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Infections associated with mesh repairs of abdominal wall hernias: Are antimicrobial biomaterials the longed-for solution?


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Abstract

The incidence of mesh-related infection after abdominal wall hernia repair is low, generally between 1 and 4%; however, worldwide, this corresponds to tens of thousands of difficult cases to treat annually. Adopting best practices in prevention is one of the keys to reduce the incidence of mesh-related infection. Once the infection is established, however, only a limited number of options are available that provide an efficient and successful treatment outcome. Over the past few years, there has been a tremendous amount of research dedicated to the functionalization of prosthetic meshes with antibacterial properties, with some receiving regulatory approval and are currently available for clinical use. In this context, it is important to review the clinical importance of mesh infection, its risk factors, prophylaxis and pathogenicity. In addition, we give an overview of the main functionalization approaches that have been applied on meshes to confer anti-bacterial protection, the respective benefits and limitations, and finally some relevant future directions.

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1. Introduction to mesh-associated infection after hernia repair

Abdominal wall hernia is a common surgical problem affecting patient populations across the world. The main causes of abdominal wall hernia are related to collagen disorders and/or insufficient suture closing techniques after laparotomies (called incisional hernia). The surgical repair of abdominal wall hernia, involves repositioning the contents of the hernia sac (protruded organs) into the abdominal cavity, and consequently the closure and reinforcement of the defect using either a suture (known as herniorrhaphy) or a net-like prosthesis (called mesh, known as hernioplasty). The utilization of mesh materials over the last five decades has brought clear advantages compared to direct suturing, which was the previous standard protocol. Indeed, the mesh approach is generally associated with reduced recurrence rates, a quicker recovery, and lower risk of post-operative chronic pain [1].

Nevertheless, hernia repair using either suture or mesh technique can result in infectious complications [1,2], with incidence rates between 1 and 4% of all patients. Hernia mesh-related infection is “a surgical disaster” [3], with dramatic effects for the patients and incurring significant healthcare costs. Considering that more than 1 million hernia repair operations using mesh are performed annually in the USA, it is estimated that approximately 60 000 inguinal and ventral hernia (corresponding to protrusion through the inguinal canal or through the muscles of the abdominal wall respectively) repairs become infected annually, with similar numbers in Europe [4].

In the 2004 publication entitled “Post mesh herniorrhaphy infection control: Are we doing all we can?” [5], Pr. Deysine suggested that philosophical changes must be considered since surgical site infection (SSI) in hernioplasty was still unacceptably high. He compared the situation to the orthopaedic community, who achieved a tremendous reduction of SSI within the last decades (e.g.
by using filtered incoming air in theatres, local antibiotherapy, three pairs of gloves, etc.) [5]. Among the possible routes for progress, judicious surgical approaches but also technologies and innovative techniques dedicated to the prevention of mesh infection are seen to play crucial role; and have already brought promises in this challenging field [5]. As illustrated Fig.1, the hernia community is showing increasing interest in this field, with a continuous augmentation of published reports dealing with mesh-related infection and innovative strategies aiming to prevent hernia surgical site infection (SSI).

In order to facilitate the development of innovative strategies dedicated to tackle mesh related infection, we need to fully comprehend the clinical problem. Therefore, the following review is extended to 1 year post-operatively (instead of only 30 days for conventional cultivation methods to analyse the microbial population of explanted mesh following hernia recurrence [24]. The authors of this work have demonstrated for the first time that hernia meshes could be reached by bacteria, not only originating from the skin and the gut of the patient, but also from oral site (due to periodontal diseases) [24]. This study suggests as well that bacterial biofilm settled on the meshes in patients without clinical signs of infection could a priori also promote recurrence [24].

2. Incidence of SSI in herniatology

It is known that the insertion of a medical device increases the susceptibility of infection by a factor 10 000 up to 100 000 [25]. In the field of hernia repair, bacterial contamination occurs in 1/3 [19,26] up to 2/3 [24] of the implanted meshes either during mesh insertion or even after years of implantation in cases where healing is disturbed. Of those meshes colonized by microorganisms, relatively few will develop infection with clinical symptoms of SSI, but this risk persists for many decades after the surgical procedure [10]. Conventionally, the incidence of SSI in hernia surgery ranges between 1 and 4% in most of the literature reported over the last decades [5], but it depends on numerous factors. Among the risk factors of SSI, the nature of the hernia has been relatively well documented. For instance, SSI incidence is around 2–4% in open surgery for inguinal repair, but reach 6–10% in case of incisional hernia operations [27]. The surgical approach has also a direct influence on SSI, e.g. using laparoscopic route is usually correlated with lower SSI (compared to open surgeries) as it corresponds to a minimal invasive act, with no need of large dissection [28]. With the laparoscopic approach, SSI has been reduced to as low as 0.1% [29].

Fig. 1. Increasing awareness of mesh-related infections is reflected by the steady increase in scientific reports published every year. Search was done on the 8th of August 2017 on “isi web of knowledge” with key words “Mesh” + “Hernia” + “Infection”.

![Published items every year](image1.png)

![Citations in each year](image2.png)
The experience and learning curve of the surgeons performing the mesh implantation has also a tremendous impact on complications related to sepsis. Indeed, resident surgeons (non-expert in the field of hernia repair) require more time to perform the procedure, which directly impacts the risk of SSI [15,30–32]. Other important factors include the size of the implanted mesh (higher risk if mesh surface is above 300 cm²) [15,32], its architecture (higher risk when multifilament or dense membrane (such as expanded form of polytetrafluoroethylene (ePTFE) compared to porous monofilament structures) [15,19,28,33,34] or the presence of drainage placed intra-operatively in order to prevent the accumulation of fluid when placed for more than 3 days [35]. Patient demographics also influences the risk of developing mesh infection, as for other surgical fields, including smoking [12,36,37], existence of chronic pulmonary disease [31] or diabetes [38], along with patient age [12] and obesity [14,15].

However, those numbers do not necessarily and systematically represent the reality, and in some cases underestimate the true impact. Indeed, when a strict follow-up is performed, SSI rises well above 5% [39] up to 14% [40]. Bailey stressed in 1991 that, from an “acceptable” 7% of wound complication rates following hernia repair (including 3% of SSI), in reality, for the same patients undergoing rigorous postoperative surveillance, a 30% complication rates including 9% of infection was reported. Finally, he concluded that “complication rates are a reflection not only of the standards of surgical practice but also the rigour with which they are sought” [41].

3. Management of mesh-related infections

Generally, early wound SSIs (occurring within 30 days) are relatively easy to identify, with patients presenting symptoms characteristic of infection or inflammation, such as fever, focal tenderness, erythema or swelling [7]. However, late mesh infection can be indolent and more difficult to diagnose [42]. Clinically, the diagnosis of deep abdominal wall infection involving mesh material relies on the localization of peri-prosthetic inflammation with abscess or fistula using radiological imaging techniques, such as ultrasound, computerized tomography (Fig. 2) or less frequently MRI. Etiologic diagnosis is one of the cornerstones in the management of the patient with SSI. Without such diagnosis, treatment of the patient is empirical, and the risks of unsatisfying outcome increase. Those diagnoses are still based on classical methods, including a) stain and culture of aspirated fluid, b) periprosthetic tissue cultures or c) culture of liquid from sonication or agitation with vortex of totally or partially removed mesh.

Nevertheless, there are still numerous patients which have negative microbiological results, despite symptoms of infection. In consequence, improving the molecular biology tools for diagnosis is another requirement for better management of these complicated cases. In our opinion, it is crucial to further develop biomolecular techniques that will allow the detection and identification of the microorganisms present in a dormant state within mesh biofilm. Novel methodologies such as fluorescence in situ hybridization (FISH [16]) and gene sequencing [24] have already shown great potential in diagnosis, which might help to understand the pathogenicity of mesh-related infection and better tune a more “individualized” therapeutic approach.

3.1. Strategies for mesh prophylaxis

Prophylactic administration of antibiotics, either systematically or topically, is routine in some clinics, even if the real benefit in terms of protection against mesh-related infection is still controversial. Some authors do document a significant decrease in mesh infection when antibiotics are administered pre-operatively. For instance, in a prospective study of 280 patients hospitalized for prosthetic hernia repair who received either placebo (saline solution) or 1.5 g of ampicillin-sulbactam, Yerdel et al. registered an astounding +/−10-fold reduction in wound infection rates (from 9% to 0.7%), including a 3-fold decrease in deep SSI (from 2.2% to 0.7%) in the respective groups [39]. This decreased SSI had a direct impact on hospitalization duration, from 1.2 days when no complication occurred, up to 12 days in the cases of infected meshes. Similarly, reports tend to demonstrate as well that pre-operative administration of antibiotics may be helpful in institutions experiencing high rates of infection (>5%) [43] and where non-expert residents are performing the surgeries, along with high risk patients. Nevertheless, as summarized by Erdas et al., “Currently, there are no convincing arguments for recommending the routine use of antibiotic prophylaxis for groin hernia repair, especially in clinical settings with low incidence of SSI” [30].

Prophylactic administration of antibiotic relays generally in bolus injection, performed usually 30 min before starting the surgical procedure [30]. Alternatives to systemic administration of antimicrobial drugs have been proposed, using local approaches [44] by delivering antibiotics directly to the surgical wound. An early report from 1980 failed to demonstrate efficacy of local deposition (1 g of ampicillin as powder) on the incidence of hernia.
repair infection (SSI rate of 3.7% versus 4% for placebo) [45]. Using another antibiotic, Lazorthes et al. published a decade later complete prevention of SSI in patients receiving locally 750 mg of cefmanadole [46], compared to a 4.3% incidence of SSI for placebo group (p = 0.007, on 162 patients/group). In another study, wound irrigation with gentamicin (80 mg) along with IV antibiotherapy (1 g of Cefazolin) cleared all risk of mesh-related hernia infection for more than 25 years of utilization [47].

Looking at other surgical fields, e.g. orthopaedic surgery where the utilization of local drug delivery systems in combination with systemic therapy is common [48], Musella et al. significantly reduced the occurrence of mesh infection when collagen sponges impregnated with gentamicin were inserted in front of the prosthesis before suturing the wound (rate of SSI of 0.3% vs 2%, on 594 patients) [49]. Surprisingly, the utilization of such devices in hernioplasty is the exception and a limited number of reports is available in the literature to clearly estimate the benefit (refer to section 7).

3.2. Treatment of established infections of hernia implants

According to a recent issue from General Surgery: “Total expenses associated with a mesh infection came to $107,000 […] In comparison, a patient without hernia repair complications will incur hospital costs of $38,700 and an additional $1400 in follow-up charges over the next 12 months” [50]. This has to be added to the fact that hernia repair is the most common operation in general surgeries (with rate ranging for 10 per 100 000 persons in UK up to 28 per 100 000 in US, all ages included [51], resulting in approximately 60 000 mesh infections in US only [52,53].

The gravity and the treatment of infection following mesh implantation differs depending on the localization of the contamination. In hernioplasty, superficial SSI requires relatively simple treatment based on wound drainage and systemic antibiotic therapy. In contrast, the deep SSI of the implanted graft is much more serious and can even be fatal for the patient (mortality rate of 1.1% in hernioplasty of complicated clinical cases [54]).

After diagnosis of mesh infection, surgeons have either the choice of a conservative management with retention of the material, or its removal.

Whenever possible, a conservative approach with mesh salvage is preferred as it is less invasive for the patient than mesh removal, and it decreases the risk of re-herniation [37]. Following the diagnosis of infection, the basic treatment includes seroma extraction and the area is washed and disinfected using an antibiotic-containing irrigation (i.e. gentamicin solution) [18]. Patients will generally be treated with IV antibiotics initially followed by oral antibiotics for up to 12 weeks [37]. Despite these efforts, the long-term success rate is relatively limited and, frequently, the same patients can encounter recurrence of infection, which will eventually require the removal of the infected mesh [55]. In fact, the success of mesh conservation depends on the nature of the prosthesis, and salvation is relatively more efficient on monofilament mesh than on multifilament meshes or on dense PTFE or its expanded format patches (ePTFE) [56]. SSI occurring in monofilament mesh do not usually require the explantation of the material [15,57], which correlates with in vitro experiments revealing that bacteria persist better on multifilament meshes [58].

A multistage reconstruction approach is more often successful in treating contaminated meshes (Fig. 3). This method relies first on the debridement of necrotic tissues and excision of the infected materials (Fig. 3C and D), followed by routine irrigation with antibiotics and temporary closure with vacuum-assisted closure (VAC® illustrated Fig. 3B) [15]. Additionally, patients are treated with IV antibiotic therapy for few days until the symptoms of infection subside and, only at this point, a definitive closure of the wound with a new mesh material can be attempted [59]. Such a multistage approach can be relatively tedious for the patient as a clean wound situation must be achieved before the final closure, which can take few days to few weeks [60].

Fig. 3. Treatments of established mesh-related infection in hernioplasty. Illustration of ventral hernia infected mesh with high degree of tissue erosion and mesh extrusion (A, reprinted from Ref. [17]) and application of VAC® system (B, vacuum assisted closure) used to drain peri-prosthetic infectious fluid. Excision of the non-integrated portion of infected mesh, defined after local injection of methylene blue dye (B, C and D, reprinted with permission from Ref. [2]).
Mesh removal is required in 41% of the case of deep SSI [30], and more frequently in patients treated with ePTFE, as this patch cannot be drained efficiently due to its dense and laminated architecture [56]. Importantly, implanting biologic graft in dirty or contaminated environment is not advocated anymore as no study has clearly demonstrated superiority compared to macroporous synthetic meshes [61–65].

Despite such tedious protocol, mesh removal results in high risk of hernia recurrence (up to 20% [17]) and some patients need up to five re-operations for the healing to take place [42,66].

To conclude, mesh infection is not the most frequent complication occurring after mesh hernioplasty; however it does remain critical for the patients and for the healthcare systems. From this perspective, it is clear that there is substantial need for innovative solutions that could tackle mesh contamination.

4. Advances in antibacterial meshes

In order to decrease the risk of developing an infection, a significant amount of work has been done focusing on the functionalization of the prostheses to exhibit anti-infective behaviour. Those strategies can be basically categorized as passive (i.e. optimizing mesh design and macro-/micro-architecture) or active (combining therapeutics to the mesh materials) systems.

4.1. Guidance based on selection of appropriate mesh composition

The first strategy aiming to prevent mesh infection lies in the selection of appropriate prostheses, which is not as straight forward as we could think due to wide choice of meshes available in the market (more than 200 different commercialized meshes only in USA [67]). Those meshes are all characterized by specific structure, porosity, composition, weight, etc., which complicates the final decision for the surgeons [68].

Klinge et al. were among the first to investigate and compare how the morphological properties of different commercial meshes influence their susceptibility to infection [58]. They demonstrated that under in vitro condition, the ability of S. aureus to adhere to the materials was approximately 2-times reduced using monofilament mesh compared to multifilament (Fig. 4A, B and C). This was supposedly related to the increased surface area of the multifilament prostheses (of a factor 1.57 compared to monofilament meshes) along with the presence of microscopic additional niches, favouring bacteria attachment and biofilm settlement [69]. However, this hypothesis was not validated in their subsequent rat study, on which both groups showed similar degree of infection [58]. Further in vitro investigations undertaken by Bellón et al. have shown that, on polypropylene (PP) monofilament meshes bacteria grow preferentially at the node or filament crossover regions, whereas on ePTFE patches, they adhere between the internodal filaments [70]. Infected meshes do not seem to have altered mechanical properties, but the presence of microorganisms does impair the quality of integration in the host tissue [71–73].

More recently, different commercially available meshes were screened under in vivo condition (using infected rodent models) and authors observed a higher rate of bacteria clearance in monofilament compared to multifilament (Fig. 4D) [74], to composites and to laminate patches [75]. The available data on this topic indicates that such observations are true for synthetic meshes made of both permanent [69,74] and biodegradable polymers [73].

Mesh architecture in terms of weight and diameter of porosity were also shown to impact biomaterials susceptibility to infection in a rabbit infected model, favouring very large porosity (3.6 mm × 2.8 mm) and light weight (48 g/m²) knitted meshes [34].

The material composition of the meshes is another important factor to be taken into consideration regarding SSI. As already mentioned, biological grafts have been introduced in the past as suitable alternative to synthetic meshes in an infected environment. However, this is no longer considered best practice due to a number of adverse findings. Indeed, biological grafts are prone to higher bacteria adhesion compared to synthetic meshes [61,63,76,77] and graft infection can trigger premature in vivo degradation [62,78] and poor neovascularization [61]. A recent clinical study conducted on 73 patients with complex abdominal wall reconstruction showed that degradable meshes made of synthetic polymers (Phasix™ made of poly(4-Hydroxybutyrate) by

**Fig. 4.** Influence of mesh topography on susceptibility to infection. S. aureus adhesion in vitro was shown to be higher on multifilament meshes (A, SEM illustrations B and C, reprinted with permission from Refs. [58,76]). Bioluminescence signal follow-up of mesh infection on mice over 10 days on mono-versus multifilament meshes (radiance intensity correlates with degree of infection), reprinted with permission from Ref. [74].
Bard) are better able to resist infection, compared to biomes (porcine cadaveric prosthesis by Lifecell), with occurrence rate of 12.5% versus 31% respectively [79].

To withstand biomes deterioration due to the presence of collagenase-forming bacteria, several cross-linkers have been used to chemically stabilize the collagen compartment of such products (glutaraldehyde or hexamethylene diisocyanate) [63], but without any clear clinical benefits.

Such recent reports continue to foster criticisms regarding the utilization of biological implants in contaminated hernia [64], which is associated with their excessive cost (a 25 × 40 cm biologic prosthesis costs +$32 000) compared to synthetic polypropylene mesh (equivalent to $150) [80].

4.2. Utilization of meshes as drug delivery systems

4.2.1. Delivering antibiotics

The first attempt to add antibiotics to hernia meshes was reported in 1999 by Goeau-Brissoniere using simple immersion technique [81]. The rationale behind this approach was that local delivery of antibiotics maximizes specific tissue concentration and minimizes systemic toxicity. Using the implant as carrier for delivering drugs and improving therapeutic efficacy is a common strategy in some surgical fields, such as in orthopaedic surgery and has significantly helped reducing SSI [48,82]. This trend has not yet reached the field of soft tissue repair as a routine practice. Nevertheless, numerous reports have shown promising outcomes in vitro and in animal models, summarized in Table 1. Among the listed antibiotic agents, aminoglycoside (e.g. gentamicin) or glycopeptide (e.g. vancomycin) are the most common drugs delivered in combination with meshes.

Gentamicin has a broad spectrum of activity (against both Gram+ and Gram-microorganisms) and is one of the most potent antibiotics against staphylococcal infection [83]. In the 2005 review "Mesh-related infections after hernia repair surgery", Falagas was one of the first to hypothesise that embedding antibiotics directly with meshes could help in reducing bacterial adhesion and colonization [38]. The same year, pioneer report on mesh functionalization using antibiotics was published by Junge et al. using gentamicin grafted on polyvinylidene fluoride (PVDF) [84]. The authors reported a significant mesh protection against S. aureus for 24 h, but only under in vitro condition and this was unfortunately never translated to an animal study.

A limitation of aminoglycosides is that they are known to increase the risk of resistance among staphylococcal species. For instance, on a total of 250 clinical isolates of S. aureus, a recent investigation performed by Neeta et al. revealed a resistance rate against gentamicin of 26.4% (56% for MRSA stains). Consequently, as MRSA is responsible for a significant number of mesh-related infections, prophylactic monotherapy based on gentamicin, but also on fluoroquinolone, β-lactam (penicillin, cephalosporin, carbapenems) and even rifampin is not recommended.

Alternatively, vancomycin might be a better candidate and is nowadays the drug of choice for treating most MRSA infections in clinics, caused by multi-drug resistant strains. Vancomycin-loaded meshes were reported by four different groups [85–87], with complete bacteria clearance obtained in 3 out of 4 studies involving infected animal models (on mice [86,87], rat [88] and rabbit model [85]), requiring a loading charge of approximately 10 000 mg/cm² of prosthesis. Using a higher vancomycin loading (1.75 mg/cm²) on similar bioactive mesh allowed to clear infection in an infected pig model [59].

Mesh coatings using amoxicillin or ofloxacin could also protect the meshes from E. coli contamination in a rat model [90], but no solid data proves the same efficacy on staphylococcal infections (other than in vitro results presented by Laurent et al. [91]) and MRSA are commonly resistant to such antibacterial agents [92].

In order to enlarge the spectrum of activity of the antibacterial meshes, and to decrease risk of resistance, one strategy is to combine antibiotics using multi-therapy. This is particularly true for rifampicin, which is a potent staphylococcal drug (active against MRSA) able to penetrate biofilm, but resistance develops quickly during long-term treatment, and should always be used in combination with other antibiotics. For instance, combining rifampicin with a fluoroquinolone in a dual-coating allowed the in vitro inhibition of a large panel of microorganisms and to significantly decrease biofilm formation on PP meshes (Fig. 5B and C) [93]. In a rabbit model, bioprostheses impregnated with rifampicin and minocycline resulted in a complete prevention of MRSA and E. coli infection [94]. Such dual-therapy, including one bactericidal and one bacteriostatic agent, is highly efficient against both Gram-positive and Gram-negative bacteria (Fig. 5 A).

Even though lots of studies have demonstrated substantial efficacy under in vitro condition, very few have been able to completely protect the graft from contamination in infected animal models.

4.2.2. Delivering antiseptics

The misuse of antibiotics in prophylaxis promotes the occurrence of resistance and results in difficult situation for the clinicians hoping to treat patients suffering of SSI. Alternatives, including the local administration of antiseptics, have become more a more commonly observed approach to prevent such complications.

Along with antibiotic-loaded meshes, antiseptics have also been combined with prosthetic materials for hernia repair (Table 2). We found the record of two animal studies using dual-antiseptic strategies to prevent S. aureus infection, but with somewhat limited performance (only partial diminution of bacteria loading) [102,103]. Antiseptics have the great advantage of a broad spectrum of efficacy and rarely trigger resistance. Among antiseptics, triclosan has been used in clinics since more than 30 years (under the form of surgical scrubs, handwashes, dental hygiene solution, etc.). Sutures coated with triclosan are commercially available since 2003 (trademark VICRYL® Plus Antibacterial, from Ethicon) and has recently been approved as a recommendation by the World Health Organization to address a key risk factor for infection, independently of the type of surgery [104]. By using similar approach, polypropylene meshes were functionalized with a biodegradable adhesive chitosan gel embedding triclosan drug. In vitro, the diffusion of triclosan was relatively fast (80–90% was released within 24 h), which allows, in an infected in vivo model, to reduce partially S. aureus mesh infection after 8 days [102].

4.2.3. Delivering metallic antimicrobials

Doping medical devices using silver coating or silver nanoparticles (AgNPs) is a frequent strategy to confer protection against microorganisms (Table 3). AgNPs have a high potential to solve the problem of multidrug-resistant bacteria because microorganisms are unlikely to develop resistance against silver as compared with antibiotics. However, it is important to note that only silver in its soluble form (i.e. Ag+) exhibits biological activity, which is directly related to the concentration, the size, the shape and the morphology of the silver nano-particles [106]. Nanotechnology has been of tremendous impact in the field of antimicrobial silver-based therapeutics, as it is now possible to control and standardize the abovementioned nano-scale characteristics of the AgNPs. The still hypothetical mechanisms of action rely in either the alteration of cell membrane permeability or/and on the inhibition of DNA replication. Interestingly, by blocking exopoly-saccharide biosynthesis, silver can also disturb biofilm formation.
### Table 1
List of antibiotic-loaded meshes developed and main outcomes of the studies.

<table>
<thead>
<tr>
<th>Therapeutical agent</th>
<th>Technique of mesh functionalization</th>
<th>Mesh substrate</th>
<th>Amount loaded</th>
<th>Model</th>
<th>Micro-organisms targeted</th>
<th>Main outcomes</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mono-therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Plasma activation of PVDF followed</td>
<td>Polyvinylidene fluoride (PVDF)</td>
<td>45 μg/cm²</td>
<td>In vitro</td>
<td><em>S. aureus</em></td>
<td>Diameter of inhibition ranged from 18.5 to 25.1 mm² More than 99.9% reduction after 24 hrs</td>
<td>[84]</td>
</tr>
<tr>
<td></td>
<td>by graft polymerization of polyacid and covalent immobilization of gentamicin</td>
<td></td>
<td></td>
<td></td>
<td><em>S. epidermidis</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>impregnation</td>
<td>Polyester (PE) PP with PGCL membrane</td>
<td>1.68 mg/cm² 0.24 mg/cm²</td>
<td>In vitro</td>
<td>3 different strains of <em>S. aureus</em></td>
<td>Complete bacteria eradication</td>
<td>[96]</td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>impregnation</td>
<td>gelatin-coated PE mesh</td>
<td>0.10</td>
<td>0.21 mg/cm²</td>
<td>In vivo</td>
<td><em>S. aureus</em></td>
<td>Complete bacteria eradication</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>First chemical coating of cyclodextrin and then incubation of antibiotic Idem</td>
<td>PE</td>
<td>11.8 % wt</td>
<td>In vivo</td>
<td><em>S. aureus</em></td>
<td>Complete bacteria eradication</td>
<td>[86]</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>PE</td>
<td>9 % wt</td>
<td>In vivo</td>
<td><em>S. aureus</em></td>
<td>Complete bacteria eradication</td>
<td>[87]</td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>PE</td>
<td>1.75 mg/cm²</td>
<td>In vivo</td>
<td>MRSa</td>
<td>Complete bacteria eradication</td>
<td>[88]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dispersion of drug in methacrylate-based matrix used as coating by solvent casting</td>
<td>PP</td>
<td>0.32 mg/cm²</td>
<td>In vivo</td>
<td><em>S. epidermidis</em></td>
<td>Inhibition of bacteria development for 14 days Good tissue response and limited inflammatory reaction in treated group (no bacteria detected)</td>
<td>[85]</td>
</tr>
<tr>
<td></td>
<td>Mesh soaking</td>
<td>PE, PE with collagen antiadhesive barrier, PP and composite PP with antiadhesive membrane</td>
<td>From 0.04 up to 2.1 mg/cm²</td>
<td>In vivo</td>
<td>Rat model</td>
<td>MRSA Partial bacteria clearance from 50 to 80%</td>
<td>[88]</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>First chemical coating of cyclodextrin and then incubation of antibiotic</td>
<td>PP</td>
<td>40 mg/g</td>
<td>In vitro</td>
<td><em>S. aureus</em></td>
<td>Significant bacteria inhibition for 12−24 hrs</td>
<td>[91]</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Plasma treatment to load drug then entrapment via PEG polymerization</td>
<td>PP</td>
<td>60 % wt</td>
<td>In vitro</td>
<td><em>S. aureus</em></td>
<td>Addition of drug does not improve S. aureus inhibition (45 mg²)* but for *E. coli 750 mm²</td>
<td>[97]</td>
</tr>
<tr>
<td>Tetracyclin</td>
<td>Drug incorporated in electrospin mat</td>
<td>PLGA and PEUU electrospin mat</td>
<td>up to 7.7 % wt</td>
<td>In vitro</td>
<td><em>E. coli</em></td>
<td>Partial inhibition of bacteria proliferation for 3 to 7 days Limited wound dehiscence</td>
<td>[88]</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Drug dispersed in <em>PLA</em> solution and casted on mesh</td>
<td>PP</td>
<td>0.67 mg/cm² 0.33 mg/cm²</td>
<td>In vitro</td>
<td><em>E. coli</em></td>
<td>No viable bacteria detected</td>
<td>[90]</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>Bi-layer coating of polyester (PCL and <em>PLA</em>) containing drug</td>
<td>PP</td>
<td>0 up to 1.1 mg/cm²</td>
<td>In vitro</td>
<td><em>E. coli</em></td>
<td>Significant inhibition of bacteria proliferation* and biofilm formation at 0.11 mg/cm² 750 mm²</td>
<td>[99]</td>
</tr>
<tr>
<td>Cefalozin</td>
<td>Infusion in mesh</td>
<td>PGA-TMC</td>
<td>10 mg/cm²</td>
<td>In vivo</td>
<td>Rat model</td>
<td>MRSA Partial decrease of bacteria colonization</td>
<td>[100]</td>
</tr>
<tr>
<td><strong>Bi-therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin with chitosan</td>
<td>Oxidation of substrate followed by coating deposition via foulard method</td>
<td>PP</td>
<td>±48 μg chitosan and 4.3 μg of drug</td>
<td>In vitro</td>
<td><em>S. aureus</em></td>
<td>Absence of CFU after 1, 2 and 7 days</td>
<td>[101]</td>
</tr>
<tr>
<td>Ofloxacin + rifampicin</td>
<td>Tri-layer coating of polyester (PCL and <em>PLA</em>) containing drugs</td>
<td>PP</td>
<td>0.11 mg/cm² for each</td>
<td>In vitro</td>
<td><em>E. coli, S. aureus, S. epidermidis, MRSa, Enterococcus faecalis P. aeruginosa Klebsiella pneumoniae</em></td>
<td>Large ZOI (for up to 72 h) and absence of bacteria colonization Drastic diminution of Biofilm formation</td>
<td>[93]</td>
</tr>
<tr>
<td>Minocyclin + rifampicin</td>
<td>Impregnation of drugs on tyrosin-based matrix</td>
<td>Biomesh</td>
<td>115 μg/cm² for each</td>
<td>In vitro</td>
<td>MRSA</td>
<td>Large ZOI of 36 and 16 mm Limited acute inflammatory response and total bacteria clearance</td>
<td>[94]</td>
</tr>
</tbody>
</table>

In vitro assessments using either an *agar diffusion test or a *colony counting (colony forming unit, CFU). ZOI: Zone of inhibition. Abbreviation: poliglecaprone (PGCL), poly(lactic-co-glycolic acid) (PLGA), poly(etherurethane urea) (PEUU), poly(glycolic acid−trimethylene carbonate) (PGA-TMC).
Indeed, it was shown in vitro that a treatment for 2 h with 100 nM of silver nanoparticles resulted in a decrease of 95% and 98% of the biofilm formed by *P. aeruginosa* and *S. epidermidis* respectively [107]. Diverse substrates have been functionalized using silver nanoparticles, as listed Table 3 and illustrated Fig. 6. For instance, macroporous PP meshes coated with nano-Ag significantly reduced *in vitro* *E. coli* proliferation (Fig. 6A, B and C) [108]. Another study reported the feasibility of agglomerating silver particles onto biological prosthesis by simple immersion, with a relatively fine control of loading depending on the initial concentration of the immersion baths (Fig. 6C, D and E) [78]. Experiments performed on infected models have only shown partial protection of meshes containing silver nanoparticles [78,108] and further results are truly needed to positively appreciate such technology.

As an alternative to silver, Saygun et al. presented metallic coating performed on PP mesh based on gold and gold-palladium [109]. A 5 nm coating completely prevented *in vivo* mesh colonization by *S. epidermidis* for the alloy Au-Pd, whereas 30% and 100% of infection rates were registered for Au alone and for the control mesh respectively. The anti-bacterial mechanism is not fully understood, but according to the author's point of view, it mainly depends on the surface hydrophilicity, which was increased following Au-Pd deposition over the hydrophobic PP mesh. This explains why *S. epidermidis*, known to be hydrophobic, adhered preferably on PP than on Au-Pd coated PP meshes. Nevertheless, this preventive strategy might not be as efficient on other hydrophilic bacteria, such as *S. aureus*.

### 4.2.4. Delivering antimicrobial peptides

Another class of antimicrobial arsenal that has been combined with meshes are the antimicrobial peptides (AMPs) (Table 4). For instance, lysozyme is a potent antimicrobial agent against staphylococcal strains (including *S. aureus* MRSA and *S. epidermidis*). As endopeptidase, lysozyme rapidly lyses bacteria by creating microporformation, disrupting bacteria cell walls. Those naturally occurring enzymes have the ability to penetrate biofilm...
and exhibit bactericidal activity against both dividing and quiescent *Staphylococcus* sp. Based on literature, minimum inhibitory concentration MIC 90 of lysostaphin against *S. aureus* ranged from 0.001 to 0.064 µg/mL, which is much lower than other potent antibiotic alternatives (i.e. vancomycin is 2 µg/mL) [112]. Given that *S. aureus* is causative microorganism responsible for around 90% of mesh-related infections, such enzyme could be of tremendous interest [112]. Preliminary in vivo experiments performed on mice revealed that such systems are effective as treatment of established infection or as prophylaxis tool [113]. Another positive point is that lysostaphin does not have a direct effect on eukaryote cells and exhibits low toxicity [114,115]. Several investigations reported the

<table>
<thead>
<tr>
<th>Therapeutical agent</th>
<th>Technique of mesh functionalization</th>
<th>Mesh substrate</th>
<th>Amount loaded</th>
<th>Model</th>
<th>Micro-organisms Targeted</th>
<th>Main outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gold and Gold-Palladium (ratio 60/40)</td>
<td>Plasma deposition</td>
<td>PP</td>
<td>0.05 mg/cm²</td>
<td>In vitro</td>
<td><em>S. epidermidis</em></td>
<td>Both coatings decreased drastically mesh contamination (after 6 h up to 72 h of incubation)² Complete prevention of infection in Au-Pd. 30% of infection for Au group.</td>
</tr>
<tr>
<td>Silver nanoparticle (size of 11 nm)</td>
<td>Plasma polymerization of PAA followed by physical entrapment of nano-Ag</td>
<td>PET</td>
<td>1% w/w = 1.4 µg/cm²</td>
<td>In vivo</td>
<td><em>S. aureus</em> E. coli</td>
<td>Clear ZOI on both microorganisms¹ A 3 and 5 log₁₀ reduction in bacteria proliferation was detected compared to control mesh.</td>
</tr>
<tr>
<td>Nanocrystalline silver coating</td>
<td>Physical Vapor Deposition</td>
<td>PP</td>
<td>0.31/0.64/1.13 mg/cm²</td>
<td>In vitro</td>
<td><em>S. aureus</em></td>
<td>Direct relation between ZOI and the silver loading¹ Complete eradication of bacteria proliferation (decrease of 8-log within 8 h)³</td>
</tr>
<tr>
<td>Silver nanoparticles (size of 24 nm)</td>
<td>Not reported</td>
<td>PP</td>
<td>Not reported</td>
<td>In vivo</td>
<td>E. coli</td>
<td>A 3 to 4-log reduction after 1 h of adhesion assay³ and absence of biofilm formation Prevention of infection in 70% of the animals</td>
</tr>
<tr>
<td>Silver</td>
<td>Immersion in AgNO₃ solution</td>
<td>Polyurethane nanofibrous mat</td>
<td>Not reported</td>
<td>In vitro</td>
<td><em>S. aureus</em> <em>E. coli</em></td>
<td>Partial diminution in bacteria adhesion³ Large diameter of inhibition (antibacterial activity against <em>S. aureus</em> last up to 2 wks)⁵</td>
</tr>
<tr>
<td>Silver nanoparticles (size 15 nm)</td>
<td>Immersion in solution of silver nanoparticles</td>
<td>Biological graft</td>
<td>15 µg/cm²</td>
<td>In vitro</td>
<td><em>S. epidermidis</em> P. aeruginosa E. coli S. aureus</td>
<td>Partial protection: Incidence of SSI is 14% in silver group versus 38.8% in control</td>
</tr>
</tbody>
</table>

In vitro assessments using either.
¹ Agar diffusion test. ² Colony counting (colony forming unit, CFU) or. ³ SEM observation. ZOI: Zone of inhibition.

---

![Fig. 6. Silver coating strategies employed on synthetic or biological prostheses to reduce susceptibility to infection.](image)

Microscopic illustration of macroporous monofilament PP meshes coated with 24 nm silver nanoparticles embedded in a gel (A and B), allowing to significantly decrease in vitro mesh colonization by E. coli (compared to uncoated PP mesh, C). Silver nanoparticles can also be dispersed onto Porcine Small Intestinal Submucosa (PSIS, D and E), by simple immersion technique which permits to easily control the amount of loaded Ag depending on the silver concentration in the bath (F). Reprinted with permission from Refs. [78,108].
antibiotics was reported in 1999 by direct immersion in solutions of femA encoding for mutant strains losing the peptidoglycan enzymatic targets (gene 24). Vices is by immersion. The limitations which will be presented in the next paragraphs.

Several physical and chemical methodologies have been offered for the manufacturing of such bioactive materials. To do so, researchers have proposed to locally deliver IgG for polypropylene meshes (polymers) and only 2.1 for monofilament meshes (polymers) and only 2.1 for monofilament meshes [116].

As an alternative to staphylococcus-specific lysostaphin, other non-specific enzymes have been briefly tested in this field, such as lysozymes [116]. The advantage is their larger spectra of activity compared to lysostaphin, as lysozymes target as well the cells wall of Gram-positive bacteria, impairing or lysing bacteria cell membrane [121]. Nevertheless, the only report on lysozyme-impregnated meshes did not support their further development [116] (Table 4).

Another option is to prolong the levels of protective immunoglobulin, which is naturally secreted during any surgical procedures. To do so, researchers have proposed to locally deliver IgG directly from the mesh (using a coating based on hydrogel of carboxymethylcellulose and pooled polyclonal human IgG) [120].

5. Manufacturing technologies

Another important aspect to take into consideration in the development of antimicrobial meshes relies on the available options which are offered for the manufacturing of such bioactive implants. Several physical and chemical methodologies have been reported to combine antimicrobial components to mesh substrates, which will be presented in the next paragraphs.

5.1. Dipping/soaking

The simplest way to combine therapeutics to any medical device is by immersion. The first attempt to combine mesh with antibiotics was reported in 1999 by direct immersion in solutions of either gentamicin (10 mg/mL), rifampicin (20 mg/mL) or vancomycin (10 mg/mL). The loading efficiency was estimated to be around 0.10–0.20 mg/cm² of prosthesis, which was sufficient to prevent contamination in an infected rabbit model [81].

Table 4

<table>
<thead>
<tr>
<th>Therapeutical agent</th>
<th>Technique of mesh functionalization</th>
<th>Mesh substrate</th>
<th>Amount loaded</th>
<th>Model</th>
<th>Micro-organisms targeted</th>
<th>Main outcomes</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzymes</td>
<td>Lysozymes</td>
<td>Non-specific adsorption</td>
<td>PP</td>
<td>Not reported</td>
<td>In vitro</td>
<td>S. aureus</td>
<td>100% survival rate</td>
</tr>
<tr>
<td></td>
<td>Lysostaphin (Staphylococcal endopeptidase)</td>
<td>Non-specific adsorption</td>
<td>PP</td>
<td>Not reported</td>
<td>In vitro</td>
<td>S. aureus</td>
<td>25% survival rate</td>
</tr>
<tr>
<td></td>
<td>Lysostaphin</td>
<td>Chemical immobilization (Sulfo-SAND)</td>
<td>PP</td>
<td>Not reported</td>
<td>In vitro</td>
<td>S. aureus</td>
<td>98% survival rate</td>
</tr>
<tr>
<td></td>
<td>Polyclonal AMPs</td>
<td>Human IgG</td>
<td>CMC-IgG gel applied on mesh</td>
<td>PP</td>
<td>up to 30 µg/cm²</td>
<td>Rat model</td>
<td>S. aureus</td>
</tr>
<tr>
<td></td>
<td>AMPs</td>
<td>Human beta defensin (HBD-3)</td>
<td>Rat model</td>
<td>10 mg/cm²</td>
<td>In vivo</td>
<td>S. aureus</td>
<td>High rate of death of sepsis n non-lysostaphin groups</td>
</tr>
<tr>
<td></td>
<td>AMPs</td>
<td>Human cathelicidin (LL-37)</td>
<td>Mice model</td>
<td>Not reported</td>
<td>In vitro</td>
<td>S. aureus</td>
<td>Complete eradication</td>
</tr>
<tr>
<td></td>
<td>AMPs</td>
<td>Non-specific adsorption</td>
<td>Rat model</td>
<td>10 mg/cm²</td>
<td>In vivo</td>
<td>S. aureus</td>
<td>Complete eradication</td>
</tr>
<tr>
<td></td>
<td>AMPs</td>
<td>Compared to covalent immobilization</td>
<td>Rat model</td>
<td>10 mg/cm²</td>
<td>In vivo</td>
<td>MRSA</td>
<td>Complete eradication</td>
</tr>
<tr>
<td></td>
<td>AMPs</td>
<td>Non-specific adsorption</td>
<td>Rat model</td>
<td>10 mg/cm²</td>
<td>In vivo</td>
<td>P. aeruginosa</td>
<td>Complete eradication</td>
</tr>
<tr>
<td></td>
<td>AMPs</td>
<td>Compared to covalent immobilization</td>
<td>Rat model</td>
<td>10 mg/cm²</td>
<td>In vivo</td>
<td>S. aureus</td>
<td>Complete eradication</td>
</tr>
<tr>
<td></td>
<td>AMPs</td>
<td>PP and PE</td>
<td>Mice model</td>
<td>Not reported</td>
<td>In vitro</td>
<td>S. aureus</td>
<td>Complete eradication</td>
</tr>
</tbody>
</table>

Another option is to prolong the therapeutic window and to prolong the duration of activity. As an alternative to staphylococcus-specific lysostaphin, other non-specific enzymes have been briefly tested in this field, such as lysozymes [116]. The advantage is their larger spectra of activity compared to lysostaphin, as lysozymes target as well the cells wall of Gram-positive bacteria, impairing or lysing bacteria cell membrane [121]. Nevertheless, the only report on lysozyme-impregnated meshes did not support their further development [116] (Table 4).

Another option is to prolong the levels of protective immunoglobulin, which is naturally secreted during any surgical procedures. To do so, researchers have proposed to locally deliver IgG directly from the mesh (using a coating based on hydrogel of carboxymethylcellulose and pooled polyclonal human IgG) [120]. The rationale of this prophylactic treatment is to exacerbate the phagocytosis of planktonic bacteria by adding exogenous opsonic antibodies. Such approach has been successfully used in clinic since several decades through IV administration in a number of disorders [122]. In the presented IgG-delivery mesh, no beneficial effect was reported on MRSA infected mice when employed as monotherapy and showed only partial efficacy in implant-associated P. aeruginosa contamination [120].

5.2. Physical coating

In order to facilitate the loading of the prosthesis, to protect the therapeutics, or to control the elution profile, degradable polymers have been commonly employed as drug carriers through several mesh coating technologies. Functionalization of mesh has been proposed using a solvent casting methodology. Solvent casting is either performed by drop-by-drop deposition of the coating agents using a pipette onto the mesh [85,90,123] or by immersion of the mesh in the mixture [102], before a final drying step. Alternatively,
mesh coating can also be accomplished using foulard apparatus, requiring the passage of the mesh between two rolls foulard pre-impregnated with the antibiotic solution [101]. Several mesh coatings, based on water soluble (chitosan [102] [101], or poly-acrylic [85]), or organo-soluble (PLA<sub>90</sub> [90]) biomaterials have been presented using solvent casting technique. Such physical embedding of antibiotics in polymeric matrices allows for sustained release of drugs, from 7 days [90,101] up to one month [85] (experimented under in vitro [90,101] or in vivo [85] conditions). However, it remains relatively difficult to control the deposition and the thickness of the formed peri-prosthetic layers and to preserve the macroscopic porosity of the mesh substrate.

Taking example of previously described endo-prostheses coating technology, Guillaume et al. employed an airbrush system to deposit organic-based solution containing therapeutics combined with polymeric carrier onto macroporous meshes [93,99] (Fig. 7A). Compared to the aforementioned technologies, this spraying technique is relatively versatile in terms of control of the amount of materials to be deposited and allows for multiple layering approaches. Indeed, three successive polymeric coating layers were created surrounding the mesh (of a total thickness of 1-20 μm), allowing for the dual sustained release of ofloxacin and rifampicin. Advantageously, those techniques result only on a physical coating surrounding the mesh (Fig. 7B and C), and do not involve chemical modification of the mesh material by itself. However, the deposition of hard-shell polymeric biomaterials over the mesh knots and inter-filament spaces limits the filament mobility and ultimately impacts on the elastic behaviour of the hybrid mesh [99]. Additionally, coating delamination during mesh handling and implantation (for instance through laparoscopic approach) could potentially lead to treatment failure and should be systematically investigated, as shown Fig. 7D and E.

5.3. Chemical surface functionalization

Meshes functionalized by dipping/coating based technologies are commonly characterized by a burst release profile of the drug and a short-term period of antibacterial protection. In order to circumvent such limitations, one option is to stabilize the therapeutic onto the surface of the mesh through not only physical but chemical interactions. Such approaches have the advantages of not dramatically impairing the mechanical behaviour of the mesh substrate, as it i) does not involve chemical alteration of the bulk material in the filament but only the superficial molecular layers, ii) does not result in excessive agent deposition in the inter-filament and knot spaces (no major modification of materials elasticity).

However, being able to graft bioactive compounds onto a mesh substrate first requires the pre-activation of the surfaces, as the main polymeric components of meshes are relatively inert chemically without reactive groups to be used as initiators for further chemical functionalization (i.e. PP, PTFE, PET, PVDF, etc.). To alleviate such restriction, several studies employed a plasma treatment under controlled environmental condition (e.g. under oxygen atmosphere) in order to trigger the formation of intermediate reactive species and functional groups [84,97,110,125]. Subsequently, mesh activated by plasma treatment can either directly enhance drug-surface interaction (i.e. meshes become more hydrophilic [97]), or be used as anchorage points to molecular tethering (i.e. plasma-induced graft polymerization [84,101,110,125]) (Fig. 8A).

One first approach requires the chemical grafting of a polymeric backbone spacer onto the mesh materials that will then serve as a drug carrier. Using polymeric chain carriers alleviates the problem of steric hindrance between the activated mesh and the drug and the limited availability or accessibility of chemical groups, and potentially increases the drug loading yield compared to a direct drug-mesh grafting. Such option was developed by Junge et al., who activated PVDF mesh material using plasma treatment in order to create chemically active sites, which then allowed for acrylic acid graft polymerization (polyacrylic acid (PAA)) from the PVDF surface (Fig. 8A). Following the surface functionalization of the PVDF with PAA, the antibiotic (e.g. gentamicin) was covalently immobilized on the carboxylic acid groups of the PAA pendant chains [84,95,125]. The stability of the antibiotic-PAA covalent interaction was directly responsible for a limited burst effect (in vitro release of gentamicin was 48% in 1 day and 73% in 7 days) and a potent inhibitory effect on S. aureus growth after at least 24 h of incubation (reduction of S. aureus concentration in suspension was above 99.9% [95], Fig. 8B). Despite promising in vitro results, the antibacterial activity of PVDF-PAA-Gentamicin to prevent infection in animal models has not been made publicly available.

Indeed, covalent binding of anti-bacterial agents does not always correlate with a better efficacy, due to the restricted amount of therapeutic released and made available for the bacteria. This was also emphasized by Yurko et al., who observed that covalent immobilization of antimicrobial peptides prevented its diffusion from PP mesh, resulting in high bacterial survival rate compared to a non-specific absorption approach [116].

As an alternative, nano-scale chemical coating surrounding the prostheses can be created to act as an advanced drug reservoir, increasing the physico-chemical interactions between the antibiotics and the substrate (Fig. 8C). For example, efficacy of ampicillin loading to PP mesh was increased by a successive dual plasma treatments of the PP fibres, aiming to 1- increase the interaction drug-PP (via alteration of wettability, surface roughness, presence of bonding sites), and 2- prevent cytotoxicity (by masking the drug to eukaryote cells after entrapment within a PEG-grafted brush-like matrix, Fig. 8D) [97]. This delivery strategy has shown benefits not
only on antibiotics [97,101] but also on silver nanoparticles [110], Fig. 8E.

To further increase the adsorption property of mesh to targeted therapeutics, several authors have incorporated macromolecular traps in the chemical coating [86,87,91]. Cyclodextrins are cyclic 6–8 oligomers which exhibit the very advantage to have a hydrophobic cavity surrounded by hydrophilic corona containing active chemical groups (hydroxyl), Fig. 8F. The hydrophobic core can take up a wide range of organic compounds, such as vancomycin [86,87] or ciprofloxacin [91] and has shown promising efficacy as drug delivery system in numerous field of application. The available hydroxyl groups are usually employed as anchorage points for cross-linkers, in order to stabilize the cyclodextrin (CD)-based assembly in a chemical coating surrounding the mesh filaments. Polyethylene glycol diglycidyl ether (PEGDGE) [87], citric acids [91] or hexamethylene disocyanate [86] are among the reported reactive species to crosslink CD on the surface of polymer meshes. Successful drug absorption of up to 42 mg/g of CD-mesh (compared to < 10 mg/g for non-modified mesh) was reported by Laurent et al. (Fig. 8G), which allowed for S. aureus and E. coli growth inhibition for 24 h in vitro [91]. The available in vivo studies on mice (infected dorsal subcutaneous pocket) revealed complete bacteria clearance for groups treated with vancomycin-loaded meshes (‘bacteriological inhibition significantly improved compared to native meshes and to a local wound cleaning with an equivalent antibiotic flush solution, Fig. 8H) [86,87].

6. New strategies to endow mesh with antibacterial resistance

Among the alternatives to pharmaceutical drugs combined to implants to endow anti-bacterial properties, surfaces tethered with polycationic macromolecules have gained lots of interest. Positively charged long-chain quaternary ammoniums are among the ones with the greatest potential. Indeed, polyquaternary ammoniums (PQAs) can interact with the negatively charged membranes of bacteria, inducing biocidal activity by cell lysis. Diverse synthetic substrates have been functionalized using PQAs (such as PP [126], PET [127], PVDF [128] and PLA [129]) showing in vitro efficacy against a large number of bacteria (e.g., 99.999% of adhesion reduction observed on modified PLA for E. coli, P. aeruginosa, S. aureus and S. epidermidis [129]). Those preliminary investigations offer great promise in the field of antimicrobial surfaces as they confirm the relative non-specificity of PQAs and their bactericidal activity against multi-drug resistant microorganisms. The only available report on meshes (PP) coated with PQAs for infection prophylaxis revealed that, even though no zone of inhibition was observed surrounding the modified meshes, authors did observe a significant reduction of bacteria adhesion (which was further enhanced by loading the polymer with chlorhexidine) [123]. These studies can bring clear advantages compared to the previous options (i.e. using antibiotics), but we have to keep in mind that such antimicrobial surfaces i) do not entirely counterbalance risk of resistance, as adaptation has already been reported on microorganisms treated with quaternary ammonium based-biocides [130], and ii) might be readily covered by proteins and subsequently by fibrous tissue after their implantation in the body, decreasing their bactericidal activity.

Creating anti-fouling implant surfaces which are either superhydrophilic (i.e. immobilizing PEG [131]) or super-hydrophobic (i.e. dimethylchlorosilane [132]) is another common approach to decrease material colonization by infectious agents. Biomimetic omniphobic surfaces (repelling both aqueous and organic liquids) have been recently created by infusing microporous ePTFE alloplastic prostheses with several bio compatible fluorinated lubricants (at 40 µL/cm²) [133]. The resulting SLIPS-ePTFE materials (slippery liquid-infused porous surfaces) demonstrated in vitro S. aureus adhesion reduction of approximately 2-log (compared to non-coated ePTFE) after 48 h of incubation. In an infected rat model, SLIPS-ePTFE resisted bacteria contamination 3 days post-
inoculation. Additionally, authors observed that SLIPS surfaces attenuated peri-prosthetic inflammatory reaction and fibrosis formation (capsule thickness reduced of 50% around SLIPS-ePTFE compared to unmodified ePTFE). As the manipulation of the prosthesis with the SLIPS lubricant takes only few minutes, this process could be applied by the surgical team just prior to the implantation, which is a clearly more attractive and feasible technology than the others detailed previously.

Alternatively, anti-infective delivery systems could be implanted as adjunct devices to the main prosthesis to confer antibacterial protection (Fig. 9). This approach has been successfully employed in the field of orthopaedic and trauma surgery, where non-degradable PMMA beads or resorbable collagen fleece loaded with gentamicin are among the most popular products to prevent implant-related infection (Fig. 9A) [48]. Musella et al. presented one clinical study using similar bioactive collagen fleece placed in front of the mesh [49]. Unfortunately, such practice has never reached a routine utilization despite promising low rate of mesh-related sepsis (0.3% versus 2.1% in control group). The local administration of anti-infective delivery systems (adjunct to the prosthesis) through minimal invasive route could bring benefits for some specific abdominal wall surgeries (i.e. using laparoscopic approach). For instance, the peri-prosthetic administration of vancomycin-releasing microspheres (drug loading of ±10% w/w) was able to prevent multifilament PE mesh infection (in mice model challenged with 10⁶ S. aureus) [86] (Fig. 9B). Several “off-the-shelf” vehicles have been developed as prophylaxis tool, for example in bone surgery, using thermo-responsive hyaluronic derived hydrogel [134].

This system offers the advantage to be storable as a powder and to be reconstituted as a liquid with the appropriate therapeutic(s) just prior the surgery. Being a liquid at room temperature, the surgeon can easily inject or administer the formulation at the surgical site surrounding the prosthesis. Once placed within the wound, the HA-pNIPAM forms a gel after reaching its LCST (Lower Critical Solution Temperature set at above ±25 °C), allowing to maintain in-situ the antibiotic and to control its diffusion (Fig. 9C). In a rabbit model with contaminated bone fracture, such sol-gel formulation loaded with gentamicin sulphate (at 1% w/v) offered a total prevention of infection, showing that it could be as well of great interest as adjunct to meshes in abdominal wall reconstruction [134]. Another hyaluronic acid–based medical device, DAC® developed by Novagenit (http://www.dac-coating.com/), recently obtained the CE-marking. This biodegradable hydrogel formulation can be loaded with antibiotic and be applied by the surgeon in the theatre as coating to osteosynthesis implants to prevent SSI [135,136]. Such strategy is versatile as it can be employed to coat diverse implants, using diverse antibiotics as well. In addition, using bioactive adjuvants avoids the need to obtain the FDA-authorization for every single type of mesh (in case of bioactive mesh), but rather only for the adjuvant product. Such adjuvant could also be used in herniorrhaphy, where no mesh is used to fix the hernia defect, only suturing materials.

7. Commercially available products and clinical efficacy

Innovation in biomaterials and bioactive systems have paved the way to the development and to the recent commercialization of advanced meshes offering, among the activities, anti-infective protection [124]. Few companies have succeeded in obtaining the FDA clearance of antibiotic-loaded grafts (listed Table 5 and illustrated Fig. 10). The first antibiotic-loaded meshes were developed by GORE (MycroMesh® Plus and DualMesh® Plus, Fig. 10A and B) based on ePTFE patches impregnated with a synergistic chlorhexidine diacetate and silver carbonate mixture. As early as 1999, one of the first reports regarding the reconstruction of hernia defects with MycroMesh® Plus and DualMesh® Plus on patients was published [137]. This short-term clinical study (on 37 patients with a follow-up of 84 days post-operatively) aiming to investigate the adverse effect of those bioactive patches rather than their real anti-

![Fig. 9. Degradable additive adjuvants to prostheses aiming to confer temporary protection against mesh-related infection.](Image 133x263 to 472x343)

**Table 5**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Company</th>
<th>Patient numbers</th>
<th>Outcomes</th>
<th>Year of publication</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MycroMesh® Plus and DualMesh® Plus: ePTFE patches impregnated with chlorhexidine diacetate and silver carbonate</td>
<td>GORE</td>
<td>18</td>
<td>No adverse effects and similar complications compared to normal ePTFE</td>
<td>1999</td>
<td>[137]</td>
</tr>
<tr>
<td>DualMesh® Plus</td>
<td>GORE</td>
<td>65</td>
<td>No recorded infection but presence of non-infectious post-operative fever</td>
<td>2005</td>
<td>[141]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>82</td>
<td>Infection rates (5.8 up to 27.8%) significantly higher than non ePTFE mesh (±2%)</td>
<td>2013</td>
<td>[28]</td>
</tr>
<tr>
<td>XenMatrix AB Surgical Graft: Bioprosthesis with a coating of rifampin/minocycline</td>
<td>BARD</td>
<td>74</td>
<td>Within 30 days: 5 cases of re-infection</td>
<td>2016</td>
<td>[142]</td>
</tr>
<tr>
<td></td>
<td>Davol</td>
<td></td>
<td>Within 6 months: 0 SSI, but 4 cases of hernia recurrence, 3 cases of seroma and 3 of wound dehiscence</td>
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infective property, concluded to the safety of those products (similar to non-drug loaded ePTFE), with an overall infection rate of 2.7%.

Then, more recently, the potential of those commercialized patches to clear infection was screened on a contaminated animal model (mice infected with *S. aureus*). It showed that Myromesh<sup>®</sup> Plus significantly diminished bacteria colonization of a 4-log unit compared to competitive non-bioactive grafts [77]. Similar outcomes were also obtained using inoculated rat model, where authors observed that after 5 days of implantation, only the drug-loaded ePTFE patches could completely eradicate *S. aureus* (in 10 out of 12 specimens) [138]. Those pre-clinical results did not corroborate with a more recent clinical retrospective review focusing on infection prophylaxis using DualMesh<sup>®</sup> Plus, that did not show any beneficial protection [28].

Since then, competitor BARD Davol has launched two different hernia grafts endowed with antimicrobial properties. The 2012 FDA cleared “Ventrio<sup>™</sup> Light Hernia Patch with TRM Antimicrobial Coating” is a composite mesh based on one-side macroporous PP and anti-adhesive ePTFE on the second-side (designed to face the viscera, Fig. 10E). The structure is coated with a degradable matrix containing equal rifampin/minocycline loading of 115 μg/cm² each, embedded in a biore sorbable tyrosine-based polyarylute polymeric matrix (called PIVIT A/B<sup>ST</sup> Bioactive coating developed by TYRX Pharma). The few available data regarding its efficacy, performed on a laparotomy rabbit model inoculated with MRSA, demonstrated a significant decrease (compared to non-bioactive grafts) or a complete eradication of bacteria (depending on the initial inoculum concentration) [139].

Another prosthesis was FDA approved in 2014 from the same company, based on a biological graft coated with similar dual-antibiotics mixture (XenMatrix AB Surgical Graft, Fig. 10C). In a rabbit model with subcutaneous implantation and inoculation of MRSA or *E. coli*, no remnant bacteria could be isolated after 7 days due to the local release of the therapeutics from the mesh [94]. Bacterial protection was supported by the slow and sustained release of the incorporated drugs, as around 40% of active ingredients was still present on mesh materials after 5–7 days post-implantation [94].

Last, but not the least, the first drug-eluting mesh made of only macroporous polypropylene knitted filaments has been introduced using Ariste Medical coating technology (with rifampin and minocycline as active ingredients, Fig. 10D) with a FDA approval foreseen in the next month [140].

Nevertheless, the scarce amount of scientific reports publicly available regarding those emerging technologies and products does not allow to draw any unanimous conclusions.

Further studies are warranted and needed to validate the utilization of such bioactive infection-fighting meshes for high-risk patient groups. Nevertheless, the authors are well aware that such clinical studies dedicated to mesh infection prophylaxis or to the treatment of established infection would be difficult to carry out, as a large number of participants will be required to demonstrate statistically significant advantages [17]. Only one clinical study is under investigation on Cook<sup>®</sup> Antimicrobial Hernia Repair Device, on 24 enrolled patients with first completion date planned mid-2018 (study number NCT02401334).

8. Conclusion

The purpose of this review is to provide a broad vision of the problem of mesh-related infection in abdominal wall reconstruction and to expose how the hernia community endeavours to address it. From Deysine’s 2004 provoking question “Are we doing all we can?”, we can affirm that tremendous effort has been undertaken from every actor in this field, from biomaterial scientists, microbiologists up to clinicians. One must be aware that, to an apparently minimal 1–4% risk of mesh-related infection in hernia repairs, it does concretely correspond to several tens of thousands of complicated clinical cases to treat annually. Advanced in anti-infective biomaterial meshes is definitely one part of the solution to prevent and/or to treat mesh sepsis, which is the principal focus of this report. A huge variety of strategies are presented to confer mesh protection against infection, using appropriate *in vitro* and *in vivo* models. Such evolution is materialized by the recent FDA approval of several options including meshes loaded with antibacterial compounds, which might motivate and pave the way for further exciting developments. In the authors’ opinion, the main challenges in the field of mesh-related infection are, *i*) to develop or adopt a standardized animal model with infected hernia, *ii*) to develop further analytic techniques allowing to better diagnose dormant infection on patients presenting no sign of infection, *iii*) to develop versatile antimicrobial adjuvants to meshes rather than modified meshes (which will then require extensive Bioactive Medical Device Regulatory authorization for every bioactive mesh types), and finally *iv*) to be able to carry out larger clinical studies to validate the utilization of bioactive mesh as prophylactic or as treatment strategy.

References

[1] A.M. Grant, Collaboration EUHT, Open mesh versus non-mesh repair of groin hernia grafts endowed with antimicrobial properties. The 2012 FDA cleared “Ventrio™ Light Hernia Patch with TRM Antimicrobial Coating” is a composite mesh based on one-side macroporous PP and anti-adhesive ePTFE on the second-side (designed to face the viscera, Fig. 10E). The structure is coated with a degradable matrix containing equal rifampin/minocycline loading of 115 μg/cm² each, embedded in a biore sorbable tyrosine-based polyarylute polymeric matrix (called PIVIT A/B<sup>ST</sup> Bioactive coating developed by TYRX Pharma). The few available data regarding its efficacy, performed on a laparotomy rabbit model inoculated with MRSA, demonstrated a significant decrease (compared to non-bioactive grafts) or a complete eradication of bacteria (depending on the initial inoculum concentration) [139].

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