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Review Article

Dramatic increase of Resistant Microorganisms Can we Prevent the Increase of Mutiresistant Microorganisms. A Review

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Abstract

Clinical environments provide an ideal reservoir for the growth, proliferation, and transmission of pathogenic organisms. Surfaces in hospitals e.g., hospital furniture, ECG lead wires and other cables, push buttons of infusion pumps, control knobs of ventilation machines, textiles as well as implantable biomaterials like central venous catheters, urologic catheters, endotracheal tubes are contaminated increasingly frequent with multiseriate microorganisms. These microorganisms are distributed by the hands of the nursing personnel throughout the hospital with serious, life-threatening consequences. 1.8 million patients suffer from a nosocomial infection per year in Europe; approximately 180,000 deaths are attributed to these infections. The Centers for Disease Control (CDC) estimates that 2 million U.S. patients per year acquire a hospital-related infection. These infections cause 90,000 deaths each year and cost an average of $47,000 per patient to treat. The added cost to hospitals is $4.8 billion annually for extended care treatment. Microorganisms show an increasing rate of resistance against most antibiotics including carbapenems as the last available antibiotic. 700,000 deaths have been reported worldwide, 30 000 deaths alone in Europe during the last year due to infections where no effective antimicrobial substance was available. The use of disinfectants is ostensibly intended to remove/kill pathogens on surfaces. However, studies have shown that more than one-half the time, surfaces are not adequately cleaned or are re-contaminated within minutes. Much emphasis has been put therefore on hand disinfection. However, there are also reports of the emergence of alcohol tolerant/insensitive microorganisms e.g., vancomycin resistant enterococci. This phenomenon has the potential to undermine the effectiveness of alcohol based disinfectant standard precautions. The reason for this dramatic development of resistant microorganisms is still under debate. The indiscriminate use of antibiotics for prevention of a bacterial superinfections e.g., sinusitis, otitis media after a viral infection is frequently incriminated, however this seems to have little impact on the occurrence of multi-resistant hospital pathogens in general. However individual patients are seriously affected by the selection of multi-resistant pathogens. In contrast there is increasing evidence that the widespread use of disinfectants is responsible: disinfectants - analogous to antibiotics - must be incorporated into the metabolism of microorganisms. This is inevitably associated with induction of resistance by transfer of resistance plasmids e.g., induction of efflux pumps. 10246 publications (PubMed Jan 2022) are available in the international literature which document the resistance of microorganisms against disinfectants; 649 publications describe the cross resistance with antibiotics, at the same time there are 11 440 reports on the toxicity of disinfectants.

Introduction

For people in the 21st century, it is hard to imagine the world before antibiotics. At the beginning of the 20th century, as many as nine women out of every 1,000 who gave birth died, 40 percent from sepsis. In some cities as many as 30 percent of children died before their first birthday. One of every nine people who developed a serious skin infection died, even from something as simple as a scrape or an insect bite. Pneumonia killed 30 percent of those who contracted it; bacterial meningitis was almost universally fatal. Ear

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infections caused deafness; sore throats were not infrequently followed by rheumatic fever and heart failure. Surgical procedures were associated with high morbidity and mortality due to infection. This picture changed dramatically with three major developments: improvements in public health, vaccines, and antibiotics. Over the course of the 20th century, deaths from infectious diseases declined markedly and contributed to a substantial increase in life expectancy. Antibiotics have saved millions of lives. But the world is now at dire risk of losing this progress. Bacteria and other microbes evolve in response to their environment and inevitably develop mechanisms to resist being killed by antibiotics but also disinfectants [1,2]. For many decades, the problem was manageable as the growth of resistance was slow and the pharmaceutical industry continued to create new antibiotics. Over the past decade, however, this brewing problem has become a crisis. The evolution of antibiotic resistance is now occurring at an alarming rate and is outpacing the development of new countermeasures capable of thwarting infections in humans [3]. This situation threatens patient care, economic growth, public health, agriculture, economic security, and national security.

The UN Interagency Coordination Group on Antimicrobial Resistance demands therefore immediate, coordinated, and ambitious measures to combat this problem [4].

1) Investigations to improve our surveillance of the rise of antibiotic-resistant bacteria are required to enable an effective response, stop outbreaks, and limit the spread of antibiotic-resistant organisms to implement appropriate infection control.

2) Increase the longevity of current antibiotics, by improving the appropriate use of existing antibiotics, preventing the spread of antibiotic-resistant bacteria and

3) scaling up proven interventions to decrease the rate at which microbes develop resistance to current antibiotics.

4) Increasing the rate at which new antibiotics, as well as other interventions, e.g., alternative antimicrobial substances and modes of application are developed

Ad 1: Human Health Care

Use and overuse of antibiotics. Antibiotics are among the most prescribed drugs used in human medicine. CDC estimates, however, that up to 50 percent of all the antibiotics prescribed for patients who don't need them or are not optimally use them [5]. Reasons for antibiotic overuse in health care include lack of rapid diagnostic tests and pressure from the patient (or the patient's family) due to insufficient understanding of antibiotic use. This misuse and overuse of antibiotics in human medicine, both in the United States and internationally, is a major contributor to rising antibiotic resistance in individual patients [6]. The impact on the development of multi resistant microorganisms in intensive care units, however, is underestimated and effective countermeasures are not adequately investigated. Fact is, that bacterial superinfection ensues in 25 – 40% of infants and children because of a viral respiratory tract infection by clogging the paranasal opening, the Eustachian tube and impairing mucociliary clearance. Stagnant secretions in the paranasal sinus and the middle ear cavity are contaminated with bacterial microorganisms and result in serious infections – early administration of antibiotics it thought to prevent this. However, this is less effective than anticipated and simultaneously induces the emergence of resistant microorganisms. It is feasible to prevent bacterial superinfections by anti-inflammatory medication and by the improvement of the mucociliary clearance by herbal extracts Triterpenes and 1.8. Cineol is contained in a few herbal extracts e.g., thyme, gentian, sorrel, primulae [7]. These herbal extracts contain substances which decrease the formation of proinflammatory cytokines by inhibition of the arachidonic acid metabolism – the precursors of cytokines. By those means cineol as well as triterpenes exhibit strong antiinflammatory properties which prevent the emergence of submucous edema responsible for bacterial superinfections of paranasal sinus and middle ear cavity [8]. Simultaneously these herbal remedies improve the mucociliary clearance by increasing ciliary motility, harmonisation of the viscosity of nasal and tracheal secretion. Clinical trials CPMP/ICH/135/95 show excellent efficacy with complete lack of side effects [9].

Ad 2: Animal Agriculture.

Medically important antibiotics are also extensively used in animal agriculture not only to treat sick animals, but also to promote animal growth and to prevent infections. All these uses promote the development of antibiotic resistance among bacteria in animals, and these resistant strains do, at least in some cases, spread to humans. Antibiotics administered to piglets prevent diarrhoea and death and result in improved gain of weight. Usually non absorbable antibiotics e.g., colistin are administered. These antibiotics select resistant microorganisms in the faecal flora which are excreted by slurry. This is distributed as fertiliser into the environment contaminating vegetables and fruits (Figure 1). The extent to which antibiotic resistant strains in animal agriculture contributes to human infections is a matter of controversy, the risks to human health posed by the agricultural use of antibiotics are however, appropriately, a matter of serious concern. There is a highly efficient innovative technology which prevents adherence and colonization of mucous membranes in the gut – a necessary requirement for pathogenicity of microorganisms. Gram negative bacteria, mainly E. coli adhere on gal 1-4 gal structures on epithelial cells with their fimbriae. Pectin is composed of several gal 1 – 4 galactose molecules. These di- or tri terpenes i.e., acid galacturonides obtained by cooking of pectineus function as receptor analogues and prevent the adherence of bacterial microorganisms on epithelial cells; the microorganisms are eliminated in the faeces without induction of resistance [10]. Figure 2 shows the prevention of diarrhoea in piglets comparing acid galacturonides versus an antibiotic (tylosis phosphate). The galacturonide turns out to be more effective in prevention of diarrhoea than the antibiotic just as well as in the prevention of death due to adnexitis in a laying hen population. The treatment of children with diarrhea can be substantially improved by the use of these acid galacturonides i.e. Moros Carrot soup preventing small bowel overgrowth and protracted diarrhea [13].

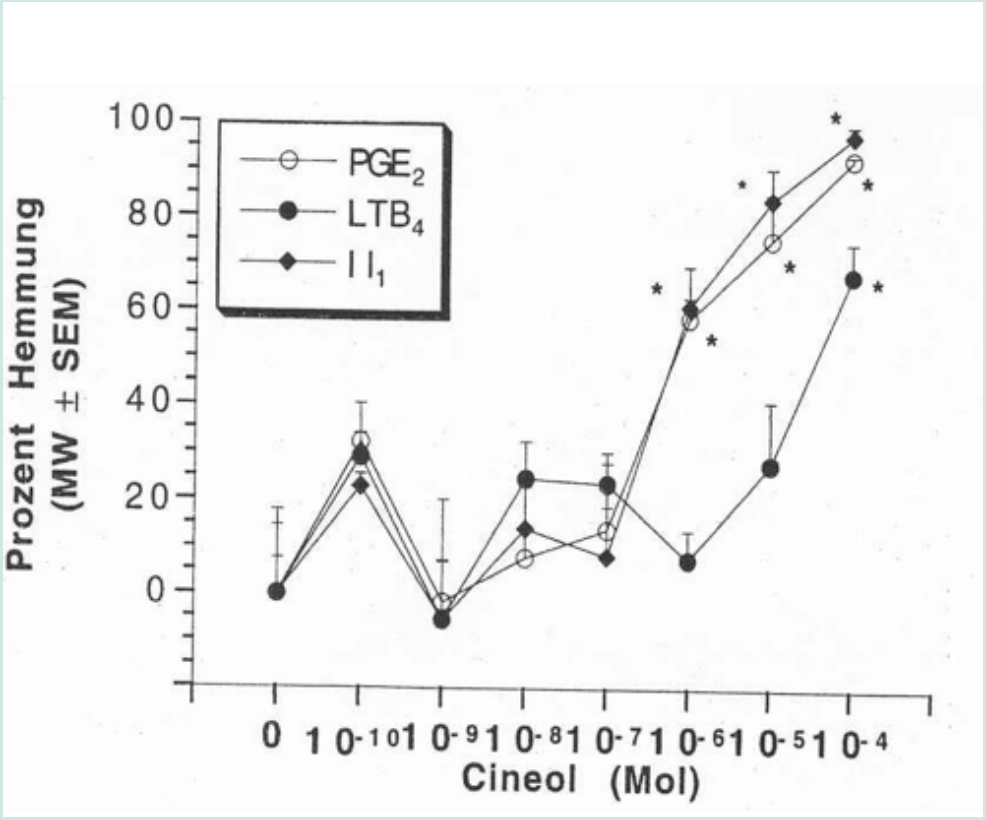

Figure 1: Shows the inhibition of proinflammatory cytokines prostaglandin E2 , Leukotriene B4 and interleukin I1 by 1.8. Cineol or Triterpenes from herbal extracts. Prostaglandin E2 (PGE2) is an arachidonic acid derivative generated by the actions of cyclooxygenase COX1 and COX2 involved in inflammatory process by increasing capillary permeability and thereby increasing submucous edema.

Tab. 1 Duration of diarrhea in 3 groups

group	With		without diarrhea			
Karotte	10	14,7%	58	85,3%	68	100%
Kontrolle	31	50,0%	31	50,0%	62	100%
LF Tylosinphosphat	17	24,6%	52	75,4%	69	100%
Gesamt	58	29,1%	141	70,9%	199	100%

Figure 2: Prophylaxis of diarrhea in newborn piglets by acid galacturonides in comparison with an antibiotic (Tyrosine Phosphate) and negative control. Acid galacturonides from herbal extracts are effective, not toxic, and highly cost effective [11, 12].

Ad 3: Increasing the longevity of current antibiotics,

by improving the appropriate use of existing antibiotics and thereby preventing the spread of antibiotic-resistant bacteria. Certain antibiotics in use favor the emergence of resistant microorganisms. Broad spectrum antibiotics with incomplete bioavailability e.g., cefixime shows a bioavailability of 75 %. The 25 % unabsorbed cephalosorine selects cephalosporin resistant microorganisms in the fecal flora which can contribute to bacterial superinfections e.g., urinary tract infections with multi resistant Gram-negative pathogens [14]. Absorption can be facilitated by modification of the original drug to optimize intestinal absorption. The formation of an ester is an example of a prodrug methodology for modification of a functional group of the active drug to improve lipophilicity for passive membrane transport to increase aqueous solubility (Figure 3). Cefpodoxime proxetil is an esterified pro-drug of cefpodoxime. After absorption it is de-esterified into an active compound with good and broad antimicrobial activity. If Cefpodoxime is eliminated by the biliary route it results in the accumulation of an unabsorbed antimicrobial active substance in the large intestine again with selection of multi resistant microorganisms. For prodrugs renal elimination is therefore mandatory [15]. Another problem is the excessively long half-life of an antibiotic. The usually observed half-life of a macrolide antibiotic is 60 minutes. Azitromycin has a halflife to 3 days which results in subinhibitory concentrations of more than 10 days in the oral cavity responsible for the broad induction of macrolide resistant microorganisms [16]. In addition, the initial poor absorption does not result in rapid bactericidal concentration at the site of an infection. It is therefore mandatory for the approval of antibiotics to also take pharmacokinetic and pharmacodynamic properties of antimicrobial agents into serious consideration.

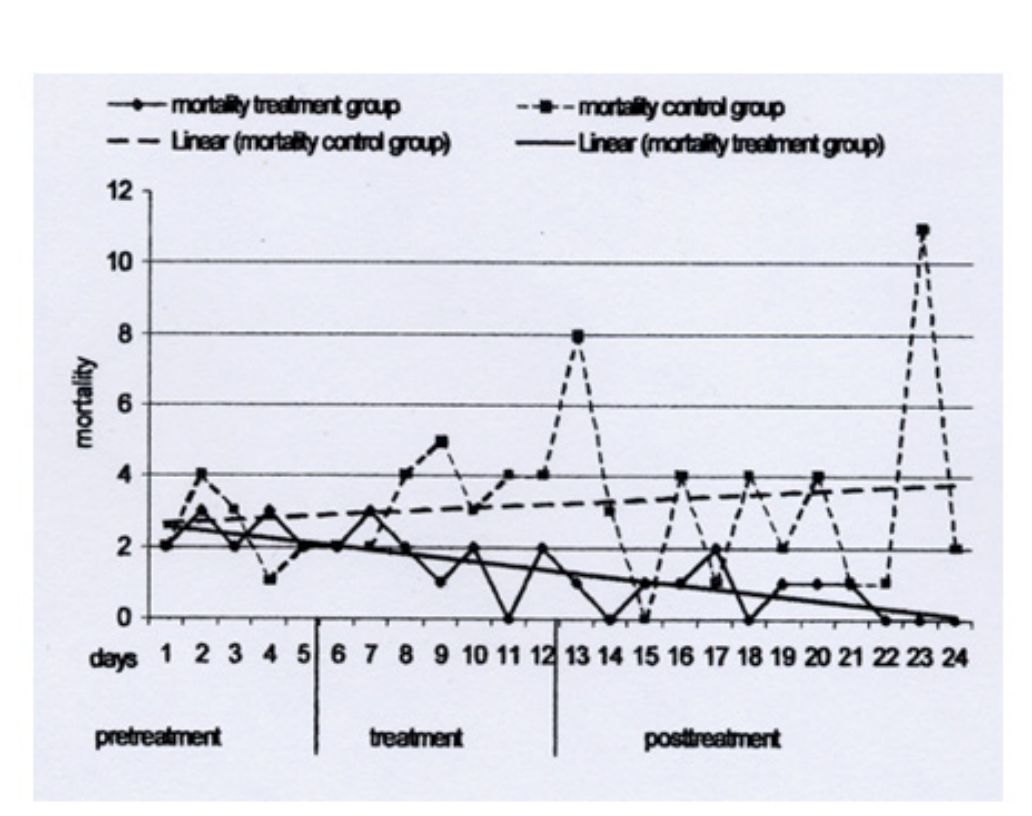

Figure 3 Treatment of an outbreak of adnexitis in a laying hen population with acid galacturonides. Acid galacturonides can prevent death in free living hens in a laying hen population due to adnexitis with enterohemorrhagic E. coli.

Ad 4: Drug Development.

The pharmaceutical industry concentrates mainly on the development of new compounds with antimicrobial activity. The world lacks a robust pipeline of new antibiotics to replace those being steadily lost to antibiotic resistance. The number of new systemic antibacterial agents approved by the Food and Drug Administration (FDA) each year has decreased steadily over the past three decades. The drug development pipeline is failing for a variety of reasons – including scientific challenges in discovering and developing new drugs; practical challenges in conducting the clinical trials needed for new-drug approval; and low economic returns that have made the development of new antibiotics an unattractive investment. As a result, large pharmaceutical companies have decreased or eliminated their investments in antibiotic drug development. There is an important observation which makes the development of new antimicrobial substances also less attractive. It has been observed that microorganisms develop resistance to new antimicrobial substances within a period of a few months. A law by nature indicates

that every antimicrobial substance which must be incorporated into the metabolism of microorganisms induces resistance. Alternative modes of antimicrobial activity must be designed which are not connected with induction of resistance. It is highly necessary to look for additional methods to combat the dramatic increase of multi resistant microorganisms and initiate an ambitious, innovative, and cooperative approach.

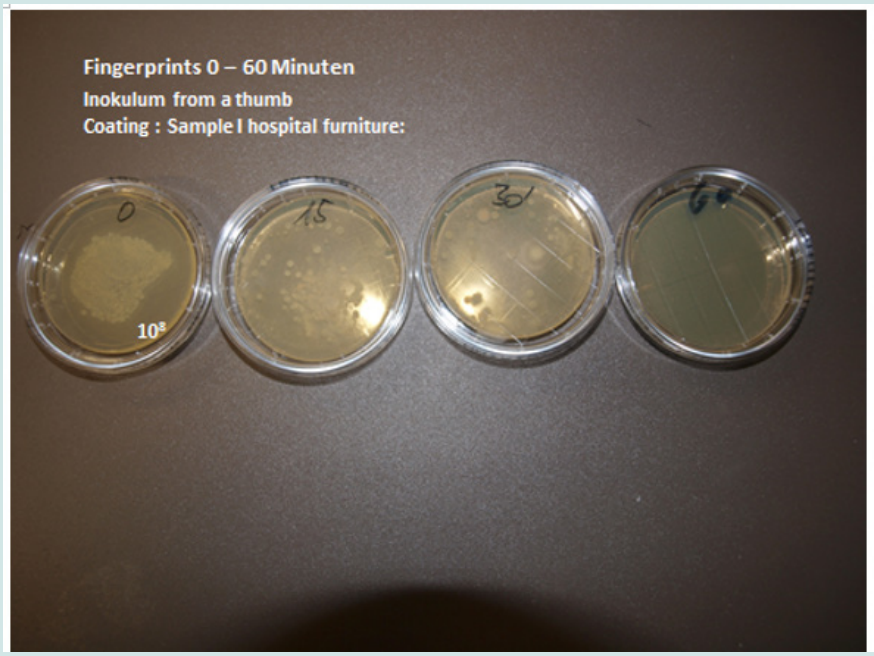

Figure 4: Eradication of microorganisms on melamin resin coated Hospital furniture containing 2 % of Zinc molybdate contaminated by fingerprints.

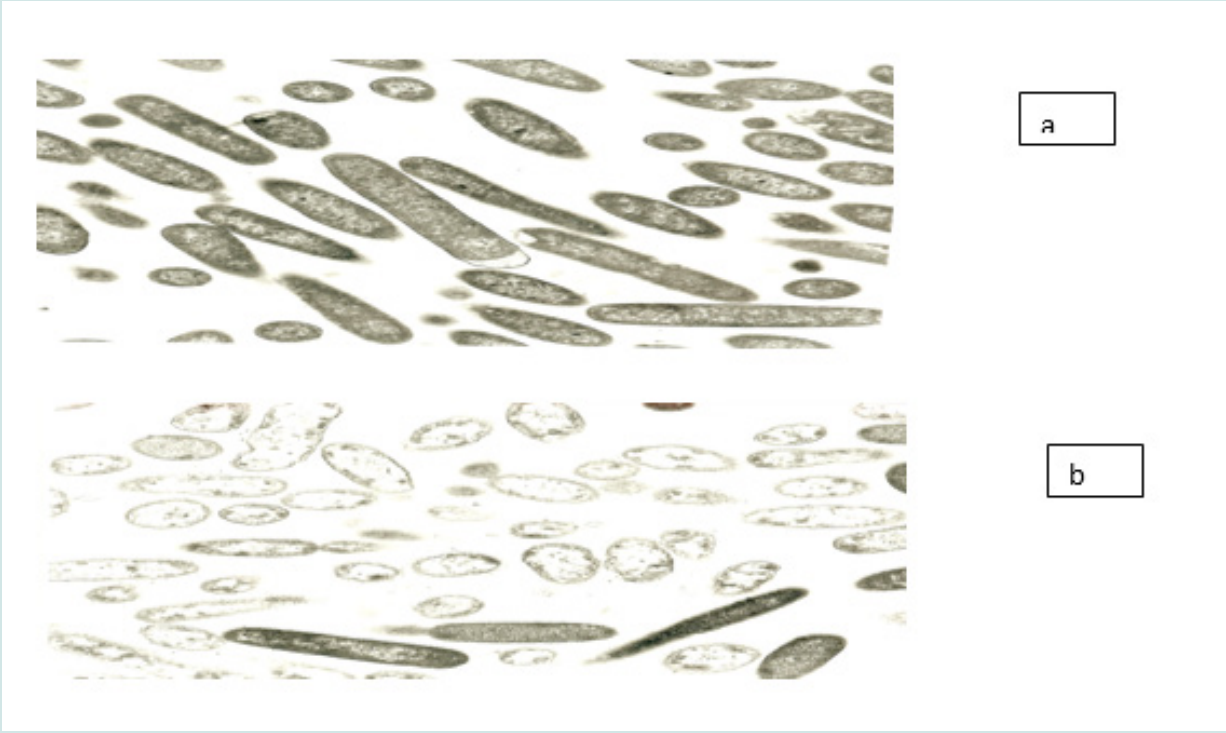

Figure 5: Microorganisms (E. coli) in a surface are in contact with nasal secretions containing antimicrobial peptides (ß Defensin)
a) Electron microscopical documentation of the initial contamination
b) Electron microscopical documentation after 30 minutes of contact. The destroyed cell membrane shows an effluence of cell contents of the microorganisms.

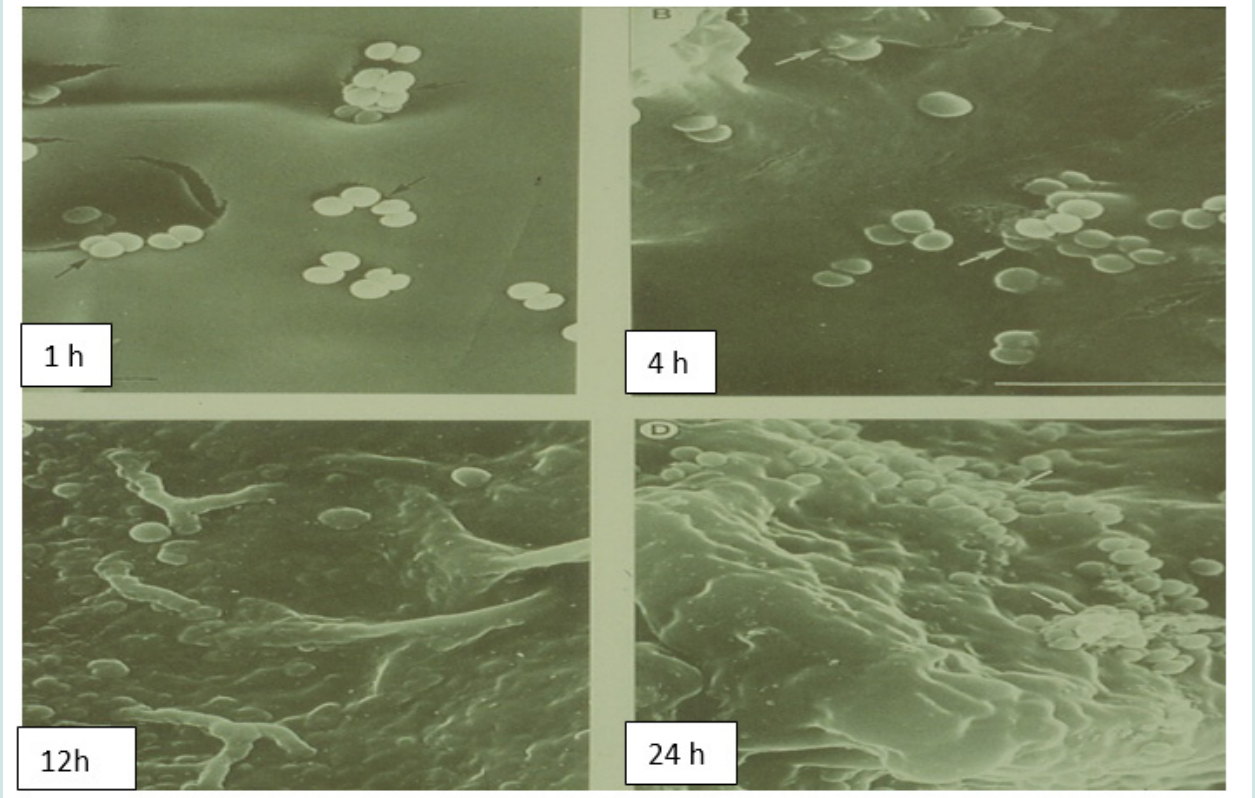

Figure 6 demonstrates the fast proliferation of microorganisms on surfaces with biofilm formation already visible after 12 hours.

Ad 5: Investigation of the origin of resistant microorganisms

10 years ago, a multi resistant microorganism was isolated on a surface which had been just disinfected with a quaternary ammonium base disinfectant (QAC). Initially this was a surprise but initiated intensive investigative work. QAC resistance is widespread among a diverse range of microorganisms and is facilitated by several mechanisms such as modifications in the membrane composition, expression of stress response and repair systems, or expression of efflux pump genes which results in a widespread resistance against virtually all antibiotics. Development of QAC resistance in both pathogenic and nonpathogenic bacteria has been related to application in human medicine and the food industry. The induction of resistance to disinfectants and cross resistance with antibiotics has been confirmed by the Norwegian food and fishery administration which prohibited the use of quaternary ammonium compound disinfectants in the fish industry [17].

Review of the international literature (PubMed) provides more than 8800 articles which describe the resistance of microorganisms against disinfectants and 800 papers report the cross resistance with antibiotics. Disinfectant resistance has the potential to change our way of life, threatening our medical health systems, compromising food security, and impacting the socioeconomic wellbeing of society. Resistance to antimicrobial agents occurs through either intrinsic or acquired resistance mechanisms. Acquired resistance occurs through the efficient transfer of mobile genetic elements, which can carry single, or multiple resistance determinants. Drug resistance genes may form part of integrins, transposons and insertion sequences which are capable of intracellular transfer onto plasmids or gene cassettes. Thereafter, resistance plasmids and gene cassettes mobilize by self-transmission resistance even between different bacterial species, increasing the prevalence of drug resistance determinants in a bacterial population. New methods, in addition or as an alternative to appropriate use of disinfectants and antibiotics, are required to reduce microbial associated infections and to reverse the increase in antimicrobial resistance. A promising alternative for the disinfection of surfaces are self-sanitizing surfaces which eradicate microorganisms fast from a surface and prevent the distribution of resistant microorganisms within the hospital by the personnel to patients. Bactericidal coatings – the correct term is self-sanitizing surfaces - are interesting in healthcare because of the capability of these coatings to kill pathogens upon contact. Different chemical strategies and technologies for antimicrobial coatings of surfaces are described in the literature with variable success [18]. It is well known that microorganisms in a biofilm cannot be eradicated by antibiotics nor disinfectants [19].

The initial investigative work excluded the theory that antimicrobial substances are prevented from diffusion into the biofilm [20]. Further investigations disclosed that microorganisms in a biofilm are hibernating and don't take up anything from the outside

[21]. However, they can be eradicated by a technology which affects the pathogens from the outside. Hard, nonporous environmental surfaces in health care settings are now receiving due recognition for their role in the spread of several types of nosocomial pathogens. The corresponding increase in the means to decontaminate such surfaces to interrupt the spread of infections is leading to a plethora of products and procedures, including the "green" variety, with varying claims of microbicidal activity, human and environmental safety, and materials compatibility. The widening use of environmental surface disinfectants is also raising concerns on their human and environmental safety at many levels along with the realization that routine surface disinfection procedures in health care settings are frequently inadequate and possibly counterproductive.

All this points to an urgent review of the basic procedures for assessing existing and new environmental surface disinfectants for their microbicidal activity, label claims, registration requirements, overall safety, and routine practices of environmental surface decontamination. Strategies to achieve antimicrobial coatings can be classified according to their functional principles as: antiadhesive, contact active, and biocide release. Whereas the first two principles may be considered as SbD, biocide release incorporates the release of a toxic substance and can therefore be considered as potentially toxic by design. Sometimes two functional principles are combined to achieve synergistic effects, e.g., by embedding biocidal substances into anti-adhesive surfaces. The requirements of self-sanitizing surfaces for application in hospitals, public transportation, and the food industry are extraordinarily high.

a) Intensive and broad antimicrobial activity, against Gram-positive, Gram-negative microorganisms, irrespective of their antibiotic susceptibility, fungi, legionella, moulds, virus documented by the RODAC plate method.

b) Fast eradication of microorganisms i.e., minimum 5 log 10 reduction within 1 hour

c) Activity against a high inoculum size of 109 CFU on an area of 3 cm^2

d) No induction of resistance

e) Nontoxic, skin and soft tissue compatibility, no allergenicity, sbD (safe by design)

f) Long lasting/permanent antimicrobial activity

g) water-, acid-, alkaline-, alcohol insoluble, UV Light stabile

h) Cleanable with detergents

i) Uncomplicated technical processability, heat stabile up to 400°C, non-corrosive

j) Physical stability, activity irrespective of sweat, grease, blood, pus

k) Not flammable, smoke reduction

l) BP authorization by the European commission on biocidal products.

m) Favourable cost/benefit analysis

Self-sanitizing surfaces are mostly focused on solid air interfaces in health-care units, such as hospital furniture e.g., tables, doorhandles, computer keyboards, textiles, although solid liquid surfaces are also of great concern in hospitals such as taps, showers and drains, where biofilms appear frequently. Finally certain technologies for a self-sanitizing surface can also be used for implantable biomaterials [21]. Besides the engagement with known antimicrobial agents' emphasis should have been exerted in evaluating

a) Documentation of the mechanism of action of presently available compounds

b) Investigation of new principles with new and promising antimicrobial activity.

A. Active eluting agents

Antibacterial coatings may contain active eluting agents (e.g., ions or nanoparticles of silver, copper, zinc, or antibiotics, chloride, iodine, quaternary ammonium polymers or antimicrobial peptides, or light-activated molecules (e.g., TiO2), immobilized molecules that become active upon contact [22]. In addition, there is a new innovative technology based on in situ generated biocides which meets all the requirements described above.

The active substances must be eluted from the surface i.e., the polymer or the coating. This means that these substances are eluted into the environment with unforeseeable environmental burden und toxicity. In addition, their activity is limited to a short period of time. For antibiotics this means a duration of activity of less than 3 days, for silver 3 weeks [23, 24, 25]. Copper cannot embed into polymers to achieve a sufficient antimicrobial activity; in addition, the activity of copper is too low to be considered as a valuable compound [26]. Quaternary ammonium compounds must be excluded from considerations as these products may even enhance the growth of microorganisms on surfaces and induce cross resistance with antibiotics by induction of efflux pumps [17]. Various drug eluting substances e.g., Paliguanids, halogenated phenols, and polyethyleneimines have been investigated but showed toxic side effects with human tissues once they are eluted from the polymer of the surface into the environment [27, 28].

B. Chemical modifications to achieve functional antimicrobial coatings.

In addition to chemical modifications, the topography of a surface can by itself significantly affect its hygienic status, either in a beneficial manner (reducing microbial retention) or otherwise (increasing retention). As such, modifications of surfaces to enhance antimicrobial properties should always consider the effect of surface wear on subsequent fouling and cleanability. Therefore, efforts should be undertaken to characterize typical wear, assess interactions with the most likely microorganisms in that environment, and define the most appropriate and least damaging cleaning and sanitizer regimes. Antimicrobial agents adjacent to a surface showed the risk of abrasion with cleaning. The agents must be consistently insoluble in water-, alcohol-, detergents, acid, alkaline. In addition, UV light stability must be confirmed. Today, most chemical modifi-

cations include hydrogels or poly (ethylene glycol) (PEG) to repel approaching microbes, metals (in particular, silver and copper), antimicrobial peptides, (AMPs), quaternary ammonium compounds (QACs), and various nanoparticles [29, 30]. Beyond those established approaches, state-of-the-art or potentially new strategies towards antimicrobial coatings were identified. For many of these antimicrobial strategies, the mechanism of antimicrobial activity is still under investigation and there is not enough information available on whether antimicrobial activity happens directly at the surface or whether small amounts of active compounds are released into the test media where they will exert their antimicrobial activity, or last whether both mechanisms are acting in parallel.

C. Anti-adhesive surfaces

Anti-adhesive surfaces could reduce the adhesion force between bacteria and a solid surface to enable the easy removal of bacteria before a biofilm layer is formed on the surface. Attachment of bacteria or cells starts with an initial adsorption of proteins on to the material surface. Such surfaces may suppress HCAI by blocking transmission paths involving surfaces, but they will not reduce the number of germs on the contacting media by killing them [31]. Strategies to prevent protein attachment include superhydrophobic surfaces, often augmented by a hierarchical nanostructure as well as zwitterionic polymers, but show several disadvantages: [32]

a) Superhydrophobic surfaces are characterized by a water contact angle >150" and they are inspired by the lotus leaf in nature. It was further revealed that the lotus leaf has a hierarchical micro/nanostructure. Microorganisms contaminating such surfaces must be removed by a continuous flow; this is missing on surfaces in hospitals and public use [33]. Reducing bacterial adhesion via super hydrophobicity is a relatively new topic and has yet to be studied thoroughly and systematically [34]. The most important requirement of a "self-sanitizing" surface is the ability of the surface to actively eradicate pathogens within a short period of time. It must be emphasized that microorganisms are deposited by the hand of the personnel with considerable force. For prevention of recontamination of a second person, rapid eradication of microorganisms is mandatory (i.e., less than 1 hour or shorter). Reduction of adherence, blockage of proliferation and biofilm formation – although also important – are in no way as single method sufficient as "self-sanitizing" surfaces for clinical use to prevent recontamination of persons. Contamination of a surface (melamine resin with 2% Zinc Molybdate) has been performed with thumb prints. The initial number of CFU on the surface is 108 CFU (lawn) on an area of 2 cm^2. There is a substantial reduction of microorganisms after 15 and 30 minutes. At 60 minutes no germs are isolated on the surface. This has been investigated by the push plate (RODAC plate) method.

Analysis of superhydrophobic siloxane and fluor siloxane surfaces also showed minimal protein adsorption, both before and after protein adsorption trials [35]. Nanostructures are important, since effective air entrapment in the three-dimensional nanomorphology (nanopillars) renders them superhydrophobic and slippery. On inherently nanostructured hydrophilic aluminum, adhesion forces of bacteria were reduced by a factor of 4 down to 2e4 nN compared to the electropolished flat surface, resulting in an 88% reduction of colony-forming units (CFU) for Staphylococcus aureus. This effect was even more pronounced after applying a hydrophobic Teflon coating, yielding a 99.9% reduction under flow conditions. If microorganisms however are contained on a surface with an adherent soling (sweat, grease, pus, blood) the antimicrobial activity is obliterated. All these hyper hydrophobic properties which require nanotechnology are facing the problems of approval by the biocidal regulation authorities. Easier cleaning is not the answer – contaminating microorganisms must be eradicated fast from the surface.

b) Nanostructured surfaces. A potential and promising weapon against bacterial growth and possibly the development of multidrug-resistant bacteria has been found in antimicrobial (nano)coatings (AMC). Antimicrobial technologies using nanomaterials e.g. Chitosan, cellulose etc. have to be applied into nanorods or nanosats which can however not stabile anchored on the surface [36]. If incorporated into polymers the activity is substantially diminished or extinguished.

Nanostructured surfaces were also prepared using electro spun polystyrene nanofibers [37]. Oxygen plasma-treatment generated a super hydrophilic surface, which exhibited limited Escherichia coli attachment due to negative zeta potential of e40 mV. After fluorination, a superhydrophobic surface was obtained, which exhibited self-cleaning ability against bacteria. However, the initial adhering bacteria had to be effectively removed with subsequent washing [38]. Anti-adhesion and killing required a combination of an upper superhydrophobic surface layer (silane coated poly (acrylic acid) with limited bacterial adhesion and self-cleaning properties with a hydrophilic bottom layer (poly(ethyleneimine)e Agþ complex) which could deliver bactericidal silver ions with known disadvantages [39,40,41].

The addition of silver has been described as a technology for antimicrobial surfaces. One technology describes that only free silver ions are antimicrobials active – where silver must be released from the surface and incorporated into the bacterial metabolism [42- 44]. A serious disadvantage has been described – it is a limited activity of silver of a few days! Silver submicron particles can be incorporated into polymers and coatings, a hydrophilizing agent must also be added for an enhanced activity! Silver in form of nanoparticles function in a different way: Some studies have reported that nano-silver causes oxidative damage, leading to the production of reactive oxygen species (ROS) as well as free-radicals, and it has been suggested that the production of ROS is one of the primary mechanisms of nanoparticle toxicity [45]. Hence, it was suggested that nano-silver affects bacterial membrane permeability by attaching to the cell membrane surface and modifying the cell potential. Observation of large numbers of nanoparticles inside bacteria suggests that this could be of importance to the antibacterial mechanism. An interesting anti-adhesive and killing approach is found in

nature. The nano-patterned cicada wing surface uses an adsorption and stretching mechanism with eventual rupture [46]. As the bacterial cells adsorb on to the nano pillared structures present on the wing surfaces, the bacterial cell membrane stretches in the regions suspended between the pillars. If the degree of stretching is sufficient, cell rupture will occur. The cicada wings technology – as well as the gecko foot technology which relies on the same properties - is not physically stabile – the cicada wings surface can be easily destroyed by mechanical wiping/cleaning, rubbing.

c) Zwitterionic polymer brushes

May also delay or even prevent microbial attachment to a surface, since the hydration layer surrounding the ionic surface prevents non-specific protein adsorption. Zwitterionic polymer brushes cannot inactivate bacterial cells. Therefore, synergistic anti-adhesion and bacterial inactivation was necessary by grafting zwitterionic poly (sulfamethazine methacrylate) brushes again with embedded biocidal silver nanoparticles [47]. The addition of silver is possible but only silver ions are active – in other words silver must be released from the hydrophilic bottom layer and incorporated into the bacterial metabolism with its well-known mode of action. Limited activity which probably lasts just a few hours! The more important problem is the fast inactivation of silver ions by ppb of sulfur present also in the environment. The importance of anti-adhesive properties for biofilm formation was also demonstrated by measuring the adhesive forces on brush-coated silicone rubber and uncoated silicon rubber [48]. On the brush-coated rubber, adhesion was so weak that the bacteria were no longer able to sense the surface and therefore remained in their planktonic state, susceptible to antibiotics rather than forming a protective biofilm.

d) Contact-active surfaces

Contact-active surfaces exhibit antimicrobial activity without releasing biocidal substances. Several mechanisms are believed to take place in contact-active surfaces. These are: a so-called spacer effect, where the biocidal group is attached to the surface through a polymer chain, allowing the biocide to reach the cytoplasmic membrane of the bacteria and to perforate them; alternatively, positively charged QACs, e.g., 3-aminopropyl trimethoxy silane grafted to cellulose nanofibers, can detach phospholipids from the cell membrane and thereby kill the bacteria [49]. This approach is also referred to as biomimetic with respect to the activity of chitosan, a polysaccharide derived from exoskeleton of crustaceans or cell walls of fungi. Hydrophobic parts of a surface can act similarly to QACs by deforming the membrane through adhesion. The activity of the spacer effect is obliterated by grease, proteins, sweat, pus and blood. The activity of nano - chitosan has been investigated and a poor antimicrobial activity has been found. Besides a practical obstacle, i.e., fixation on surfaces has been encountered.

e) Polymer brushes

Have been widely used in preparing contact-active antimir. Theia surfaces with biocide-release as the polymer brushes have no integrated antimicrobial activity. The rationale behind polymer brushes is the observation that antimicrobial molecules lose much of their activity once attached to a surface. When providing an anchor for the active molecule through a flexible covalently bound polymeric chain, the active molecule should still be able to reach the site of action at or within the bacterium, e.g., by penetrating its cell wall, but leaching is still suppressed. Important parameters for polymer brush anchors are chain length and chain density. Polymer brushes have been shown to be effective for anchoring QACs or AMPs [50,51].

The frequent occurrence of multidrug-resistant strains to conventional antimicrobials has led to a clear decline in antibiotic therapies. Therefore, new molecules with different mechanisms of action are mandatory. Due to their unique properties, antimicrobial peptides (AMPs) i.e., cationic, amphophilic, acid peptides and are part of the body's defense mechanisms known as ß defensins. These molecules present a broad spectrum of action against different microorganisms and frequently present promiscuous action, with anticancer and immunomodulatory activities and represent a valid alternative to conventional antibiotics. Furthermore, AMPs were intended to be used as biopharmaceuticals in the treatment of hospital-acquired infections and other serious diseases with relevant social and economic impacts. The idea behind is attractive – however there are several shortcomings which make their use not feasible in a hospital environment [52]. AMPs can also not be used for intravenous or intramuscular application. AMPs must be eluted from the surface [53]. Their mechanism of activity is the direct attachment to the microorganisms for their activity by disruption of the cell wall. Therefore, the activity is limited to a few days. Limited duration of activity is seen within 1 – 3 days, the AMPs must be reapplied to a surface. AMPs are not easy to obtain. They could be obtained as Magainin's from frog skin (Xenopus leaves) with very limited availability. Synthesis of AMPs is not solved as AMPs are lethal factors for microorganisms. Investigations over 2 years have been performed to achieve synthetic AMPs. Synthetic AMPs induced fast resistance against the test microorganisms – these microorganisms are in turn also insensitive to natural AMPs produced by the body. Polymer brushes with QACs have therefore not proved to be useful for the application in a clinical setting as resistant microorganisms are selected.

f) Definitely to be avoided!

Using surface-initiated atom transfer radical polymerization, QACs with charge densities of >1.5e1015 accessible quaternary amine units/cm2 were anchored through poly-2-(dimethylamine) ethyl methacrylate chains [54]. Interestingly, these surfaces were bioactive even though the polymer chains were too short to penetrate the cells with envelope thicknesses of 46 nm for Gram-negative E. coli and 45.55 nm for Gram-positive Bacillus subtilis. However, the propensity of induction of resistance genes by induction of efflux pumps makes QACs far less attractive as the most important requirement of a self-sanitizing surface is the prevention of induction of resistance.

Polymer brushes have also successfully been used for anchoring AMPs. AMPs are a logical alternative to conventional antibiotics due to their broad-spectrum antimicrobial activities [56]. Antimicrobial activity of cationic acid peptides formed by contact of epithelial cells with microorganisms is an innate defense mechanism against colonization of epithelial surfaces. Polycations on a surface are not heat resistant an cannot be extrusion molded, in addition the activity is obscured by any compounds e.g. grease, sweat etc. which are abundantly coating hospital surfaces close to patients. Anchoring AMPs is again not helpful, see above. In addition, technology is complicated and expensive. These compounds cannot be added to various coatings. Surface concentrations of AMPs up to 5.9 mg/cm2 were achieved by conjugating the peptides to surface-immobilized primary amine functionalized polymer chains obtained by aqueous surface-initiated atom transfer radical polymerization of N,N- dimethylacrylamide and aminopropyl methacrylamide hydrochloride. The efficacy of AMPs attached to catheter material surface using polymer brushes was verified in vivo by using a catheter-associated urinary tract infection mouse model [57]. Antimicrobial peptides have a broad-spectrum against bacteria and fungus, low level of induced resistance, but may cause toxicity at high doses in order to be efficient and are more costly to produce. By adding arginine glycine aspartate peptides to promote host-tissue cell adhesion to AMPs anchored through the block copolymer Pluronic F-127, two effects were achieved, namely thwarting bacteria from approaching and attaching to the surface and, simultaneously, enhancing tissue integration [58].

The problem is the availability of AMPs for clinical application. Synthetic AMPs resulted in a product which induced resistance of bacterial microorganisms. These microorganisms have been resistant even against natural antimicrobial peptides. A completely different approach is given by immobilizing bacteriophages on surfaces [59]. Bacteriophages are viruses that infect bacteria and are highly efficient and relatively cost- effective. Bacteriophages are host specific, but they can have a broad host range, infecting several strains or species of bacteria, both Gram-positive and Gram-negative. They proved to be efficient in preventing bacterial contamination and recently they became accepted for food treatment to counter food contamination during storage. In addition, the fact that the EU is contributing V3.8 million to the Phagoburn study shows that it is willing to consider the approach [60]. Attachment of bacteriophages to a surface can be achieved through physisorption, electrostatic attachment, and covalent bonding [61]. Sample surfaces, which exhibited antimicrobial activities with immobilized phages plus included gold, glass, cellulose membrane, and hydrogels have been designed. [62]. Phages are specifically sensitive to moisture and can be deactivated when dried. However, reactivation upon wetting is feasible, and addition of polysaccharides improves their stability [63]. It cannot be incorporated onto coatings on stainless steel, aluminum, enamel etc. as it is not heating stable. Different microorganisms require different phages – there is no uniform broad spectrum of activity against bacteria, fungi, molds, and viruses. Phage therapy is therefore inefficient for the prevention of hospital acquired infections in hospital surfaces and it is not suitable as prophylaxis embedded into surfaces. Besides phages are not heat resistant and are also eluted from the surfaces with limited duration of activity.

Another naturally occurring antimicrobial is claimed as alternatives to antibiotics: bacterial cell wall hydrolases (BCWHs) [64]. BCWHs have limitations towards Gram-negative bacteria, due to the presence of the outer membrane, and some important Gram-positive pathogens such as S. aureus are already resistant to lysozymes. Biocide-releasing surfaces may have some conceptual disadvantages since they are toxic by design in terms of releasing biocidal substances. In addition, they will gradually become inactive, and they may induce the formation of resistance. Any substance eluting from the surface is also emanating into the environment. Toxic substances incorporated into the body may affect various cell lines e.g., epithelia cells, osteoblasts, fibroblasts. The chance that these biocides meet the requirements of the European Commission is improbable and requires extensive testing.

g) Catalysts

Many of the reported antimicrobial surfaces contain the photocatalyst TiO2, which generates antimicrobials active oxygen-radicals but also OH-radicals in the presence of water, oxygen and UV-A light which are able to destroy bacteria. The most effective mode of antimicrobial activity is, however, an electric current formed by catalysts [65]. This has been documented by laser scanning microscopy which showed eradication of bacteria - even in a biofilm – within 15 minutes. The antimicrobial activity of reactive free radicals formed upon UV radiation or light by TiO2 has been investigated as an alternative to antibiotics and disinfectants [66]. Antimicrobial activity has been observed on surfaces endowed with TiO2 molecules. Due to the self-regenerating biocidal effect of the catalytically released reactive oxygen species, such surfaces remain active throughout their lifetime.

The activity of a photocatalytic mechanism based in the formation of oxygen radicals alone, however, vanishes rapidly by evaporation into the environment. The time for effective eradication of microorganisms is too short – the ensuing concentration too low. The antimicrobial activity can therefore only be documented by coating the contaminated surface with a foil (JIS Japanese industrial standard). By this method the antimicrobial activity is determined in the capillary space between the surface and a foil which prevents these free radicals formed by the photocatalytic molecules from evaporating into the environment. [67]. At the same time free radicals accumulate in the capillary space in unrealistic high concentrations. This is a highly arbitrary method of testing and is far away from the requirements of antimicrobial surfaces for a "real life situation" investigation by the push plate method (RODAC Plate method). The antimicrobial activity of technologies based only on formation of free oxygen radicals cannot be documented by the push plate (RODAC plate Replicate Organism Detection and Counting) method which is relevant for germfree surfaces.

Photocatalytic oxidation however remains still a valuable alternative strategy for antimicrobial coatings in the hospital envi-

ronment if these shortcomings can be eliminated [68]. Current research has been focusing on shifting the photocatalytic activity of such coatings towards the visible light range, or by adding silver nanoparticles which can act through their surface plasmon resonance effects, or molybdenum. When incorporating a combination of photosensitive dyes such as Crystal Violet with the inherently antimicrobial ZnO nanoparticles into polymer surfaces, synergistic photocatalytic antimicrobial activity was reported. The polymers exhibited significant bacterial kills using typical white light sources of hospital environments within 1h against Gram-positive bacteria and within 6 h against Gram-negative bacteria. By combining a dye with Ag nanoparticles, bactericidal activity of the Ag nanoparticles could be enhanced under white light illumination. It is believed that the enhancement effect is due to an increase in bactericidal activity through the triplet state of the dye by biomolecular reaction rather than by enhancement of the concentration of reactive oxygen species.

Prohibitive for the sole use of a technology based only on the formation of oxygen radicals is the fact, that the antimicrobial activity can only be documented by the JIS method investigating the activity underneath a foil. Finally, oxygen radicals also don't penetrate the thick layer of a biofilm and are inactive against microorganisms in a biofilm. Additional intense investigation of the photocatalytic technology revealed mechanisms with a potential to eradicate all bacterial microorganisms, fungi and viral pathogens including Corona Virus without incorporation of the additives into the bacterial metabolism. Catalysts e.g., transition metal oxides e.g., molybdenum oxide and Tungsten oxide Zinc Molybdate and Polyoxometallates have been investigated. These investigation based on the photocatalytic activity of transition metal oxides revealed a mechanism with a potential to eradicate bacteria also in biofilms and without an additional light source. In situ generated surface by transition metal oxides surfaces decorated with metal oxide Lewis's acids such as MoO3, WO3, Zinc molybdate or the recently developed polyoxometalate where Molybdenum oxide is incorporated into the tungsten crystal lattice have shown a broad-band and strong antimicrobial activity resulting in a reduction of the number of colonies forming units by 6 – 7 log 10 within 1-3 hours [69]. No additional light source is required. The mechanism of action of this biocidal technology is based on a synergy of three mechanisms.

a) The in-situ generation of H3O+ ions through the reaction with moisture from the air inspired by the body's own defense mechanism imitating e.g., the acid coating of the skin [70]. The resulting acidified surfaces have a pH of 4.5 and the H3O+ ions can diffuse through the cell membranes where they can distort the pH-equilibrium and transport systems of the cell [71].

b) The formation of free radicals is not only oxygen radicals but also hydroxyl radicals.

c) In addition, by this mechanism a synergistic mode of action including a positive zeta potential has been observed. This is reflected by an extraordinarily fast eradication of microorganisms i.e., a reduction of 5 log 10 within 10 minutes, documented by laser scanning microscopy.

This technology is the only one which meets all the requirements described initially for prevention of hospital acquired infections. No side effects after application of such 5 x 5 cm surfaces endowed with Zinc molybdate 2% in a gloss paint on a forearm in a wet chamber for 120 hours has been observed. No allergenicity has been seen, the additives are essential trace elements in the body! No induction of resistant microorganisms has been seen. Molybdenum has some water solubility and does not provide UV light stability. It has been found that only the 5 % oxygen deficient tungsten blue oxide has an excellent antimicrobial activity in contrast to the oxygen saturated oxygen yellow tungsten with limited antimicrobial activity. Tungsten is water insoluble; Molybdenum shows a moderate water solubility of 0.003 mol/l at a pH value > 7.55.

The incorporation of Molybdenum oxide into the zinc oxide crystal lattice showed a comparable antimicrobial activity to Molybdenum oxide. Zinc Molybdate is water and alcohol insoluble. This, the white color and UV light stability makes the compound highly suitable for addition to melamine resin for antimicrobial furniture. The incorporation of Molybdenum oxide into the tungsten blue crystal lattice results in a water and alcohol insoluble compound with additional antimicrobial activity e.g., against molds (Aspergillus spp), various viral pathogens e.g., influenza virus, hepatitis B and C. Treated articles with polyoxometalates showed an 88 % reduction of coronavirus surrogate initially [70]. After formation of a hydrophilic surface excellent antiviral activity of Polyoxometalates has been achieved.

Also strong activity against algae has been detected. The incorporation of both molecules into the same crystal lattice is feasible due to a virtually identical ion radius. Easy cleaning and eradication of microorganisms on surfaces endowed with transition metal oxides has been documented with water and detergents as microorganisms don't adhere on acid surfaces and don't form a biofilm. However, the technology is also active against microorganisms embedded in a biofilm! Microorganisms in a biofilm are hibernating and don't take up anything from the outside. Therefore, technologies which are based on incorporation of the antimicrobial agent into the bacterial metabolism are ineffective. Again, technologies which attack microorganisms from the outside also eradicate microorganisms in a biofilm, an important asset [71].

Technologies based on oxygen radicals only are substantially less active compared to technologies which provide a synergistic activity of a positive zeta potential and the formation of acid water molecules. The positive Zeta potential, formed on the surface, is responsible for the observed rapid eradication of microorganisms on surfaces documented by laser scanning electron microscopy. A 6 log 10 reduction within 15 minutes is documented. The technology is approved by the BPR as in situ generated biocide and is legitimately on the market. In situ generated biocides remain in a polymer or a coating and are not eluted. This is the reason for an activity lasting at least 10 years documented with several samples. In case minute amounts of the additive is eluted, the additives are

essential trace elements and function as stabilizing enzymes for the detoxification of sulfur in the body (xanthine oxidase, aldehyde oxidase, sulfite oxidase etc.) The allowed intake is 0.01 mg/kg BW/day [72]. The concentrations observed in treated articles are 500-fold below the threshold.

Reduced toxicity and prolonged durability of the antimicrobial effect has also been described by the triggered release of biocidal molecules. Recent strategies are based on quorum sensing: quorum-sensing molecules (e.g., homoserine lactones for Gram-negative bacteria) enable bacteria to detect the presence of other bacteria and to communicate with them [63]. The concentration of quorum-sensing molecules increases with bacterial multiplication and at certain threshold concentrations the expression of many genes is affected, such as genes encoding for adhesion or lipases, which are particularly abundant at sites of infection. The antimicrobial activity of quorum sensing technology has never been documented beyond reasonable doubt [64]. It is considered an interesting idea but no one has ever investigated the activity in comparison with other technologies. The "idea" has been in the air for 20 years – no effective samples have ever been presented with documented antimicrobial activity. The technology also requires approval of the BPR of the European Union. Alternatively, anti-quorum sensing enzymes could prevent bacteria from forming biofilms by suppressing the quorum-sensing molecule concentration below the threshold value. [75].

The incorporation of antibiotics in particular results in the induction of resistance to a group of antibiotics indispensable in clinical practice. The duration of the activity is limited to a few days. This is in no way a practical approach and has to be banned. Also, the incorporation of disinfectants has to be banned due to the induction of cross resistance with antibiotics. One of the problems of a technology due to biocide releasing agents is the induction of resistance. There is a law by nature that all substances with antimicrobial activity which require the incorporation of the agent into the metabolism of microorganisms induce resistance. This is well known for antibiotics but also disinfectants. Therefore, it is required that a technology is developed which is not incorporated to the bacterial metabolism but attacks microorganisms from the outside in a synergistic activity of acid water molecules, free radicals and most important a positive zeta potential i.e. the positive electrostatic charge at the surface which ruptures the phospholipid bilayer of microorganisms upon contact within minutes [76].

Surface coating with carbon nanotubes (CNTs), graphene or diamond-like carbons (DLCs) promised interesting antimicrobial activity, since these materials show relatively low cytotoxicity towards mammalian cells. Whether these materials are active on the surface or whether they achieve antimicrobial activity through releasing traces into the aqueous phase is not yet resolved, but their activity in microbial suspensions is clearly demonstrated, e.g., higher toxicity is found for surfactant dispersed CNTs [77]. The most frequently proposed mechanisms of action fall under four categories: (i) oxidative stress induction, (ii) protein dysfunction, (iii) membrane damage, and (iv) transcriptional arrest. Recently, it was also demonstrated that the mechanism of action depends on the concentration of the bacteriocide in this case graphene oxide (GO): low GO concentrations cut membranes of the micro-organisms S. aureus and E. coli whereas high concentrations induce the formation of GO aggregates shielding their edges. When cluster size increases, bacterial deactivation through wrapping is observed. Graphene-based materials differ in their morphology (mono and multilayers) as well as in their surface chemistry (graphene, GO, reduced graphene oxide (rGO)). Lateral size for instance is important to enhance bacterial adhesion whereas the sharp edges may act as nanoknifes. GOs can enhance the antimicrobial activity through oxidative stress with or without the production of reactive oxygen species.

When comparing the antibacterial activity of graphite, graphite oxide, GO, and rGO towards E. coli under similar conditions, GO showed the highest antibacterial activity, followed by rGO, graphite, and graphite oxide. Synergistic effects are reported for graphene-based silver nanocomposites and composites with other antibacterial nanoparticles, as well as with polymeric or enzymatic bactericides. Graphene by itself show a very limited antimicrobial activity. However, in combination with silver the antimicrobial activity is enhanced. However again only silver ions show antimicrobial activity and must be incorporated into the metabolism of microorganisms: consequences: limited duration of activity whereas graphene is enhancing the release of silver ions. Carbon nanotubes have also been widely studied as antimicrobial material since they can be easily embedded into polymers. Again, a variety of morphologies has been studied such as single wall or multi-wall, but it seems that GO-based materials show higher antimicrobial activity.

a. Summary: The technology using in situ generated biocides namely Zinc molybdate 0.25 µm particle sizes << 1 % in melamin resin can be suitable to prevent the transition into the postantibiotic era in the future [78].

Impact of Topography on Surface Effectiveness

It is generally acknowledged that defects or design features on any inert surface can retain soil and/or micro-organisms, and therefore affect cleanability, disinfection, and hygienic status of the surface. Implications in the clinical environment in terms of cross-infection control, the choice of surface material to be used, and the cleaning and sanitization protocols are significant. However, the assumption 'the rougher the surface, the worse the hygienic status' is somewhat simplistic, although many publications make this type of claim. Cells are easily removed from 'smooth' surfaces, but they may be retained within features approximating in size to that of the cells. In larger features, the cells may again be relatively easily removed. Easy cleaning is in addition to an optically attractive surface one of the prerequisites. If easy cleaning is also accompanied by a germfree surface this is the ideal approach as this can avoid the use of disinfectants which hence are responsible for the dramatic induction of resistant microorganisms seen. Technologies which combine easy cleaning and antimicrobial activity are prefer-

able. It has been documented that the technology with surfaces decorated with metal oxide Lewis's acids such as MoO3, WO3 and Zinc molybdate have also shown besides the broad-band and strong antimicrobial activity that the surfaces withstand 1000 cleaning cycles with flowing water and a detergent without decrease in antimicrobial activity [79]. Self-sanitizing surfaces are highly cost efficient as the save the daily application of disinfectants for years. At the same time the emergence of resistant microorganisms is prevented by stopping the application of disinfectants.

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