, A novel antibacterial and antifouling nanocomposite coated endotracheal tube to prevent ventilator-associated pneumonia, J. Nanobiotechnology. 20 (2022) 1–19.
[80] L.R. Redman, E. Lockey, Colonisation of the upper respiratory tract with Gram-negative bacilli after operation, endotracheal intubation and prophylactic antibiotic therapy, Anaesthesia. 22 (1967) 220–227.
[81] F.D. Sottile, T.J. Marrie, D.S. Prough, C.D. Hobgood, D.J. Gower, L.X. Webb, J.W. Costerton, A.G. Gristina, Nosocomial pulmonary infection: Possible etiologic significance of bacterial adhesion to endotracheal tubes, Crit. Care Med. 14 (1986) 265–270.
[82] C. Sarda, F. Fazal, J. Rello, Management of ventilator-associated pneumonia (VAP) caused by resistant gram-negative bacteria: which is the best strategy to treat? Expert Rev. Respir. Med. 13(2019) 787-798.
[83] X. Xie, J. Lyu, T. Hussain, M. Li, Drug Prevention and Control of Ventilator-Associated Pneumonia, Front. Pharmacol. 10 (2019) 298.
[84] L.A. Mandell, M.S. Niederman, Aspiration Pneumonia, N. Engl. J. Med. 380 (2019) 651–663.
[85] C.G. Adair, S.P. Gorman, B.M. Feron, L.M. Byers, D.S. Jones, C.E. Goldsmith, J.E. Moore, J.R. Kerr, M.D. Curran, G. Hogg, C.H. Webb, G.J. McCarthy, K.R. Milligan, Implications of endotracheal tube biofilm for ventilator-associated pneumonia, Intensive Care Med. 25 (1999) 1072–1076.
[86] T.F.C. Mah, G.A. O'Toole, Mechanisms of biofilm resistance to antimicrobial agents, Trends Microbiol. 9 (2001) 34–39.
[87] J.C. Nickel, I. Ruseska, J.B. Wright, J.W. Costerton, Tobramycin resistance of Pseudomonas aeruginosa cells growing as a biofilm on urinary catheter material, Antimicrob. Agents Chemother. 27 (1985) 619–624.
[88] C. Garzoni, S.D. Brugger, W. Qi, S. Wasmer, A. Cusini, P. Dumont, M. Gorgievski-Hrisoho, K. Mühlemann, C. von Garnier, M. Hilty, Microbial communities in the respiratory tract of patients with interstitial lung disease, Thorax. 68 (2013) 1150–1156.
[89] M. Hilty, C. Burke, H. Pedro, P. Cardenas, A. Bush, C. Bossley, J. Davies, A. Ervine, L. Poulter, L. Pachter, M.F. Moffatt, W.O.C. Cookson, Disordered Microbial Communities in Asthmatic Airways, PLoS One. 5 (2010) e8578.
[90] B.J. Kelly, I. Imai, K. Bittinger, A. Laughlin, B.D. Fuchs, F.D. Bushman, R.G. Collman, Composition and dynamics of the respiratory tract microbiome in intubated patients, Microbiome. 4 (2016) 7.
[91] R. Gupta, A. Malik, M. Rizvi, M. Ahmed, A. Singh, Epidemiology of multidrug-resistant Gram-negative pathogens isolated from ventilator-associated pneumonia in ICU patients, J. Glob. Antimicrob. Resist. 9 (2017) 47–50.
[92] D.R. Park, The microbiology of ventilator-associated pneumonia, Respir Care. 50 (2005) 742–763.
[93] H.-C. Wang, M.-H. Tsai, S.-M. Chu, C.-C. Liao, M.-Y. Lai, H.-R. Huang, M.-C. Chiang, R.-H. Fu, J.-F. Hsu, Clinical characteristics and outcomes of neonates with polymicrobial ventilator-associated pneumonia in the intensive care unit, BMC Infect. Dis. 21 (2021) 965.
[94] E. Iosifidis, G. Pitsava, E. Roilides, Ventilator-associated pneumonia in neonates and children: a systematic analysis of diagnostic methods and prevention, Future Microbiol. 13 (2018) 1431–1446.
[95] S.P. Lopes, M.E. Rodrigues, C.R. Pereira, N.F. Azevedo, A. Lourenço, M. Henriques, M.O. Pereira, Polymicrobial ventilator-associated pneumonia: Fighting in vitro Candida albicans-Pseudomonas aeruginosa biofilms with antifungal-antibacterial combination therapy, PLoS One. 12 (2017) e0170433.

[96] J.S. Garland, Strategies to Prevent Ventilator-Associated Pneumonia in Neonates, Clin. Perinatol. 37 (2010) 629–643.
[97] M. Cernada, M. Brugada, S. Golombek, M. Vento, Ventilator-associated pneumonia in neonatal patients: an update, Neonatology. 105 (2014) 98–107.
[98] S.D. Perkins, K.F. Woeltje, L.T. Angenent, Endotracheal tube biofilm inoculation of oral flora and subsequent colonization of opportunistic pathogens, Int. J. Med. Microbiol. 300 (2010) 503–511.
[99] A. Hotterbeekx, B.B. Xavier, K. Bielen, C. Lammens, P. Moons, T. Schepens, M. Ieven, P.G. Jorens, H. Goossens, S. Kumar-Singh, S. Malhotra-Kumar, The endotracheal tube microbiome associated with Pseudomonas aeruginosa or Staphylococcus epidermidis, Sci Rep. 6 (2016) 1–11.
[100] G. McAlester, F. O'Gara, J.P. Morrissey, Signal-mediated interactions between Pseudomonas aeruginosa and Candida albicans, J. Med. Microbiol. 57 (2008) 563–569.
[101] M. Hamet, A. Pavon, F. Dalle, A. Pechinot, S. Prin, J.P. Quenot, P.E. Charles, Candida spp. airway colonization could promote antibiotic-resistant bacteria selection in patients with suspected ventilator-associated pneumonia, Intensive Care Med. 38 (2012) 1272–1279.
[102] T. de O. Ferreira, R.Y. Koto, G.F. da C. Leite, G.B. Klautau, S. Nigro, C.B. da Silva, A.P.I. da F. Souza, M.J. Mimica, R.G. Cesar, M.J.C. Salles, Microbial investigation of biofilms recovered from endotracheal tubes using sonication in intensive care unit pediatric patients, Braz. J. Infect. Dis. 20 (2016) 468–475.
[103] I. Vandecandelaere, N. Matthijs, H.J. Nelis, P. Depuydt, T. Coenye, The presence of antibiotic-resistant nosocomial pathogens in endotracheal tube biofilms and corresponding surveillance cultures, Pathog. Dis. 69 (2013) 142–148.
[104] J.A. Aas, B.J. Paster, L.N. Stokes, I. Olsen, F.E. Dewhirst, Defining the normal bacterial flora of the oral cavity, J. Clin. Microbiol. 43 (2005) 5721–5732.
[105] V.L. Yu, N. Singh, Excessive antimicrobial usage causes measurable harm to patients with suspected ventilator-associated pneumonia, Intensive Care Med. 30 (2004) 735–738.
[106] M.H. Kollef, Inadequate antimicrobial treatment: an important determinant of outcome for hospitalized patients, Clin. Infect. Dis. 31 Suppl 4 (2000) S131-8.
[107] J.C. Lacherade, B. De Jonghe, P. Guezennec, K. Debbat, J. Hayon, A. Monsel, P. Fangio, C.A. De Vecchi, C. Ramaut, H. Outin, S. Bastuji-Garin, Intermittent subglottic secretion drainage and ventilator-associated pneumonia: a multicenter trial, Am. J. Respir. Crit. Care Med. 182 (2010) 910–917.
[108] Z. Mao, L. Gao, G. Wang, C. Liu, Y. Zhao, W. Gu, H. Kang, F. Zhou, Subglottic secretion suction for preventing ventilator-associated pneumonia: an updated meta-analysis and trial sequential analysis, Crit. Care 20 (2016) 353.
[109] G.L. Bassi, N. Luque, J.D. Martí, E.A. Xiol, M. Di Pasquale, V. Giunta, T. Comaru, M. Rigol, S. Terraneo, F. De Rosa, M. Rinaudo, E. Crisafulli, R.C.P. Lepe, C. Agusti, C. Lucena, M. Ferrer, L. Fernández, A. Torres, Endotracheal Tubes for Critically Ill Patients: An In Vivo Analysis of Associated Tracheal Injury, Mucociliary Clearance, and Sealing Efficacy, Chest. 147 (2015) 1327–1335.
[110] A. Monsel, M. le Corre, R. Deransy, H. Brisson, C. Arbelot, Q. Lu, J.L. Golmard, O. Langeron, J.J. Rouby, Modification of Tracheal Cuff Shape and Continuous Cuff Pressure Control to Prevent Microaspiration in an Ex Vivo Pig Tracheal Two-Lung Model, Crit. Care Med. 45 (2017) e1262–e1269.
[111] S.I. Blot, J. Poelaert, M. Kollef, How to avoid microaspiration? A key element for the prevention of ventilator-associated pneumonia in intubated ICU patients, BMC Infect. Dis. 14 (2014) 1–6.
[112] M.H. Kollef, B. Afessa, A. Anzueto, C. Veremakis, K.M. Kerr, B.D. Margolis, D.E. Craven, P.R. Roberts, A.C. Arroliga, R.D. Hubmayr, M.I. Restrepo, W.R. Auger, R. Schinner, Silver-Coated Endotracheal Tubes and Incidence of Ventilator-Associated Pneumonia: The NASCENT Randomized Trial, JAMA. 300 (2008) 805–813.
[113] A. Mahmoodpoor, S. Sanaie, R. Parthvi, K. Shadvar, H. Hamishekar, A. Iranpour, H. Nuri, S. Rahnemayan, N.D. Nader, A clinical trial of silver-coated and tapered cuff plus supraglottic suctioning endotracheal tubes in preventing ventilator-associated pneumonia, J. Crit. Care. 56 (2020) 171–176.
[114] H. Liedberg, T. Lundeberg, Silver alloy coated catheters reduce catheter-associated bacteriuria, Br. J. Urol. 65 (1990) 379–381.
[115] J.R. Morones, J.L. Elechiguerra, A. Camacho, K. Holt, J.B. Kouri, J.T. Ramírez, M.J. Yacaman, The bactericidal effect of silver nanoparticles, Nanotechnology. 16 (2005) 2346.
[116] H.A. Hemeg, Nanomaterials for alternative antibacterial therapy, Int. J. Nanomedicine. 12 (2017) 8211.
[117] M. Hartmann, J. Guttmann, B. Muller, T. Hallmann, K. Geiger, Reduction of the bacterial load by the silver-coated endotracheal tube (SCET), a laboratory investigation, Techno. Health Care 7 (1999) 359–370.
[118] M.E. Olson, B.G. Harmon, M.H. Kollef, Silver-Coated Endotracheal Tubes Associated With Reduced Bacterial Burden in the Lungs of Mechanically Ventilated Dogs, Chest. 121 (2002) 863–870.

[119] D.J. Balazs, K. Triandafillu, P. Wood, Y. Chevolot, C. van Delden, H. Harms, C. Hollenstein, H.J. Mathieu, Inhibition of bacterial adhesion on PVC endotracheal tubes by RF-oxygen glow discharge, sodium hydroxide and silver nitrate treatments, Biomaterials. 25 (2004) 2139–2151.
[120] M. Ramstedt, R. Houriet, D. Mossialos, D. Haas, H. Jö Rg Mathieu, Wet Chemical Silver Treatment of Endotracheal Tubes to Produce Antibacterial Surfaces, J. Biomed, Mater. Res. B. Appl. Biomat. 83 (2007) 169-180.
[121] F. Paladini, M. Pollini, A. Sannino, L. Ambrosio, Metal-based antibacterial substrates for biomedical applications, Biomacromolecules. 16 (2015) 1873–1885.
[122] C.Y. Loo, P.M. Young, W.H. Lee, R. Cavaliere, C.B. Whitchurch, R. Rohanizadeh, Non-cytotoxic silver nanoparticle-polyvinyl alcohol hydrogels with anti-biofilm activity: designed as coatings for endotracheal tube materials., Biofouling. 30 (2014) 773–788.
[123] C. Daengngam, S. Lethongkam, P. Srisamran, S. Paosen, P. Wintachai, B. Anantravanit, V. Vattanavanit, S. Voravuthikunchai, Green fabrication of anti-bacterial biofilm layer on endotracheal tubing using silver nanoparticles embedded in polyelectrolyte multilayered film, Mater. Sci. Eng. C. Mater. Biol. Appl. 101 (2019) 53–63.
[124] K. Loeschner, N. Hadrup, K. Qvortrup, A. Larsen, X. Gao, U. Vogel, A. Mortensen, H.R. Lam, E.H. Larsen, Distribution of silver in rats following 28 days of repeated oral exposure to silver nanoparticles or silver acetate, Part. Fibre Toxicol. 8 (2011) 18.
[125] D.P.K. Lankveld, A.G. Oomen, P. Krystek, A. Neigh, A. Troost - de Jong, C.W. Noorlander, J.C.H. van Eijkeren, R.E. Geertsma, W.H. de Jong, The kinetics of the tissue distribution of silver nanoparticles of different sizes, Biomaterials. 31 (2010) 8350–8361.
[126] X. Jiang, B. Lv, Q. Shen, X. Wang, Preparation of silicon-modified antimicrobial polyethylene endotracheal tubes, J. Biomed. Mater. Res. B. Appl. Biomater. 105 (2017) 91–98.
[127] I.I. Raad, J.A. Mohamed, R.A. Reitzel, Y. Jiang, T.L. Dvorak, M.A. Ghannoum, R.Y. Hachem, A.M. Chaftari, The prevention of biofilm colonization by multidrug-resistant pathogens that cause ventilator-associated pneumonia with antimicrobial-coated endotracheal tubes, Biomaterials. 32 (2011) 2689–2694.
[128] G. Björling, D. Johansson, L. Bergström, S. Jalal, I. Kohn, C. Frostell, S. Kalman, Tolerability and performance of BIP endotracheal tubes with noble metal alloy coating - a randomized clinical evaluation study, BMC Anesthesiol. 15 (2015) 1–10.
[129] P. Damas, C. Legrain, B. Lambermont, N. Dardenne, J. Guntz, G. KisokPneumonia Riska, P. Demaret, A.F. Rousseau, L. Jadot, S. Piret, D. Noirot, A. Bertrand, A.F. Donneau, B. Misset, Prevention of ventilator-associated pneumonia by noble metal coating of endotracheal tubes: a multi-center, randomized, double-blind study, Ann. Intensive Care 12 (2022) 1.
[130] R.C. Tincu, C. Cobilinschi, I.F. Tincu, R.A. Macovei, Efficacy of Noble Metal–alloy Endotracheal Tubes in Ventilator-associated Pneumonia Prevention: a Randomized Clinical Trial, Balkan Med. J. 39 (2022) 167–171.
[131] P.P. Mahamuni, P.M. Patil, M.J. Dhanavade, M. v. Badiger, P.G. Shadija, A.C. Lokhande, R.A. Bohara, Synthesis and characterization of zinc oxide nanoparticles by using polyol chemistry for their antimicrobial and antibiofilm activity, Biochem. Biophys. Rep. 17 (2018) 71–80.
[132] B.L. Guo, P. Han, L.C. Guo, Y.Q. Cao, A.D. Li, J.Z. Kong, H.F. Zhai, D. Wu, The Antibacterial Activity of Ta-doped ZnO Nanoparticles, Nanoscale Res. Lett. 10 (2015) 1–10.
[133] G. Wagner, V. Korenkov, J.D. Judy, P.M. Bertsch, Nanoparticles Composed of Zn and ZnO Inhibit Peronospora tabacina Spore Germination in vitro and P. tabacina Infectivity on Tobacco Leaves, Nanomaterials. 6 (2016) 50.
[134] K. Ghule, A.V. Ghule, B.J. Chen, Y.C. Ling, Preparation and characterization of ZnO nanoparticles coated paper and its antibacterial activity study, Green Chem. 8 (2006) 1034–1041.
[135] M.J. McGuffie, J. Hong, J.H. Bahng, E. Glynos, P.F. Green, N.A. Kotov, J.G. Younger, J.S. VanEpps, Zinc oxide nanoparticle suspensions and layer-by-layer coatings inhibit staphylococcal growth, Nanomedicine. 12 (2016) 33–42.
[136] M. Shaban, F. Mohamed, S. Abdallah, Production and Characterization of Superhydrophobic and Antibacterial Coated Fabrics Utilizing ZnO Nanocatalyst, Sci. Rep. 2018 8:1. 8 (2018) 1–15.
[137] J.T. Seil, T.J. Webster, Reduced Staphylococcus aureus proliferation and biofilm formation on zinc oxide nanoparticle PVC composite surfaces, Acta Biomater. 7 (2011) 2579–2584.
[138] B.M. Geilich, T.J. Webster, Reduced adhesion of Staphylococcus aureus to ZnO/PVC nanocomposites, Int. J. Nanomedicine. 8 (2013) 1177–1184.
[139] A. Sirelkhatim, S. Mahmud, A. Seeni, N.H.M. Kaus, L.C. Ann, S.K.M. Bakhori, H. Hasan, D. Mohamad, Review on Zinc Oxide Nanoparticles: Antibacterial Activity and Toxicity Mechanism, Nanomicro. Lett. 7 (2015) 219–242.
[140] T.V. Duncan, Applications of nanotechnology in food packaging and food safety: Barrier materials, antimicrobials and sensors, J. Colloid Interface Sci. 363 (2011) 1–24.

[141] C. Wang, J. Lu, L. Zhou, J. Li, J. Xu, W. Li, L. Zhang, X. Zhong, T. Wang, Effects of Long-Term Exposure to Zinc Oxide Nanoparticles on Development, Zinc Metabolism and Biodistribution of Minerals (Zn, Fe, Cu, Mn) in Mice, PLoS One. 11 (2016) e0164434.
[142] Y. Zhang, K.C. Nguyen, D. Caldwell, J.H. Fine, D.E. Lefebvre, A.F. Tayabali, Immune responses during single and repeated murine endotracheal exposures of zinc oxide nanoparticles, NanoImpact 7 (2017) 54–65.
[143] B. Yu, Y. Zhang, W. Zheng, C. Fan, T. Chen, Positive surface charge enhances selective cellular uptake and anticancer efficacy of selenium nanoparticles, Inorg. Chem. 51 (2012) 8956–8963.
[144] H. Forootanfar, M. Adeli-Sardou, M. Nikkhoo, M. Mehrabani, B. Amir-Heidari, A.R. Shahverdi, M. Shakibaie, Antioxidant and cytotoxic effect of biologically synthesized selenium nanoparticles in comparison to selenium dioxide, J. Trace Elem. Med. Biol. 28 (2014) 75–79.
[145] M. Shakibaie, H. Forootanfar, Y. Golkari, T. Mohammadi-Khorsand, M.R. Shakibaie, Anti-biofilm activity of biogenic selenium nanoparticles and selenium dioxide against clinical isolates of Staphylococcus aureus, Pseudomonas aeruginosa, and Proteus mirabilis, J. Trace Elem. Med. Biol. 29 (2015) 235–241.
[146] Y. He, S. Chen, Z. Liu, C. Cheng, H. Li, M. Wang, Toxicity of selenium nanoparticles in male Sprague-Dawley rats at supranutritional and nonlethal levels, Life Sci. 115 (2014) 44–51.
[147] P.A. Tran, T.J. Webster, Antimicrobial selenium nanoparticle coatings on polymeric medical devices, Nanotechnology. 24 (2013) 155101–155101.
[148] G. Jori, C. Fabris, M. Soncin, S. Ferro, O. Coppellotti, D. Dei, L. Fantetti, G. Chiti, G. Roncucci, Photodynamic therapy in the treatment of microbial infections: basic principles and perspective applications, Lasers Surg. Med. 38 (2006) 468–481.
[149] V.K. Yemmireddy, Y.C. Hung, Using Photocatalyst Metal Oxides as Antimicrobial Surface Coatings to Ensure Food Safety—Opportunities and Challenges, Compr. Rev. Food. Sci. Food Saf. 16 (2017) 617–631.
[150] H.A. Foster, I.B. Ditta, S. Varghese, A. Steele, Photocatalytic disinfection using titanium dioxide: spectrum and mechanism of antimicrobial activity, Appl. Microbiol. Biotechnol. 2011 90:6. 90 (2011) 1847–1868.
[151] M. Azizi-Lalabadi, A. Ehsani, B. Divband, M. Alizadeh-Sani, Antimicrobial activity of Titanium dioxide and Zinc oxide nanoparticles supported in 4A zeolite and evaluation the morphological characteristic, Sci. Rep. 9 (2019) 1–10.
[152] G. Carré, E. Hamon, S. Ennahar, M. Estner, M.C. Lett, P. Horvatovich, J.P. Gies, V. Keller, N. Keller, P. Andre, TiO2 Photocatalysis Damages Lipids and Proteins in Escherichia coli, Appl. Environ. Microbiol. 80 (2014) 2573.
[153] S.P. Krumdieck, R. Boichot, R. Gorthy, J.G. Land, S. Lay, A.J. Gardecka, M.I.J. Polson, A. Wasa, J.E. Aitken, J.A. Heinemann, G. Renou, G. Berthomé, F. Charlot, T. Encinas, M. Braccini, C.M. Bishop, Nanostructured TiO 2 anatase-rutile-carbon solid coating with visible light antimicrobial activity, Sci Rep. 9 (2019).
[154] V. Caratto, L. Ball, E. Sanguineti, A. Insorsi, I. Firpo, S. Alberti, M. Ferrett, P. Pelosi, Antibacterial activity of standard and N-doped titanium dioxide-coated endotracheal tubes: an in vitro study, Rev. Bras. Ter. Intensiva 29 (2017) 55.
[155] W. Deng, S. Ning, Q. Lin, H. Zhang, T. Zhou, H. Lin, J. Long, Q. Lin, X. Wang, I-TiO2/PVC film with highly photocatalytic antibacterial activity under visible light, Colloids Surf. B. Biointerfaces 144 (2016) 196–202.
[156] H. Shi, R. Magaye, V. Castranova, J. Zhao, Titanium dioxide nanoparticles: a review of current toxicological data, Part. Fibre Toxicol. 10 (2013) 1–33.
[157] P. Wu, D.W. Grainger, Drug/device combinations for local drug therapies and infection prophylaxis, Biomaterials. 27 (2006) 2450–2467.
[158] T.A.G. van Vugt, J.J. Arts, J.A.P. Geurts, Antibiotic-Loaded Polymethylmethacrylate Beads and Spacers in Treatment of Orthopedic Infections and the Role of Biofilm Formation, Front. Microbiol. 10 (2019) 1626.
[159] H. Wang, H. Tong, H. Liu, Y. Wang, R. Wang, H. Gao, P. Yu, Y. Lv, S. Chen, G. Wang, M. Liu, Y. Li, K. Yu, C. Wang, Effectiveness of antimicrobial-coated central venous catheters for preventing catheter-related blood-stream infections with the implementation of bundles: a systematic review and network meta-analysis, Ann. Intensive Care 8 (2018).
[160] G. Chaiban, H. Hanna, T. Dvorak, I. Raad, A rapid method of impregnating endotracheal tubes and urinary catheters with gendine: a novel antiseptic agent, J. Antimicrob. Chemother. 55 (2005) 51–56.
[161] V. Pacheco-Fowler, T. Gaonkar, P.C. Wyer, S. Modak, Antiseptic impregnated endotracheal tubes for the prevention of bacterial colonization, J. Hosp. Infect. 57 (2004) 170–174.

[162] D.S. Jones, J.G. Mcgovern, A.D. Woolfson, C.G. Adair, S.P. Gorman, Physicochemical Characterization of Hexetidine-Impregnated Endotracheal Tube Poly(Vinyl Chloride) and Resistance to Adherence of Respiratory Bacterial Pathogens, Pharm. Res. 19 (2002) 818-824.
[163] S. Venkateswaran, O.D. Henrique Dos Santos, E. Scholefield, A. Lilienkampf, P.J. Gwynne, D.G. Swann, K. Dhaliwal, M.P. Gallagher, M. Bradley, Fortified interpenetrating polymers – bacteria resistant coatings for medical devices, J. Mater. Chem. B. 4 (2016) 5405–5411.
[164] K.H. Homeyer, P. Singha, M.J. Goudie, H. Handa, S-Nitroso-N-acetylpenicillamine impregnated endotracheal tubes for prevention of ventilator-associated pneumonia, Biotechnol. Bioeng. 117 (2020) 2237–2246.
[165] E.J. Brisbois, T.C. Major, M.J. Goudie, R.H. Bartlett, M.E. Meyerhoff, H. Handa, Improved hemocompatibility of silicone rubber extracorporeal tubing via solvent swelling-impregnation of S-nitroso-N-acetylpenicillamine (SNAP) and evaluation in rabbit thrombogenicity model, Acta Biomater. 37 (2016) 111–119.
[166] J. Sundaram, J. Pant, M.J. Goudie, S. Mani, H. Handa, Antimicrobial and Physicochemical Characterization of Biodegradable, Nitric Oxide-Releasing Nanocellulose-Chitosan Packaging Membranes, J. Agric. Food Chem. 64 (2016) 5260–5266.
[167] M.J. Goudie, E.J. Brisbois, J. Pant, A. Thompson, J.A. Potkay, H. Handa, Characterization of an S-nitroso-N-acetylpenicillamine–based nitric oxide releasing polymer from a translational perspective, Int. J. Polym. Mat. 65 (2016) 769–778.
[168] D. Ren, J.S. Madsen, S.J. Sorensen, M. Burmolle, High prevalence of biofilm synergy among bacterial soil isolates in cocultures indicates bacterial interspecific cooperation, ISME J. 9 (2015) 81–89.
[169] P. Singha, J. Pant, M.J. Goudie, C.D. Workman, H. Handa, Enhanced antibacterial efficacy of nitric oxide releasing thermoplastic polyurethanes with antifouling hydrophilic topcoats, Biomater. Sci. 5 (2017) 1246–1255.
[170] M. Zasloff, Antimicrobial peptides of multicellular organisms: My perspective, Adv Exp Med Biol. 1117 (2019) 3–6.
[171] M. Riool, A. de Breij, J.W. Drijfhout, P.H. Nibbering, S.A.J. Zaat, Antimicrobial peptides in biomedical device manufacturing, Front. Chem. 5 (2017) 63.
[172] D. Alves, M. Olivia Pereira, Mini-review: Antimicrobial peptides and enzymes as promising candidates to functionalize biomaterial surfaces, Biofouling. 30 (2014) 483–499.
[173] M.R. Aronson, S. Ali Akbari Ghavimi, P.M. Gehret, I.N. Jacobs, R. Gottardi, Drug-Eluting Endotracheal Tubes for Preventing Bacterial Inflammation in Subglottic Stenosis, Laryngoscope. 132 (2022) 1356–1363.
[174] R.N. Murugan, B. Jacob, M. Ahn, E. Hwang, H. Sohn, H.N. Park, E. Lee, J.H. Seo, C. Cheong, K.Y. Nam, J.K. Hyun, K.W. Jeong, Y. Kim, S.Y. Shin, J.K. Bang, De Novo Design and Synthesis of Ultra-Short Peptidomimetic Antibiotics Having Dual Antimicrobial and Anti-Inflammatory Activities, PLoS One. 8 (2013) e80025.
[175] R.W. Scott, W.F. DeGrado, G.N. Tew, De novo designed synthetic mimics of antimicrobial peptides, Curr Opin Biotechnol. 19 (2008) 620–627.
[176] X.Z. Lai, Y. Feng, J. Pollard, J.N. Chin, M.J. Rybak, R. Bucki, R.F. Epand, R.M. Epand, P.B. Savage, Ceragenins: Cholic acid-based mimics of antimicrobial peptides, Acc. Chem. Res. 41 (2008) 1233–1240.
[177] R.M. Epand, R.F. Epand, P.B. Savage, Ceragenins (cationic steroid compounds), a novel class of antimicrobial agents, Drug News Perspect. 21 (2008) 307–311.
[178] A. Dao, R.J. Mills, S. Kamble, P.B. Savage, D.G. Little, A. Schindeler, The application of ceragenins to orthopedic surgery and medicine, J. Orthop. Res. 38 (2020) 1883–1894.
[179] K. Leszczyńska, A. Namiot, K. Cruz, F.J. Byfield, E. Won, G. Mendez, W. Sokołowski, P.B. Savage, R. Bucki, P.A. Janmey, Potential of ceragenin CSA-13 and its mixture with pluronic F-127 as treatment of topical bacterial infections, J. Appl. Microbiol. 110 (2011) 229–238.
[180] M.M. Hashemi, J. Rovig, S. Weber, B. Hilton, M.M. Forouzan, P.B. Savage, Susceptibility of Colistin-Resistant, Gram-Negative Bacteria to Antimicrobial Peptides and Ceragenins, Antimicrob. Agents Chemother. 61 (2017).
[181] J.N. Chin, R.N. Jones, H.S. Sader, P.B. Savage, M.J. Rybak, Potential synergy activity of the novel ceragenin, CSA-13, against clinical isolates of Pseudomonas aeruginosa, including multidrug-resistant P. aeruginosa, J. Antimicrob. Chemother. 61 (2008) 365-370.
[182] B. Durnaœ, U. Wnorowska, K. Pogoda, P. Deptuła, M. Wa tek, E. Piktel, S. Głuszek, X. Gu, P.B. Savage, K. Niemirowicz, R. Bucki, Candidacidal Activity of Selected Ceragenins and Human Cathelicidin LL-37 in Experimental Settings Mimicking Infection Sites, PLoS One. 11 (2016) e0157242.
[183] L. Rodrigues, I.M. Banat, J. Teixeira, R. Oliveira, Biosurfactants: potential applications in medicine, J. Antimicrob. Chemother. 57 (2006) 609–618.

[184] D.S. Jones, S. McMeel, C.G. Adair, S.P. Gorman, Characterization and evaluation of novel surfactant bacterial anti-adherent coatings for endotracheal tubes designed for the prevention of ventilator-associated pneumonia, J. Pharm. Pharmacol. 55 (2003) 43–52.
[185] A.P. Seitz, F. Schumacher, J. Baker, M. Soddemann, B. Wilker, C.C. Caldwell, R.M. Gobble, M. Kamler, K.A. Becker, S. Beck, B. Kleuser, M.J. Edwards, E. Gulbins, Sphingosine-coating of plastic surfaces prevents ventilator-associated pneumonia, J. Mol. Med. (Berl). 97 (2019) 1195.
[186] C. Loc-Carrillo, S.T. Abedon, Pros and cons of phage therapy, Bacteriophage 1 (2011): 111-114.
[187] V.C. Oliveira, A.P. Macedo, L.D.R. Melo, S.B. Santos, P.R.S. Hermann, C.H. Silva-Lovato, H.F.O. Paranhos, D. Andrade, E. Watanabe, Bacteriophage Cocktail-Mediated Inhibition of Pseudomonas aeruginosa Biofilm on Endotracheal Tube Surface, Antibiotics. 10 (2021) 1–14.
[188] S. Amankwah, M. Adisu, K. Gorems, K. Abdella, T.Kassa, Assessment of Phage-Mediated Inhibition and Removal of Multidrug-Resistant *Pseudomonas aeruginosa* Biofilm on Medical Implants, Infect. Drug Resist. 15 (2022) 2797-2811.
[189] Y. Yuan, M.P. Hays, P.R. Hardwidge, J. Kim, Surface characteristics influencing bacterial adhesion to polymeric substrates, RSC Adv. 7 (2017) 14254–14261.
[190] C.P. Stallard, K.A. McDonnell, O.D. Onayemi, J.P. O'Gara, D.P. Dowling, Evaluation of Protein Adsorption on Atmospheric Plasma Deposited Coatings Exhibiting Superhydrophilic to Superhydrophobic Properties, Biointerphases. 7 (2012) 31.
[191] C.I. Pereni, Q. Zhao, Y. Liu, E. Abel, Surface free energy effect on bacterial retention, Colloids Surf B Biointerfaces. 48 (2006) 143–147.
[192] P. Singha, J. Locklin, H. Handa, A review of the recent advances in antimicrobial coatings for urinary catheters, Acta Biomater. 50 (2017) 20–40.
[193] C. Desrousseaux, V. Sautou, S. Descamps, O. Traoré, Modification of the surfaces of medical devices to prevent microbial adhesion and biofilm formation, J. Hosp. Infect. 85 (2013) 87–93.
[194] M.V. Graham, N.C. Cady, Nano and Microscale Topographies for the Prevention of Bacterial Surface Fouling, Coatings 4 (2014) 37–59.
[195] K. Triandafillu, D.J. Balazs, B.O. Aronsson, P. Descouts, P. Tu Quoc, C. van Delden, H.J. Mathieu, H. Harms, Adhesion of Pseudomonas aeruginosa strains to untreated and oxygen-plasma treated poly(vinyl chloride) (PVC) from endotracheal intubation devices, Biomaterials. 24 (2003) 1507–1518.
[196] X. Ding, C. Yang, T.P. Lim, L.Y. Hsu, A.C. Engler, J.L. Hedrick, Y.Y. Yang, Antibacterial and antifouling catheter coatings using surface grafted PEG-b-cationic polycarbonate diblock copolymers, Biomaterials 33 (2012) 6593–6603.
[197] S. Yuan, D. Wan, B. Liang, S.O. Pehkonen, Y.P. Ting, K.G. Neoh, E.T. Kang, Lysozyme-coupled poly(poly(ethylene glycol) methacrylate)-stainless steel hybrids and their antifouling and antibacterial surfaces, Langmuir 27 (2011) 2761–2774.
[198] G. Reid, H. Bialkowska-Hobrzanska, H.C. van der Mei, H.J. Busscher, Correlation between genetic, physico-chemical surface characteristics and adhesion of four strains of Lactobacillus, Colloids Surf B Biointerfaces 13 (1999) 75–81.
[199] C.Y. Loo, P.M. Young, W.H. Lee, R. Cavaliere, C.B. Whitchurch, R. Rohanizadeh, Superhydrophobic, nanotextured polyvinyl chloride films for delaying Pseudomonas aeruginosa attachment to intubation tubes and medical plastics, Acta Biomater. 8 (2012) 1881–1890.
[200] S. Murthy, Nanoparticles in modern medicine: State of the art and future challenges, In. J. Nanomedicine. 2 (2007) 129-141.
[201] J. Klein, Probing the interactions of proteins and nanoparticles, Proc. Natl. Acad. Sci. U S A. 104 (2007) 2029–2030.
[202] N.G. Durmus, E.N. Taylor, F. Inci, K.M. Kummer, K.M. Tarquinio, T.J. Webster, Fructose-enhanced reduction of bacterial growth on nanorough surfaces, Int. J. Nanomedicine. 7 (2012) 537–545.
[203] M.C. Machado, K.M. Tarquinio, T.J. Webster, Decreased Staphylococcus aureus biofilm formation on nanomodified endotracheal tubes: a dynamic airway model, Int. J. Nanomedicine. 7 (2012) 3741–3750.
[204] M.C. Machado, T.J. Webster, Decreased Pseudomonas aeruginosa biofilm formation on nanomodified endotracheal tubes: a dynamic lung model, Int J Nanomedicine. 11 (2016) 3825–3831.
[205] J.T. Seil, N.M. Rubien, T.J. Webster, K.M. Tarquinio, Comparison of quantification methods illustrates reduced Pseudomonas aeruginosa activity on nanorough polyvinyl chloride, J. Biomed. Mater. Res. B. Appl. Biomater. 98 (2011) 1–7.
[206] L.M. Lacroix, M. Lejeune, L. Ceriotti, M. Kormunda, T. Meziani, P. Colpo, F. Rossi, Tuneable rough surfaces: A new approach for elaboration of superhydrophobic films, Surf. Sci. 592 (2005) 182–188.
[207] H.Y. Erbil, A.L. Demirel, Y. Avci, O. Mert, Transformation of a simple plastic into a superhydrophobic surface, Science 299 (2003) 1377–1380.

[208] C.Y. Loo, P.M. Young, W.H. Lee, R. Cavaliere, C.B. Whitchurch, R. Rohanizadeh, Superhydrophobic, nanotextured polyvinyl chloride films for delaying Pseudomonas aeruginosa attachment to intubation tubes and medical plastics, Acta Biomater. 8 (2012) 1881–1890.
[209] J. Valle, S. Burgui, D. Langheinrich, C. Gil, C. Solano, A. Toledo-Arana, R. Helbig, A. Lasagni, I. Lasa, Evaluation of Surface Microtopography Engineered by Direct Laser Interference for Bacterial Anti-Biofouling, Macromol. Biosci. 15 (2015) 1060–1069.
[210] S.T. Reddy, K.K. Chung, C.J. McDaniel, R.O. Darouiche, J. Landman, A.B. Brennan, Micropatterned surfaces for reducing the risk of catheter-associated urinary tract infection: An in vitro study on the effect of sharklet micropatterned surfaces to inhibit bacterial colonization and migration of uropathogenic Escherichia coli, J. Endourol. 25 (2011) 1547–1552.
[211] R.M. May, C.M. Magin, E.E. Mann, M.C. Drinker, J.C. Fraser, C.A. Siedlecki, A.B. Brennan, S.T. Reddy, An engineered micropattern to reduce bacterial colonization, platelet adhesion and fibrin sheath formation for improved biocompatibility of central venous catheters, Clin. Transl. Med. 4 (2015).
[212] R.M. May, M.G. Hoffman, M.J. Sogo, A.E. Parker, G.A. O'Toole, A.B. Brennan, S.T. Reddy, Micro-patterned surfaces reduce bacterial colonization and biofilm formation in vitro: Potential for enhancing endotracheal tube designs, Clin. Transl. Med. 3 (2014) 8.
[213] E.E. Mann, C.M. Magin, M.R. Mettetal, R.M. May, M.K.M. Henry, H. DeLoid, J. Prater, L. Sullivan, J.G. Thomas, M.D. Twite, A.E. Parker, A.B. Brennan, S.T. Reddy, Micropatterned Endotracheal Tubes Reduce Secretion-Related Lumen Occlusion, Ann. Biomed. Eng. 44 (2016) 3645–3654.
[214] R.J. Worthington, C. Melander, Combination approaches to combat multidrug-resistant bacteria, Trends Biotechnol. 31 (2013) 177–184.
[215] K.R. Allison, M.P. Brynildsen, J.J. Collins, Metabolite-enabled eradication of bacterial persisters by aminoglycosides, Nature 473 (2011) 216–220.
[216] J. Milenković, J. Hrenović, I. Goić-Barišić, M. Tomić, N. Rajić, Antibacterial activity of copper-containing clinoptilolite/ PVC composites toward clinical isolate of Acinetobacter baumannii, J. Serb. Chem. Soc. 80 (2015) 819–826.
[217] J. Milenkovic, J. Hrenovic, I. Goic-Barisic, M. Tomic, J. Djonlagic, N. Rajic, Synergistic anti-biofouling effect of Ag-exchanged zeolite and D-Tyrosine on PVC composite against the clinical isolate of Acinetobacter baumannii, Biofouling 30 (2014) 965–973.
[218] M. Alavi, M. Rai, Recent progress in nanoformulations of silver nanoparticles with cellulose, chitosan, and alginic acid biopolymers for antibacterial applications, Appl. Microbiol. Biotechnol. 103 (2019) 8669–8676.
[219] S. Hajji, S. ben Khedir, I. Hamza-Mnif, M. Hamdi, I. Jedidi, R. Kallel, S. Boufi, M. Nasri, Biomedical potential of chitosan-silver nanoparticles with special reference to antioxidant, antibacterial, hemolytic and in vivo cutaneous wound healing effects, Biochim. Biophys. Acta Gen. Subj. 1863 (2019) 241–254.
[220] A. Mohandas, S. Deepthi, R. Biswas, R. Jayakumar, Chitosan based metallic nanocomposite scaffolds as antimicrobial wound dressings, Bioact Mater. 3 (2018) 267–277.
[221] D.S. Jones, C.P. McCoy, G.P. Andrews, R.M. McCrory, S.P. Gorman, Hydrogel Antimicrobial Capture Coatings for Endotracheal Tubes: A Pharmaceutical Strategy Designed to Prevent Ventilator-Associated Pneumonia, Mol. Pharm. 12 (2015) 2928–2936.
[222] A.C. Zangirolami, L.D. Dias, K.C. Blanco, C.S. Vinagreiro, N.M. Inada, L.G. Arnaut, M.M. Pereira, V.S. Bagnato, Avoiding ventilator-associated pneumonia: Curcumin-functionalized endotracheal tube and photodynamic action, Proc. Natl. Acad. Sci. U S A. 117 (2020) 22967–22973.
[223] C. Adlhart, J. Verran, N.F. Azevedo, H. Olmez, M.M. Keinänen-Toivola, I. Gouveia, L.F. Melo, F. Crijns, Surface modifications for antimicrobial effects in the healthcare setting: a critical overview, J. Hosp. Infect. 99 (2018) 239–249.
[224] B. Kong, J.H. Seog, L.M. Graham, S.B. Lee, Experimental considerations on the cytotoxicity of nanoparticles, Nanomedicine 6 (2011) 929–941.
[225] M. Ojeil, C. Jermann, J. Holah, S.P. Denyer, J.Y. Maillard, Evaluation of new in vitro efficacy test for antimicrobial surface activity reflecting UK hospital conditions, J. Hosp. Infect. 85 (2013) 274–281.
[226] J.F. Fernandez, S.M. Levine, M.I. Restrepo, Technologic Advances in Endotracheal Tubes for Prevention of Ventilator-Associated Pneumonia, Chest. 142 (2012) 231–238.
[227] B.H. Mao, Z.Y. Chen, Y.J. Wang, S.J. Yan, Silver nanoparticles have lethal and sublethal adverse effects on development and longevity by inducing ROS-mediated stress responses, Sci. Rep. 8 (2018) 2445.
[228] A.A. de Lima e Silva, M.A. Ribeiro de Carvalho, S.A.L. L de Souza, P.M. Teixeira Dias, R.G. da Silva Filho, C.S. de Meirelles Saramago, C.A. de Melo Bento, E. Hofer, Heavy metal tolerance (Cr, Ag and Hg) in bacteria isolated from sewage, Braz. J. Microbiol. 43 (2012) 1620-1631.
[229] S. Sütterlin, M. Dahlö, C. Tellgren-Roth, W. Schaal, Melhus, High frequency of silver resistance genes in invasive isolates of Enterobacter and Klebsiella species, J. Hosp. Inf. 96 (2017) 256–261.

[230] B. Ozcelik, P. Pasic, P. Sangwan, C.L. Be, V. Glattauer, H. Thissen, R.A. Boulos, Evaluation of the Novel Antimicrobial BCP3 in a Coating for Endotracheal Tubes, ACS Omega. 5 (2020) 10288–10296.
[231] S.M. Dizaj, F. Lotfipour, M. Barzegar-Jalali, M.H. Zarrintan, K. Adibkia, Antimicrobial activity of the metals and metal oxide nanoparticles, Mater. Sci. Eng. C. Mater. Biol. Appl. 44 (2014) 278–284.
[232] R.K. Singh, J.C. Knowles, H.W. Kim, Advances in nanoparticle development for improved therapeutics delivery: nanoscale topographical aspect, J. Tissue Eng. 10 (2019).
[233] F. Martinez-Gutierrez, P.L. Olive, A. Banuelos, E. Orrantia, N. Nino, E.M. Sanchez, F. Ruiz, H. Bach, Y. Av-Gay, Synthesis, characterization, and evaluation of antimicrobial and cytotoxic effect of silver and titanium nanoparticles, Nanomedicine 6 (2010) 681–688.
[234] K. Gold, B. Slay, M. Knackstedt, A.K. Gaharwar, Antimicrobial Activity of Metal and Metal-Oxide Based Nanoparticles, Adv. Therapy. 1 (2018) 1700033.
[235] A. Roy, O. Bulut, S. Some, A.K. Mandal, M.D. Yilmaz, Green synthesis of silver nanoparticles: biomolecule-nanoparticle organizations targeting antimicrobial activity, RSC Adv. 9 (2019) 2673–2702.
[236] M. Schieber, N.S. Chandel, ROS function in redox signaling and oxidative stress, Curr. Biol. 24 (2014).
[237] M. Ahonen, A. Kahru, A. Ivask, K. Kasemets, S. Kõljalg, P. Mantecca, I.V. Vrček, M.M. Keinänen-Toivola, F. Crijns, Proactive Approach for Safe Use of Antimicrobial Coatings in Healthcare Settings: Opinion of the COST Action Network AMiCI, Int. J. Environ. Res. Public Health 14 (2017) 366.
[238] K. Glinel, P. Thebault, V. Humblot, C.M. Pradier, T. Jouenne, Antibacterial surfaces developed from bio-inspired approaches, Acta Biomater. 8 (2012) 1670–1684.
[239] E.J. Gudiña, V. Rangarajan, R. Sen, L.R. Rodrigues, Potential therapeutic applications of biosurfactants, Trends Pharmacol. Sci. 34 (2013) 667–675.
[240] A.L. Hilchie, K. Wuerth, R.E.W. Hancock, Immune modulation by multifaceted cationic host defense (antimicrobial) peptides, Nat. Chem. Biol. 9 (2013) 761–768.
[241] M.M. Hashemi, J. Rovig, J. Bateman, B.S. Holden, T. Modelzelewski, I. Gueorguieva, M. von Dyck, R. Bracken, C. Genberg, S. Deng, P.B. Savage, Preclinical testing of a broad-spectrum antimicrobial endotracheal tube coated with an innate immune synthetic mimic, J. Antimicrob. Chemother. 73 (2018) 143–150.
[242] N. Tawil, E. Sacher, R. Mandeville, M. Meunier, Strategies for the immobilization of bacteriophages on gold surfaces monitored by surface plasmon resonance and surface morphology, J. Phys. Chem. 117 (2013) 6686–6691.
[243] Z. Hosseinidoust, T.G.M. van de Ven, N. Tufenkji, Bacterial capture efficiency and antimicrobial activity of phage-functionalized model surfaces, Langmuir 27 (2011) 5472–5480.
[244] H. Anany, W. Chen, R. Pelton, M.W. Griffiths, Biocontrol of Listeria monocytogenes and Escherichia coli O157:H7 in meat by using phages immobilized on modified cellulose membranes, Appl. Environ. Microbiol. 77 (2011) 6379–6387.
[245] W. Fu, T. Forster, O. Mayer, J.J. Curtin, S.M. Lehman, R.M. Donlan, Bacteriophage cocktail for the prevention of biofilm formation by Pseudomonas aeruginosa on catheters in an in vitro model system, Antimicrob. Agents Chemother. 54 (2010) 397–404.
[246] Z. Hosseinidoust, A.L.J. Olsson, N. Tufenkji, Going viral: Designing bioactive surfaces with bacteriophage, Colloids Surf. B. Biointerfaces. 124 (2014) 2–16.
[247] M. Połaska, B. Sokołowska, Bacteriophages-a new hope or a huge problem in the food industry, AIMS Microbiol. 5 (2019) 324–347.
[248] K. Manoharan, S. Bhattacharya, Superhydrophobic surfaces review: Functional application, fabrication techniques and limitations, J Micromanufacturing 2 (2019) 59–78.
[249] H. Wolfmeier, D. Pletzer, S.C. Mansour, R.E.W. Hancock, New Perspectives in Biofilm Eradication, ACS Infect. Dis. 4 (2018) 93–106.
[250] W. Zimmerli, F.A. Waldvoge, P. Vaudaux, D.E. Nydegger, Pathogenesis of Foreign Body Infection: Description and Characteristics of an Animal Model, J. Infect. Dis. 146 (1982) 487–497.
[251] L. Berra, F. Curto, G. Li Bassi, P. Laquerriere, A. Baccarelli, T. Kolobow, Antibacterial-coated tracheal tubes cleaned with the Mucus Shaver: A novel method to retain long-term bactericidal activity of coated tracheal tubes, Intensive Care Med. 32 (2006) 888–893.
[252] M. Pirrone, D.A.E. Imber, F. Marrazzo, R. Pinciroli, C. Zhang, L. Bry, M.L. Delaney, A.M. Dubois, J.G. Thomas, L. Nistico, R. Melton-Kreft, E.A. Bittner, R.M. Kacmarek, L. Berra, Silver-coated endotracheal tubes cleaned with a mechanism for secretion removal, Respir. Care 64 (2019) 1–9.
[253] B. Mahmodiyeh, A. Kamali, N. Zarinfar, M.M. Joushani, The Effect Of Silver-Coated Endotracheal Tube On The Incidence Of Ventilator-Induced Pneumonia In Intubated Patients Admitted To The Intensive Care Unit (ICU), Sys. Rev. Pharm. 12 (2021) 254–258.
[254] Y. Hu, X. Ji, D. Wei, J. Deng, Antibacterial Properties and Application of Nanosilver Material in the Tracheal Tube, J. Nanosci. Nanotechnol. 20 (2020) 6542–6546.

[255] L. Berra, F. Curto, G. Li Bassi, P. Laquerriere, B. Pitts, A. Baccarelli, T. Kolobow, Antimicrobial-coated endotracheal tubes: An experimental study, Intensive Care Med. 34 (2008) 1020–1029.
[256] J. Rello, M. Kollef, E. Diaz, A. Sandiumenge, Y. del Castillo, X. Corbella, R. Zachskorn, Reduced burden of bacterial airway colonization with a novel silver-coated endotracheal tube in a randomized multiple-center feasibility study, Crit Care Med. 34 (2006) 2766–2772.
[257] A. Seitz, J.E. Baker, N.C. Levinsky, M.C. Morris, M.J. Edwards, E. Gulbins, T.C. Blakeman, D. Rodriquez, R.D. Branson, M. Goodman, Antimicrobial Coating Prevents Ventilator-Associated Pneumonia in a 72 hour Large Animal Model, J. Surg. Res. 267 (2021) 424–431.
[258] K.M. Tarquinio, N.K. Kothurkar, D.Y. Goswami, R.C. Sanders, A.L. Zaritsky, A.M. LeVine, Bactericidal effects of silver plus titanium dioxide-coated endotracheal tubes on Pseudomonas aeruginosa and Staphylococcus aureus, Int. J. Nanomedicine. 5 (2010) 177–183.

Table 2. Antimicrobial materials reported for endotracheal tubes between 2002 and 2022

Type of designed material	Approach(es)	Source material	Antimicrobial compound/feature	Microorganism(s) tested	Mode of growth/Testing model	Main Results/Remarks	Ref.
Active Material	Metal-based coatings (Silver)	Commercially available ETT	Polyamide/AgNPs composite	· *A. baumannii* (including carbapenem-resistant) · *C. albicans* · *Enterococcus faecalis* · *P. aeruginosa* (including carbapenem-resistant) · *K. pneumoniae* (including extended-spectrum b-lactamase producing strain) · *MRSA* · *S. aureus*	*In vitro*	· Coated ETT resulted in a significant difference in reducing both planktonic growth and microbial adhesion of single and mixed-species cultures, compared with uncoated ETT. · A time-kill assay demonstrated rapid bactericidal effects of the coating on bacterial growth and cell adhesion to ETT surface. · Biofilm formation by *P. aeruginosa* and *S. aureus* was inhibited (4-6 log) after 72 h. · Broad-spectrum activity against Gram-positive, and Gram-negative bacteria as well as *C. albicans*. · Prolonged antimicrobial activity (4 weeks).	[64]
		Commercially available ETT	Silver ions	· *P. aeruginosa*	*In vivo* (dog model)	· Delay (1.4 days) in bacterial colonization of ETT and reduced number of attached bacteria. · Reduced lung inflammation.	[118]
		PVC	Silver ions	· *P. aeruginosa*	*In vitro*	· Complete reduction of initial bacterial adhesion. · Reduced biofilm formation over a prolonged period of time (72 h).	[119]
		Commercially available ETT	Silver ions	· *P. aeruginosa*	*In vitro*	· 2-log inhibition of bacterial attachment to the ETT, after overnight challenge. · Zone of inhibition, indicative of silver release from the ETT.	[120]

PVA hydrogel	AgNPs	· *P. aeruginosa* · *S. aureus*	*In vitro*	· Reduction of biofilm formation of both species, especially *P. aeruginosa* (about 1 log after 18 h). · No toxicity against lung epithelial cells.	[122]
Commercially available ETT	AgNPs	· *P. aeruginosa* · *S. aureus*	*In vitro*	· Inhibition of adhesion of both species to ETT (99,9%). · No toxicity against human lung epithelial cells. · Better efficacy than a commercially available silver-coated ETT.	[123]
Polyethylene ETT	Silver-silicon dioxide	· *E. coli*	*In vitro* *In vivo* (rabbit and golden hamster model)	· Antimicrobial activity reduced after contact (93,7%). · In rabbits, no pyrogenic effect was observed and haemolysis test showed biocompatibility with red blood cells. · In gold hamsters, no irritation of oral mucosa was found.	[126]
Commercially available ETT	NMA of gold/silver/palladium (BIP ETT)	· *Enterococci spp.* · *Haemophilus parainfluenzae* · *Neisseria spp.* · *Staphylococci* · *Streptococcus*	*In vivo* (ICU patients)	· The BIP ETT was well tolerated and presented good clinical short-term performance (5 h), while presenting low level of bacterial colonization.	[128]
Commercially available ETT	NMA of gold/silver/palladium (BIP ETT)	· Unknown	*In vivo* (ICU patients)	· No significant reduction in ICU length of stay, MV duration, tracheostomy rate and hospital mortality. · VAP incidence reduced by 5.1%. · Number of antibiotic days	[129]

				reduced by 6.6%. · Tracheal pathogen colonization reduced by 3.7% in the NMA-coated compared with non-coated subglottic suctioning ETTs.	
Commercially available ETT	NMA of gold/silver/palladium (BIP ETT)	· Unknown	*In vivo* (ICU patients)	· No significant reduction in ICU length of stay, MV duration, tracheostomy rate and hospital mortality. · VAP incidence reduced by 15.3%. · Mean MV duration reduced by 1.8 days.	[130]
Commercially available ETT	NMA of gold/silver/palladium (BIP ETT)	· Unknown	*In vivo* (ICU patients)	· Reduction in the volume of secretions, incidence of purulent secretions, fever, leukocytosis, culture positive, and the onset of VAP symptoms. · Incidence of VAP reduced from 26% to 18% (intervention vs control groups).	[253]
Commercially available ETT	Nanosilver (AgNPs)-polyurethane polymer	· *E. coli* · *S. aureus*	*In vivo* (rat model)	· Potent antimicrobial and antibiofilm proliferation properties. · Thickness and cell numbers of biofilm formed by catheterization 48 and 72 h after rat operation was significantly lower than that in the control group.	[254]
Commercially available ETT	Silver sulfadiazine	· *P. aeruginosa*	*In vitro* *In vivo* (sheep model)	· No bacterial adhesion up to 72 h on ETT. · In sheep, after 24 h of ventilation, no bacterial growth was detected on the ETT, ventilator tubing or lower respiratory tract.	[255]

	Commercially available ETT	Silver ions	· *A. baumannii* · *Enterobacteriaceae* · *H. influenzae* · *P. aeruginosa* · *S. aureus* · *S. pneumoniae* · *Streptococcus viridans group* · Other Non-fermentative Gram-negative bacilli	*In vivo* (ICU patients)	· Reduced colonization rates by patient (29%). · Delayed colonization on the inner tube surface (1.8 vs. 3.2 days in control device) and on the tube · Reduced bacterial burden in tracheal aspirates.	[256]
Metal-based coatings (ZnO)	Commercially available ETT	ZnO-NPs	· *S. aureus*	*In vitro*	· Reduction of biofilm formation (55%) after 72 h. · After 24 h challenge, membrane's compromise was observed after live/dead staining.	[137]
	PVC taken from a commercially available ETT	ZnO-NPs	· *S. aureus*	*In vitro*	· Reduction (87%) of biofilm formation after 24 h.	[138]
Metal-based coatings (TiO_2)	Commercially available ETT	TiO_2-NPs (commercial and N-doped)	· *P. aeruginosa* · *S. aureus*	*In vitro*	· Inhibition of bacterial growth under visible fluorescent light, after 24 h. · N-doped NPs more efficient against *S. aureus*.	[154]
	PVC medical grade	Iodine-modified TiO2	· *E. coli*	*In vitro* *In vivo* (pig model)	· Photocatalytic activity able to kill bacteria under visible light irradiation after 30 min. · Decrease of bacterial attachment and biofilm formation after 72 h. · Reduced inflammation of tracheal and lung tissues in pigs, after 72 h ventilation.	[155]
Metal-based coatings (Se)	PVC medical grade	SeNPs	· *S. aureus*	*In vitro*	· Bacterial colonization was reduced by 80%. · Better antimicrobial efficacy than a silver-coated ETT.	[147]

Biocides impregnation	Commercially available ETT	Gardine and Gendine	· *A. baumannii* · *C. albicans* · *E. cloacae* · *K. pneumoniae* · MRSA · *P. aeruginosa*	*In vitro*	· Complete inhibition of the adhesion of all species after 24h. · Antimicrobial activity was prolonged for 2 weeks against MRSA. · Better antimicrobial efficacy than a silver-coated ETT.	[127]
	Commercially available ETT	Gendine		*In vitro*	· Antimicrobial activity evidenced by an inhibition zone up to 3 weeks against all species. · Complete inhibition of MRSA, *C. parapsilosis* and *E. coli* after 24 h. · No toxicity against mouse fibroblast cells.	[160]
	PVC	Hexetidine	· *P. aeruginosa* · *S. aureus*	*In vitro*	· Reduction of *P. aeruginosa* adhesion by 52%, after 7 days. · Reduction of S. aureus adhesion by 75%, after 7 days.	[162]
	Commercially available ETT	Poly(lauryl acrylate)-based nanocapsules encapsulating clove oil or eugenol	· *K. pneumoniae* · MRSA	*In vitro*	· Both species were affected by the antibacterial loaded nanocapsules in a dose dependent manner, with >50% inhibition at a concentration of 0.625 mg mL−1 of eugenol or clove oil. · The observed surface-binding reduction of bacteria, biocompatibility and slow release of eugenol demonstrate the potential of this strategy for clinical applications.	[163]
	PVC	NO (SNAP as NO donor)	· *P. aeruginosa*	*In vitro*	· NO release over a 7-day period without altering the mechanical properties of the ETT. · Reduction of *P. aeruginosa* adhesion by 92.72 ± 0.97% (1.5 log) compared with the control	[164]

					ETT, after 24 h.	
	Commercially available ETT	Styrylbenzene-based (BCP3)	· MSSA and MRSA · *P. aeruginosa*	*In vitro*	· A concentration-dependent release of BCP3 was observed for at least 31 days. · After 24 h, functionalized surfaces inhibited mainly the growth of MSSA (a maximum of 95 %) and MRSA (a maximum of 80 %) and to a smaller extent *P. aeruginosa* (maximum of 63 %). · No cytotoxicity against L929 fibroblasts.	[230]
Bio-inspired antimicrobials (AMPs)	Commercially available ETT	Lasioglossin-III	· *S. epidermidis* · *S. pneumoniae* · Pooled human microbiome samples	*In vitro*	· Prolonged, linear peptide release over 1 week. · Inhibition of planktonic bacterial growth and adhesion to tubes after 24 h. · No toxicity against laryngotracheal fibroblasts or lung epithelial cells.	[173]
Bio-inspired antimicrobials (Ceragenins)	Commercially available ETT	Ceragenin CSA-131	· *C. albicans* · *C. auris* · *K. pneumoniae* · MRSA · *P. aeruginosa*	*In vitro* *In vivo* (porcine model)	· Prevention of the colonization of ETT and biofilm formation for several days (from 4 to 16 days), depending on the species tested. · Prevention of mixed biofilms formation of MRSA/*P. aeruginosa* and *P. aeruginosa*/*C. auris* for up to 2 and 3 days. · In pigs ventilated for 24 h, no abnormalities were found in the oropharyngeal area, trachea or lungs. · Histological analyses showed no inflammation and CSA-131 could not be detected in blood system.	[241]

	Bio-inspired antimicrobials (Surfactants)	Commercially available ETT	Cholesterol and lecithin (different ratios)	· *P. aeruginosa* · *S. aureus*	*In vitro*	· Reduction of bacterial adhesion by more than 90%, after 8h.	[184]
		Commercially available ETT	Sphingosine	· *A. baumannii* · *P. aeruginosa* · *S. aureus*	*In vitro* *In vivo* (mice)	· Prevention of biofilm formation of all bacterial species after 24 h *in vitro*. · Prevention of bacterial colonization in vivo. · Coatings stable with no side effects on tracheal epithelial cells or inflammation.	[185]
	Bio-inspired antimicrobials (Phages)	Commercially available ETT	Phage cocktail	· *P. aeruginosa*	*In vitro*	· Antimicrobial action was strain dependent. · Phages-coated tubes did not promote substantial changes in metabolic activity. · Limited anti-biofilm effect after testing the tubes in artificial sputum medium up to 168 h.	[187]
		Commercially available ETT	Phages ΦJHS-PA1139 and ΦSMK-PA1139	· MDR *P. aeruginosa*	*In vitro*	· Phage-coated ETT segments of 12 -mm in length inhibited bacterial colonization by 1.2 log up to 3.2 log comparing with non-coated segments following 6 h coating. · Phage treatment of ETT segments yielded 1.0 log up to 1.6 log reductions in MDR biofilms for phage ΦJHS and 1.6 log up to 2.4 log reductions for phage ΦSMK.	[188]
Passive Materials	Hydrophobic/ Hydrophilic surfaces	PVC	Oxygen plasma treatment	· *P. aeruginosa*	*In vitro*	· Reduction of the number of adhered bacteria by 70%.	[195]

		PVC	Superhydrophobic surfaces	· *P. aeruginosa*	*In vitro*	· No bacterial attachment in the first 6 h. · Reduction of biofilm formation after 24 h.	[199]
	Nanomodified surfaces	Commercially available ETT	Nanoscale surface features created by a fungal lipase	· *S. aureus*	*In vitro*	· Reduction of 1.5 log of the total number of adhered bacterial cells, after 24 h.	[203]
		Commercially available ETT	Nanoscale surface features created by a fungal lipase	· *P. aeruginosa*	*In vitro*	· Reduction of 2.7 log of the total number of adhered bacterial cells, after 24 h.	[204]
		Commercially available ETT	Nanoscale surface features created by a fungal lipase	· *P. aeruginosa*	*In vitro*	· Reduction of the number of bacterial cells adhered by 40%, after 24h.	[205]
	Micropatterned surfaces	Silicon wafers	Engineered micro-pattern of surfaces using the Sharklet pattern design	· *A. baumannii* · *E. coli* · *K. pneumoniae* · MRSA · *P. aeruginosa*	*In vitro*	· Reduction on the attachment of all species (from 1 to 3 log). · Reductions of MRSA and *P. aeruginosa* biofilms (67% and 58%).	[212]
		Thermoplastic polyurethane ETT	Engineered micro-pattern of surfaces using the Sharklet pattern design	· *P. aeruginosa*	*In vitro*	· Reduction of biofilm accumulation by 71%. · Reduction of artificial mucus accumulation.	[213]

Combinatorial Materials	Commercially available ETT	CS-AgNPs@PAAm-Gelatin composite (CS=chitosan; PAAm=polyacrylamide)	· *P. aeruginosa* · *S. aureus*	*In vitro* (broncho-lung model) *In vivo* (porcine MV model)	· Excellent antibacterial properties in both *in vitro* and *in vivo* models. · Antibiofouling property by decreasing lumen occlusion · Good biocompatibility (tested after 1, 4 and 7 days against fibroblasts). · Good stability, by keeping antimicrobial performance to up to 21 days. · Coated ETTs could decrease in vivo lumen occlusion by artificial mucus for up to 97%.	[79]
	Commercially available ETT	Chlorhexidine and silver carbonate	· *A. baumannii* · *Enterobacter aerogenes* · MRSA · *P. aeruginosa* · *S. aureus*	*In vitro*	· Reduction of 4-6 log of bacterial colonization of ETT, after 5 days, using an airway model.	[161]
	Commercially available ETT	Nanoscale surface features created by a fungal lipase and Fructose	· *S. aureus*	*In vitro*	· Fructose coating alone caused a reduction of 38% of bacterial adhesion. · Nanocoated surfaces alone caused a reduction of 45% of bacterial adhesion.	[202]
	Commercially available ETT	Copper and zeolite	· MDR *A. baumannii*	*In vitro*	· A maximum reduction of immobilized cells of 14%, after 24 h. · Antimicrobial efficacy was lower than the silver coating.	[216]

	Commercially available ETT	Silver, zeolite and tyrosine	· MDR *A. baumannii*	*In vitro*	· Combination of tyrosine to natural zeolite with silver increased the antimicrobial activity against immobilized cells (from 2.5 to 2.8 log achieving almost 100% reduction) after a contact of 24 h. · Combination of both strategies caused a higher reduction of 60% of bacterial adhesion, evidence of a synergistic effect.	[217]
	Commercially available ETT	Hydrogels of hydroxyethyl methacrylate (HEMA):methacrylic acid (MAA) entrapped with nebulized gentamicin	· *P. aeruginosa* · *S. aureus*	*In vitro*	· No bacterial adherence occurred to gentamicin-containing HEMA:MAA copolymers. · 70:30 HEMA:MAA hydrogel exhibited >20 days persistence against *S. aureus* and *P. aeruginosa.* · Viable bacteria were not observed on the gentamicin-treated p(HEMA: MAA) copolymers, whereas growth was observed on gentamicin-treated p(HEMA).	[221]
	Commercially available ETT	Curcumin and photodynamic action	· *E. coli* · *P. aeruginosa* · *S. aureus*	*In vitro*	· After 24 h, the combined effect of curcumin-functionalized ETT and light application caused a reduction of about 95%, 72% and 73 % on the adhesion and biofilm formation of *S. aureus*, *E. coli* and *P. aeruginosa*, respectively. · Curcumin-ETT remains active after six photodynamic sessions every 24h up to 6 days with 23.76% of microbial reduction.	[222]

		Commercially available ETT	Antimicrobial lipid (octadecylamine), mucolytic (N-acetylcysteine), and antibiotics (doxycycline and levofloxacin)	No inoculation with exogenous bacteria	*In vivo* (pig model)	· Pigs ventilated with coated tubes were less hypoxic, had less bacterial colonization of the lungs and survived longer than pigs ventilated with uncoated tubes for 72 h.	[257]
		Commercially available ETT	Combinations of silver, TiO_2 and Degussa (metallic alloy)	· *P. aeruginosa* · *S. aureus*	*In vitro*	· Combination of TiO_2 and silver reduced *P. aeruginosa* growth after 24 h. · Combination of Degussa with TiO_2 reduced *P. aeruginosa* growth up to 48 h. · No reduction was found against *S. aureus* up to 5 days.	[258]

Legend:
AgNPs - Silver nanoparticles;
BIP - Bactiguard®'Infection Protection;
ETT - Endotracheal tube;
HEMA:MAA - hydroxyethyl methacrylate: methacrylic acid
MDR - Multidrug resistant
MRSA - methicilin-resistant *S. aureus*;
MSSA - methicilin-sensitive *S. aureus*;
NMA - Noble metal alloy;
NO - Nitric oxide
NPs -nanoparticles;
PVA- polyvinyl alcohol;
PVC- polyvinyl chloride;
Se - Selenium;
SeNPs - Selenium nanoparticles;
SNAP - S -Nitroso-N- acetylpenicillamine
TiO2-NPs - Titanium dioxide nanoparticles;
ZnO-NPs - zinc oxide nanoparticles

Statement of significance

The use of the endotracheal tube (ETT) in patients requiring mechanical ventilation is associated with the development of ventilator-associated pneumonia (VAP). Its rapid surface colonization and biofilm formation are critical events for VAP pathogenesis and relapses. This review provides a comprehensive overview on the relevance/implications of the ETT biofilm in VAP, and on how research on antimicrobial ETT surface coating/modification technology has evolved over the last two decades. Despite significant technological advances, the limited number of gathered reports (46), highlights difficulty in overcoming certain hurdles associated with VAP (e.g., persistent colonization/biofilm formation; mechanical ventilation duration; hospital length of stay; VAP occurrence), which makes this an evolving, complex, and challenging matter. Challenges and opportunities in the field are discussed.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: