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Review

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 provides 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 antimicrobial 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.

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 incurs 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 herniatology 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.*

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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 will focus on biomaterials strategies used to fight against infection, but will also include the pathogenesis of mesh-related infection, the clinical solutions currently available and the recent advances in anti-infective meshes.

2. Surgical site infection in herniatology

The Centers for Disease Control (CDC) in the US distinguishes between incisional surgical site infections (SSI) occurring superficially and deeper within the body. By definition, a superficial incisional SSI is an infection involving only the skin or subcutaneous tissues, requiring relatively simple treatment based on wound drainage accompanied by antibiotics administered systematically. Mesh-related infection occurring after hernia surgery is, in contrast, considered a deep incisional SSI, and more elaborate treatment protocols may be required. In addition, because the mesh is considered an implant, the duration of surveillance and diagnosis is extended to 1 year post-operatively (instead of only 30 days for superficial SSI not involving implants), and it involves deep soft tissues (*e.g.* fascia and muscle layers) [6,7].

2.1. Pathogenesis of mesh-related contamination

There are a small number of cases reporting non-sterile, counterfeit meshes [8] or inappropriately re-sterilized meshes resulting in sepsis and post-operative mesh infection [9]. Those clinical cases are relatively rare, and, in fact, the main origin of microorganisms remain the patient's skin or mucosa and the surgical environment (*e.g.* flora of the caregiver) [2]. Generally, contamination is believed to occur at the moment of the surgical insertion of the biomaterial prosthesis into the abdominal cavity, caused by a small number of adhering microorganisms.

Staphylococcus aureus and *S. epidermidis* are the leading causative microorganisms, responsible for approximately 90% of mesh-related infection, with Methicillin-resistant *Staphylococcus aureus* (MRSA) [10], responsible for up to 63% of mesh-related SSI [11,12]) [13]. Other bacteria have been isolated from infected meshes, including Gram-positive species such as *Streptococcus pyogenes* [14] and *Enterococcus faecalis* [15,16] and Gram-negative species such as *Pseudomonas sp.* [14] and *Enterobacteriaceae* (such as *Escherichia coli* and *Klebsiella pneumonia* [17,18]). Additionally, some reports describe infection by other microorganisms such as *Propionibacterium acnes*, mycoplasma, rapidly growing mycobacteria and *Candida albicans* [19–21].

A critically important point to highlight is that biofilms formed on medical devices are usually composed of several bacterial strains, and mesh-related infections can also involve polymicrobial infection [16,22]. In those complicated cases, the isolation, cultivation and identification of every causative agents still remains challenging and numerous pathogens may remain underestimated depending of the exact practices in the clinical microbiology lab [16,23]. The utilization of modern biotechnological tools such as gene sequencing has been recently employed as alternative to 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].

2.2. 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 be reduced to as low as 0.1% [29].

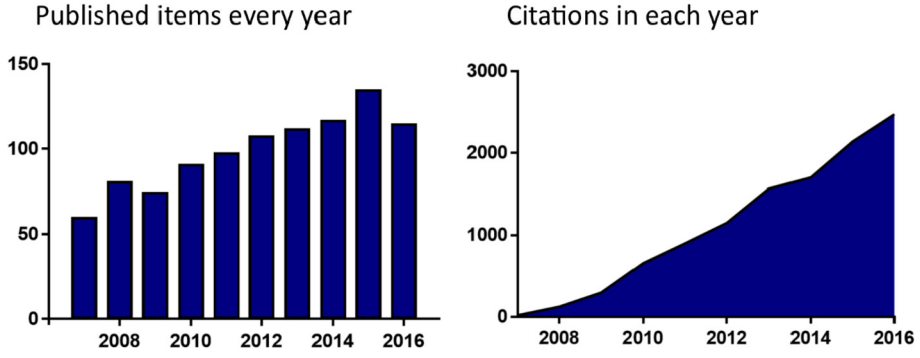


Fig. 1. Increasing awareness of mesh-related infections is reflected by the steady increase in scientific reports published every year. Search was done on the 8th of August 2017 on "isi web of knowledge" with key words "Mesh" + "Hernia" + "Infection".

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 cm^2) [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 relies 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

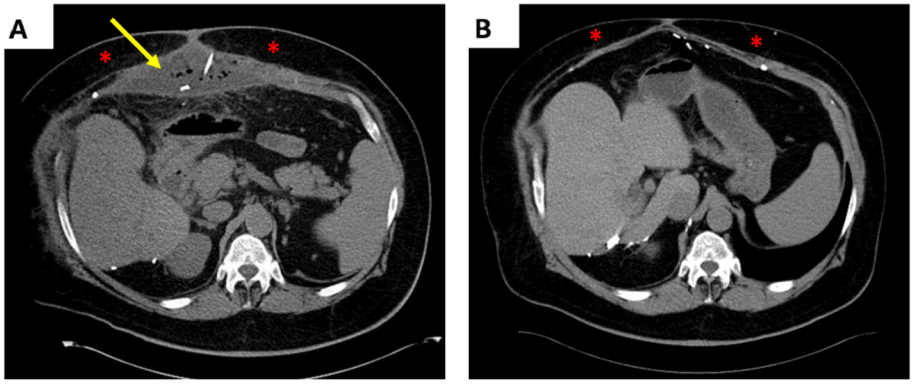


Fig. 2. Clinical diagnosis and evolution of mesh-related SSI using Computed-tomography technique.
CT illustration of peri-prosthetic fluid accumulation due to mesh contamination (by MRSA) 2 weeks post-operatively (A, abdominal wall is denoted by red stars and seroma is pointed out by the yellow arrow). Successful SSI eradication was reported after IV therapy with vancomycin (for 2 weeks) followed by local irrigation with gentamicin solution (three times daily for 4 weeks) added to a daily tablet of doxycycline for 12 months. The follow-up scan at 1 year demonstrated absence of fluid, signs of infection, or recurrence of the hernia (B). Reprinted with permission [18].

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 cefamanadole [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 salvation 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].

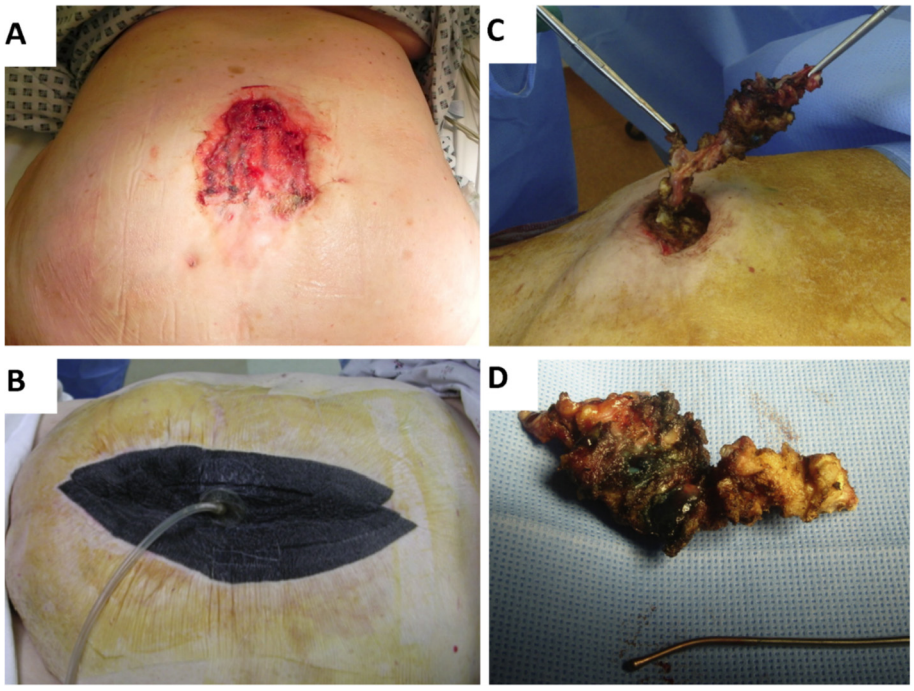


Fig. 3. Treatments of established mesh-related infection in herniatology.
Illustration of ventral hernia infected mesh with high degree of tissue erosion and mesh extrusion (A, reprinted from Ref. [17]) and application of VAC® system (B, vacuum assisted closure) used to drain peri-prosthetic infectious 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]).

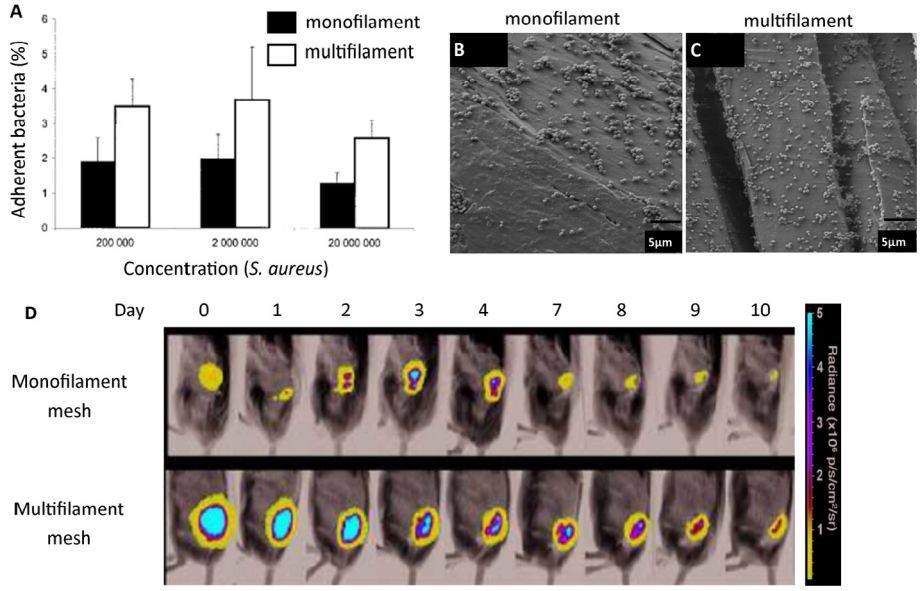


Fig. 4. Influence of mesh topography on susceptibility to infection.
S. aureus adhesion *in vitro* was shown to be higher on multifilament meshes (A, SEM illustrations B and C, reprinted with permission from Refs. [58,76]). Bioluminescence signal follow-up of mesh infection on mice over 10 days on mono-versus multifilament meshes (radiance intensity correlates with degree of infection), reprinted with permission from Ref. [74].

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 of 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/m^2) 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

Bard) are better able to resist infection, compared to biomeshes (porcine cadaveric prosthesis by Lifecell), with occurrence rate of 12.9% *versus* 31% respectively [79].

To withstand biomesh 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 therapeutical 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 %w/w (eq. to ±0.30 mg/cm^2 of prosthesis). Using a higher vancomycin loading (1.75 mg/cm^2) on similar bioactive mesh allowed to clear infection in an infected pig model [89].

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].

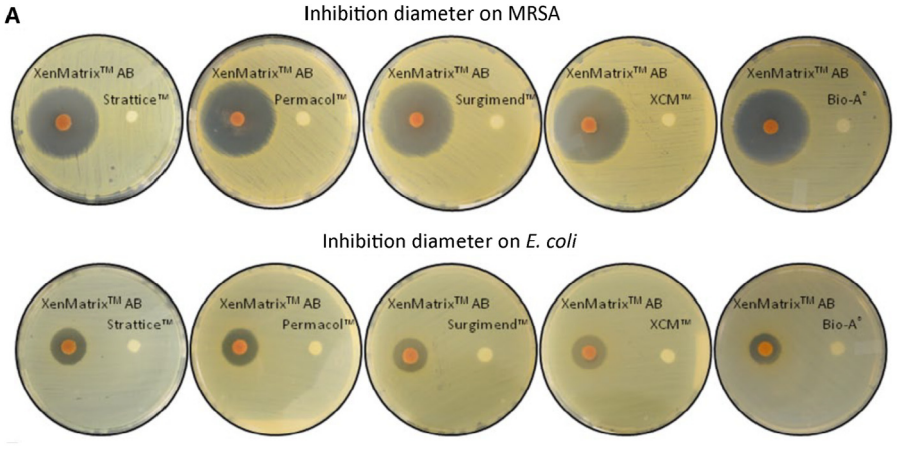
4.2.3. Delivering metallic antimicrobials

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 exopolysaccharide biosynthesis, silver can also disturb biofilm formation

Table 1
List of antibiotic-loaded meshes developed and main outcomes of the studies.

Therapeutical agent	Technique of mesh functionalization	Mesh substrate	Amount loaded	Model	Micro-organisms targeted	Main outcomes	Ref.
Mono-therapy							
Gentamicin	Plasma activation of PVDF followed by graft polymerization of polyacid acrylic and covalent immobilization of gentamicin	Polyvinylidene fluoride (PVDF)	45 μg/cm^2	*In vitro*	*S. aureus* *S. epidermidis* *E. coli* *S. aureus*	Diameter of inhibition ranged from 18.5 to 25.1 mm[a] More than 99.9% reduction after 24 hrs[b]	[84] [95]
	impregnation	Polyester (PE) PP with PGCL membrane	1.68 mg/cm^2 0.24 mg/cm^2	*In vitro*	3 different strains of *S. aureus*	Complete bacteria eradication[b]	[96]
Gentamicin Vancomycin Rifampicin	impregnation	gelatin-coated PE mesh	0.10 0.10 0.21 mg/cm^2	*In vivo* Rabbit model	*S. aureus*	Complete bacteria eradication[b]	[81]
Vancomycin	First chemical coating of cyclodextrin and then incubation of antibiotic	PE	11.8 % wt	*In vivo* Mice model	*S. aureus*	Complete bacteria eradication	[86]
	Idem	PE	9 % wt	*In vivo* Mice model	*S. aureus*	Complete bacteria eradication	[87]
	Idem	PE	1.75 mg/cm^2	*In vivo* Pig model	MRSA	Complete bacteria eradication	[89]
	Dispersion of drug in methacrylate-based matrix used as coating by solvent casting	PP	0.32 mg/cm^2	*In vitro* *In vivo* Rabbit model	*S. aureus* *S. epidermidis*	Inhibition of bacteria development for 14 days[a] Good tissue response and limited inflammatory reaction in treated group (no bacteria detected)	[85]
	Mesh soaking	PE, PE with collagen antiadhesive barrier, PP and composite PP with antiadhesive membrane	From 0.04 up to 2.1 mg/cm^2	*In vivo* Rat model	MRSA	Partial bacteria clearance from 50 to 80%	[88]
Ciprofloxacin	First chemical coating of cyclodextrin and then incubation of antibiotic	PP	40 mg/g	*In vitro*	*S. aureus* *S. epidermidis* *E. coli*	Significant bacteria inhibition for 12–24 hrs[a]	[91]
Ampicillin	Plasma treatment to load drug then entrapment via PEG polymerization	PP	60 % wt	*In vitro*	*S. aureus* *E. coli*	Addition of drug does not improve S. aureus inhibition (45 mm^2)[a] but for *E. coli* 750 mm^2	[97]
Tetracyclin	Drug incorporated in electrospun mat	PLGA and PEUU electrospun mat	up to 7.7 % wt	*In vitro* *In vivo* Rat model	*E. coli* Faecal contaminant	Partial inhibition of bacteria proliferation for 3 to 7 days[a] Limited wound dehiscence	[98]
Amoxicillin Ofloxacin	Drug dispersed in PLA_{50} solution and casted on mesh	PP	0.67 mg/cm^2 0.33 mg/cm^2	*In vitro* *In vivo* Rat model	*E. coli*	No viable bacteria detected[b] No biofilm formation No sign of infection and negative culture	[90]
Ofloxacin	Bi-layer coating of polyester (PCL and PLA_{50}) containing drug	PP	0 up to 1.1 mg/cm^2	*In vitro*	*E. coli*	Significant inhibition of bacteria proliferation[a,b] and biofilm formation at 0.11 mg/cm^2	[99]
Cefalozin	Infusion in mesh	PGA-TMC	10 mg/cm^2	*In vivo* Rat model	MRSA	Partial decrease of bacteria colonization	[100]
Bi-therapy							
Ciprofloxacin with chitosan	Oxidation of substrate followed by coating deposition via foulard method	PP	±48 μg chitosan and 4.3 μg of drug	*In vitro*	*S. aureus*	Absence of CFU after 1, 2 and 7 days[b]	[101]
Ofloxacin + rifampicin	Tri-layer coating of polyester (PCL and PLA_{50}) containing drugs	PP	0.11 mg/cm^2 for each	*In vitro*	*E. coli*, *S. aureus, S. epidermidis*, MRSA, *Enterococcus faecalis* *P. aeruginosa* *Klebsiella pneumoniae*	Large ZOI (for up to 72 h) and absence of bacteria colonization[a,b] Drastic diminution of Biofilm formation	[93]
Minocyclin + rifampicin	Impregnation of drugs on tyrosin-based matrix	Biomesh	115 μg/cm^2 for each	*In vitro* *In vivo* Rabbit model	MRSA *E. coli*	Large ZOI of 36 and 16 mm Limited acute inflammatory response and total bacteria clearance	[94]

In vitro assessments using either an [a]agar diffusion test or a [b]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).



B

Bacterial strain	Inhibition diameter (mm)
Escherichia coli	42
Staphylococcus epidermidis	34
Staphylococcus aureus	37
MRSA	36
Enterococcus faecalis	25
Pseudomonas aeruginosa	35
Klebsiella pneumoniae	35

C

	Total bacteria adhesion (CFU)			Biofilm ($Abs_{.600\ nm}$)
	24 h	48 h	72 h	
E. coli	0	0	0	0.09
S. epidermidis	0	0	0	0.14
Negative control*	$3\ 10^4$	$3\ 10^4$	$2\ 10^4$	0.62

Fig. 5. Efficacy of multi-drug loaded hernia prostheses to clear bacteria *in vitro*.
Illustration of diameter of inhibition of bioprosthesis containing rifampin and minocycline (XenMatrix™ AB) on MRSA and E. coli 24 h post-inoculation compared to non-active commercial grafts (A). Quantification of diameter of inhibition (B), anti-adherential and anti-biofilm activity (C) of PP mesh coated with rifampicin and ofloxacin (reprinted with permission from Refs. [93,94]).

Table 2
List of antiseptic-loaded meshes developed and main outcomes of the studies.

Therapeutical agent	Technique of mesh functionalization	Mesh substrate	Amount loaded	Model	Micro-organisms targeted	Main outcomes	Ref.
Chlorhexidine *versus* chlorhexidine + allicin	Soaking	PP	Not reported	*In vitro* *In vivo* Rabbit model	*S. aureus*	ZOI of 36.9 and 25.7 mm for bi- compared to mono-therapy[a] Partial bacteria clearance, but no advantage of combination	[103]
triclosan and chitosan	Mesh embedded in gel + drug	PP	Not reported	*In vivo* Rat model	*S. aureus*	3-log reduction of bacterial contamination	[102]

[a] In vitro assessments using colony counting (colony forming unit, CFU). In Perez-Kohler et al. study [103], allicin was combined to chlorhexidine as previous report has demonstrated that allicin (extracted from garlic) exerts antibacterial activity [105].

[106]. 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, lysostaphin is a potent antimicrobial agent against staphylococcal strains (including *S. aureus* MRSA and *S. epidermidis*). As endopeptidase, lysostaphin rapidly lyses bacteria by creating microperforation, disrupting bacteria cell walls. Those naturally occurring enzymes have the ability to penetrate biofilm

Table 3
List of metal-loaded meshes developed and main outcomes of the studies.

Therapeutical agent	Technique of mesh functionalization	Mesh substrate	Amount loaded	Model	Micro-organisms Targeted	Main outcomes	Ref.
Gold and Gold-Palladium (ratio 60/40)	Plasma deposition	PP	0.05 mg/cm^2 Coating of 5 nm	*In vitro* *In vivo* Rat model	*S. epidermidis*	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.	[109]
Silver nanoparticle (size of 11 nm)	Plasma polymerization of PAA followed by physical entrapment of nano-Ag	PET	1% w/w = 1.4 μg/cm^2	*In vitro*	*S. aureus* *E. coli*	Clear ZOI on both microorganisms[a] A 3 and 5 log_{10} reduction in bacteria proliferation was detected compared to control mesh[b]	[110]
Nanocristalline silver coating	Physical Vapor Deposition	PP	0.31/0.64/1.13 mg/cm^2	*In vitro*	*S. aureus*	Direct relation between ZOI and the silver loading[a] Complete eradication of bacteria proliferation (decrease of 8-log within 8 h)[b]	[53]
Silver nanoparticles (size of 24 nm)	Not reported	PP	Not reported	*In vitro* *In vivo*	*E. coli*	A 3 to 4-log reduction after 1 h of adhesion assay[b] and absence of biofilm formation Prevention of infection in 70% of the animals	[108]
Silver	Immersion in $AgNO_3$ solution	Polyurethane nanofibrous mat	Not reported	*In vitro*	*S. aureus* *E. coli*	Partial diminution in bacteria adhesion[c]	[111]
Silver nanoparticles (size 15 nm)	Immersion in solution of silver nanoparticles	Biological graft	±15 μg/cm^2	*In vitro* *In vivo* Rat model	*S. aureus* *S. epidermidis* *P. aeruginosa* *E. coli* *S. aureus*	Large diameter of inhibition (antibacterial activity against S. aureus last up to 2 wks)[a] Partial protection: Incidence of SSI is 14% in silver group *versus* 38.8% in control	[78]

In vitro assessments using either.
[a] Agar diffusion test.
[b] Colony counting (colony forming unit, CFU) or.
[c] SEM observation. ZOI: Zone of inhibition.

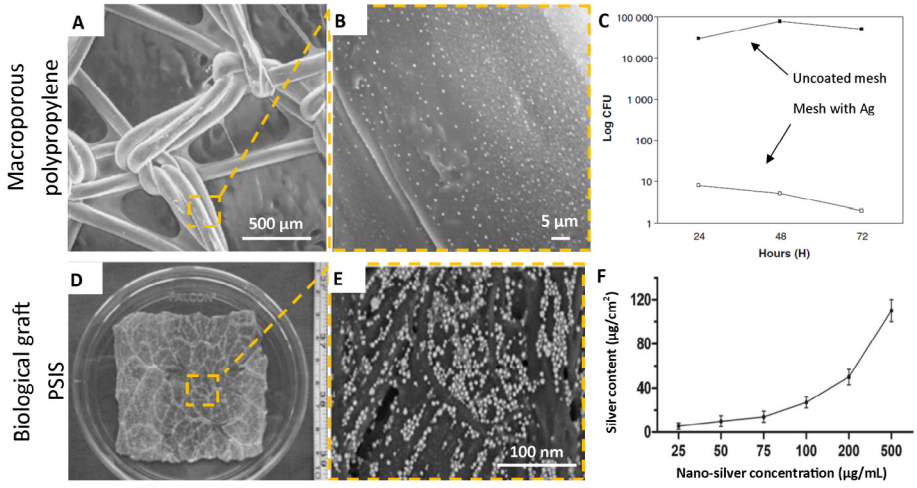


Fig. 6. Silver coating strategies employed on synthetic or biological prostheses to reduce susceptibility to infection.
Microscopic illustration of macroporous monofilament PP meshes coated with 24 nm silver nanoparticles embedded in a gel (A and B), allowing to significantly decrease *in vitro* mesh 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].

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 4
List of antimicrobial peptides combined with meshes and main outcomes of the studies.

Therapeutical agent		Technique of mesh functionalization	Mesh substrate	Amount loaded	Model	Micro-organisms targeted	Main outcomes	Ref.
Enzymes	Lysozymes	Non-specific adsorption	PP	Not reported	*In vitro*	*S. aureus*	100% survival rate	[116]
		Non-specific adsorption					25% survival rate	
	Lysostaphin (Staphylococcal endopeptidase)	Chemical immobilization (Sulfo-SAND)					98% survival rate	
	Lysostaphin	Non-specific adsorption	Biomesh	12 μg/cm^2	*In vivo* Rat model	*S. aureus*	Complete bacterial eradication High rate of death of sepsis in non-lysostaphin groups	[117,118]
		Non-specific adsorption	PP and PE	up to 30 μg/cm^2	*In vivo* Rat model	*S. aureus*	Complete eradication using 30 μg/cm^2	[112]
Polyclonal antibodies	Human IgG	CMC-IgG gel applied on mesh	PP	10 mg/cm^2	*In vivo* Mice model	MRSA *P. aeruginosa*	0% survival rate 70% survival rate	[120]
AMPs	Human beta defensin (HBD-3) Human cathelicidin (LL-37)	Non-specific adsorption Compared to covalent immobilization	PP	Not reported	*In vitro*	*S. aureus*	100% survival rate	[116]

functionalization of meshes by such Staphylococcal endopeptidase [112,116–118] and demonstrated a significant antibacterial protection under *in vitro* [116] and *in vivo* condition [117,118], higher than other AMPs (*i.e.* HDB and LL-37 [116]), listed Table 4. However, mutant strains losing the peptidoglycan enzymatic targets (gene encoding for *femA* protein) is reported inducing a complete resistance against such AMPs [119].

As alternative to *staphyloccocus*-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. 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 devices 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/cm^2 of prosthesis, which was sufficient to prevent contamination in an infected rabbit model [81]. Non-specific physical adsorption of antibiotics [81,88,96,100], antiseptics [103] and enzymes [112,116] were reported by dipping or soaking aqueous solution containing the therapeutics directly on the meshes. Under such condition, the amount of antibacterial compound loaded depends mainly on the fluid adsorption capability of the mesh substrate. Wiegering et al. determined this adsorption factor experimentally, which was equal to 3.8 for multifilament meshes (polyesters) and only 2.1 for monofilament meshes (polypropylene/poliglecaprone). Similar results were presented by Sadana et al., evaluating the antibiotic uptake for different commercial meshes following incubation in vancomycin solution at 10 mg/mL for 15 min, which ranged from 0.04 mg/cm^2 for polypropylene monofilament up to 2.1 for composite PP/hydrogel prosthesis [88], with a direct impact on *in vitro* MRSA clearing capability. This methodology has the advantage of being realisable directly in the theatre by the surgical team before the insertion of the mesh in the patient, and consequently should not necessitate specific FDA-approval has the mesh material by it-self is not modified. Presoaking meshes in antibiotic solution does not lead to prolonged delivery, but aims principally in covering the critical early postoperative period to prevent bacterial adhesion to the materials, which was defined to be around 6 h [120]. A clinical study has shown that almost no antibiotic was detectable in patient's serum 24 h following the implantation of gentamicin presoaked meshes [96]. However, such technology has not yet shown clinical superiority over systemic antibiotic therapies [27], and further optimization should be sought to improve the therapeutic window and to prolong the duration of activity.

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_{50} [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+/-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 filaments 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 acidic groups of the PAA pendent 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 benefices not

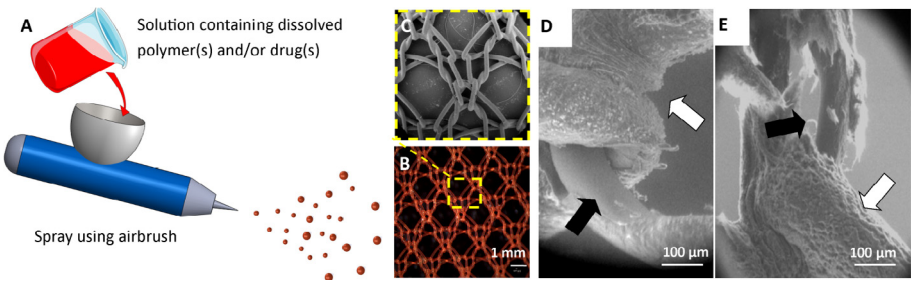


Fig. 7. Multi-layer coating on mesh using airbrush spray technology.
Illustration of the airbrush coating system allowing for the creation of a polymer reservoir entrapping antibacterial drugs (e.g. ofloxacin and rifampicin) around the filament of PP mesh (A, B and C). Material delamination and deterioration resulting from cyclic elongation assay (the coating and the supportive PP materials are denoted with the white and black arrows respectively). Reprinted with permission from Refs. [93,99,124].

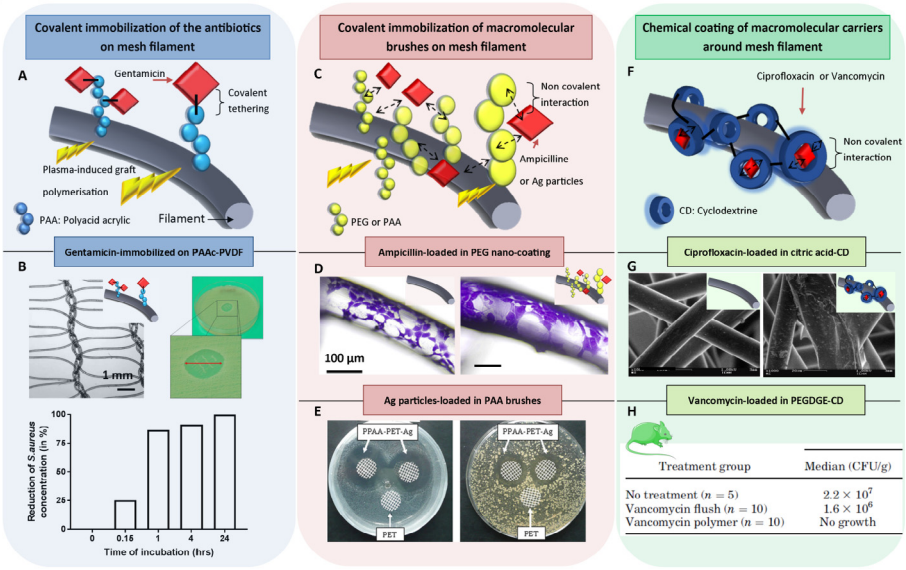


Fig. 8. Illustration of the main strategies developed to covalently graft drug polymeric carriers on hernia meshes to confer antimicrobial protection.
Following plasma activation of the surface of meshes, macromolecular spacers can polymerize from the surfaces and be used as binding sites for further covalent immobilization of antibiotics (A). This strategy does not alter mesh macroscopic features, while allowing for bacteria inhibition (after at least 24 h of incubation with *S. aureus*, B). Polymeric spacers can also act as brushes increasing drug-mesh affinity (non-covalent interaction between polymers and the therapeutics, C). The coating brushes covering meshes can mask the cytotoxic of the drug to fibroblasts (cells spreading onto mesh's surface are stained with crystal violet, D). Such strategy was not only successful for antibiotics, but also for silver nanoparticles on PET meshes (against *S. aureus* and *E. coli*, as shown by the inhibition diameters compared to non-loaded PET (PPAA stands for Plasma Polymerized Polyacrylic Acid, E). Macromolecular traps (i.e. cyclodextrin, CD) have been cross-linked surrounding the mesh filaments and loaded with hydrophobic drugs (F). The created CD molecules nano-coating can be observed using SEM (G) and allowed to treat *S. aureus* infection on mice, to a better degree than non-treated and antibiotic flush groups (H). Reprinted with permission from Refs. [84,87,91,95,97,110].

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 diisocyanate [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 super-hydrophilic (*i.e.* immobilizing PEG [131]) or super-hydrophobic (*i.e.* dimethyldichlorosilane [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 biocompatible fluorinated lubricants (at 40 µL/cm^2) [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 (adjacent to the prosthesis) through minimal invasive route could bring benefices 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 10^4 *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-

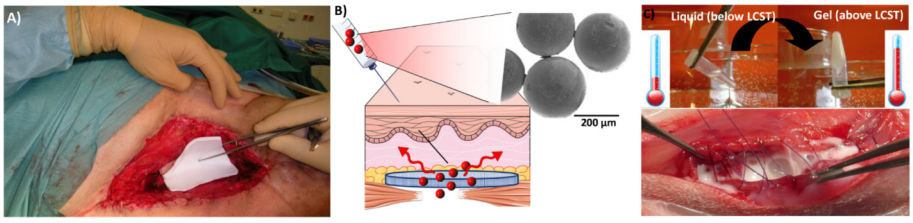


Fig. 9. Degradable additive adjuvants to prostheses aiming to confer temporary protection against mesh-related infection.
Antibiotic loaded collagen fleece applied at the surgical site before insertion of the implant (A). Example of local drug vehicle administrable through minimal invasive routes, such as microspheres loaded with vancomycin (B) or thermoresponsive HA-pNIPAM (Poly(N-isopropylacrylamide) grafted hyaluronan) loaded with gentamicin formulation for in-situ gelation (C). Reprinted with permission from Refs. [48,86,134].

Table 5
Reported clinical investigations available on anti-infective meshes in herniatology.

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

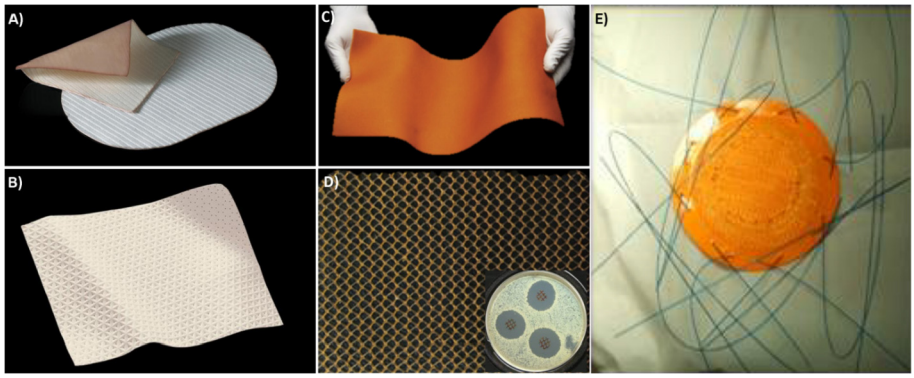


Fig. 10. Antibiotic-eluting prostheses developed for hernia repair, FDA-cleared or under approval status.
GORE launched DualMesh® Plus and MycroMesh® Plus based of ePTFE impregnated with chlorhexidine diacetate and silver carbonate (A and B). Rifampin/minocycline coated biological prosthesis (C) and synthetic mesh (D and E), developed by BARD (XenMatrix AB Surgical Graft, C and Ventrio™ Light Hernia Patch with TRM Antimicrobial Coating, E) or Ariste Medical (D). Images A, B and D are available from suppliers' websites. C and E are reprinted with permission from Refs. [139,142].

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 Mycromesh® 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 drugs-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® 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™ 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 rifampicin/minocycline loading of 115 μg/cm^2 each, embedded in a bioresorbable tyrosine-based polyarylate polymeric matrix (called PIVIT A/B™ ST 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® 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: meta-analysis of randomised trials based on individual patient data, Hernia 6 (2002) 130–136.
[2] J.F. Gillion, J.P. Palot, Abdominal wall incisional hernias: infected prosthesis: treatment and prevention, J. Vis. Surg. 149 (2012) e20–31.
[3] K. Vagholkar, A. Pawanarkar, S. Vagholkar, M. Iyengar, S. Pathan, Hernia mesh infection: a surgical disaster, Inter. Surgery J. 3 (2016) 950–953.
[4] M. Deysine, J. Abelleira, F. Guarnieri, A. Guarnieri, Historical Evolution of Asepsis and Antisepsis, Hernia Infections: CRC Press, 2003, pp. 1–16.
[5] M. Deysine, Post mesh herniorrhaphy infection control: are we doing all we can? Hernia 8 (2004) 90–91.
[6] T.C. Horan, R.P. Gaynes, W.J. Martone, W.R. Jarvis, T.G. Emori, CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections, Am. J. Infect. Contr. (20) (1992) 271–274.
[7] A.J. Mangram, T.C. Horan, M.L. Pearson, L.C. Silver, W.R. Jarvis, Guideline for prevention of surgical site infection, 1999. Centers for disease control and prevention (CDC) hospital infection control practices advisory committee, Am. J. Infect. Contr. (27) (1999) 97–132.
[8] M.K. McDermott, I.S. Isayeva, T.M. Thomas, A.S. Lee, A.D. Lucas, C.N. Witkowski, et al., Characterization of the structure and properties of authentic and counterfeit polypropylene surgical meshes, Hernia 10 (2006) 131–142.
[9] M.J. Tolino, D.E. Tripoloni, R. Ratto, M.I. Garcia, Infections associated with prosthetic repairs of abdominal wall hernias: pathology, management and results, Hernia 13 (2009) 631–637.
[10] C. Akyol, F. Kocaay, E. Orozakunov, V. Genc, I. Kepenekci Bayram, A. Cakmak, et al., Outcome of the patients with chronic mesh infection following open inguinal hernia repair, J. Korean Surg. Soc. 84 (2013) 287–291.
[11] W.S. Cobb, J.B. Harris, J.S. Lokey, E.S. McGill, K.L. Klove, Incisional herniorrhaphy with intraperitoneal composite mesh: a report of 95 cases, Am. Surg. 69 (2003) 784–787.
[12] M.N. Mavros, S. Athanasiou, V.G. Alexiou, P.K. Mitsikostas, G. Peppas, M.E. Falagas, Risk factors for mesh-related infections after hernia repair surgery: a meta-analysis of cohort studies, World J. Surg. 35 (2011) 2389–2398.
[13] M. Mehrabi Bahar, A. Jabbari Nooghabi, M. Jabbari Nooghabi, A. Jangjoo, The role of prophylactic cefazolin in the prevention of infection after various types of abdominal wall hernia repair with mesh, Asian J. Surg. 38 (2015) 139–144.
[14] A. Rios, J.M. Rodriguez, V. Munitiz, P. Alcaraz, D. Perez Flores, P. Parrilla, Antibiotic prophylaxis in incisional hernia repair using a prosthesis, Hernia 5 (2001) 148–152.
[15] S. Stremitzer, T. Bachleitner-Hofmann, B. Gradl, M. Gruenbeck, B. Bachleitner-Hofmann, M. Mittlboeck, et al., Mesh graft infection following abdominal hernia repair: risk factor evaluation and strategies of mesh graft preservation. A retrospective analysis of 476 operations, World J. Surg. 34 (2010) 1702–1709.
[16] S. Kathju, L. Nistico, R. Melton-Kreft, L.A. Lasko, P. Stoodley, Direct demonstration of bacterial biofilms on prosthetic mesh after ventral herniorrhaphy, Surg. Infect. 16 (2015) 45–53.
[17] L. Chung, G.H. Tse, P.J. O'Dwyer, Outcome of patients with chronic mesh infection following abdominal wall hernia repair, Hernia 18 (2014) 701–704.
[18] J.A. Trunzo, J.L. Ponsky, J. Jin, C.P. Williams, M.J. Rosen, A novel approach for salvaging infected prosthetic mesh after ventral hernia repair, Hernia 13 (2009) 545–549.
[19] A.F. Engelsman, H.C. van der Mei, R.J. Ploeg, H.J. Busscher, The phenomenon of infection with abdominal wall reconstruction, Biomaterials 28 (2007) 2314–2327.
[20] A. Celdrán, J. Esteban, J. Mañas, J.J. Granizo, Wound infections due to Mycobacterium fortuitum after polypropylene mesh inguinal hernia repair, J. Hosp. Infect. 66 (2007) 374–377.
[21] A. Luhmann, A. Moses, Successful conservative treatment of a candida albicans intraperitoneal mesh infection following laparoscopic ventral hernia repair, Hernia 19 (2015) 845–847.
[22] V.G. Shankar, K. Srinivasan, S.C. Sistla, S. Jagdish, Prophylactic antibiotics in open mesh repair of inguinal hernia - a randomized controlled trial, Int. J. Surg. 8 (2010) 444–447.
[23] D. Lebeaux, A. Chauhan, O. Rendueles, C. Beloin, From in vitro to in vivo models of bacterial biofilm-related infections, Pathogens 2 (2013) 288–356.
[24] O. Langbach, A.K. Kristoffersen, E. Abesha-Belay, M. Enersen, O. Rokke, I. Olsen, Oral, intestinal, and skin bacteria in ventral hernia mesh implants, J. Oral Microbiol. 8 (2016) 31854.
[25] W. Zimmerli, Infection and musculoskeletal conditions: prosthetic-joint-associated infections, Best Pract. Res. Clin. Rheumatol. 20 (2006) 1045–1063.
[26] B. Klosterhalfen, U. Klinge, B. Hermanns, V. Schumpelick, Pathology of traditional surgical nets for hernia repair after long-term implantation in humans, Chirurg 71 (2000) 43–51.
[27] B. Perez-Kohler, Y. Bayon, J.M. Bellon, Mesh infection and hernia repair: a review, Surg. Infect. 17 (2016) 124–137.
[28] R.H. Brown, A. Subramanian, C.S. Hwang, S. Chang, S.S. Awad, Comparison of infectious complications with synthetic mesh in ventral hernia repair, Am. J. Surg. 205 (2013) 182–187.
[29] L. Avtan, C. Avci, T. Bulut, G. Fourtanier, Mesh infections after laparoscopic inguinal hernia repair, Surg. Laparosc. Endosc. 7 (1997) 192–195.
[30] E. Erdas, F. Medas, G. Pisano, A. Nicolosi, P.G. Calo, Antibiotic prophylaxis for open mesh repair of groin hernia: systematic review and meta-analysis, Hernia (2016).
[31] J.R. Dunne, D.L. Malone, J.K. Tracy, L.M. Napolitano, Abdominal wall hernias: risk factors for infection and resource utilization, J. Surg. Res. 111 (2003) 78–84.
[32] J. Bueno-Lledo, A. Torregrosa-Gallud, A. Sala-Hernandez, F. Carbonell-Tatay, P.G. Pastor, S.B. Diana, et al., Predictors of mesh infection and explantation after abdominal wall hernia repair, Am. J. Surg. (2016).
[33] G.E. Leber, J.L. Garb, A.I. Alexander, W.P. Reed, Long-term complications associated with prosthetic repair of incisional hernias, Arch. Surg. 133 (1998) 378–382.
[34] A. Diaz-Godoy, M.A. Garcia-Urena, J. Lopez-Monclus, V.V. Ruiz, D.M. Montes, N.E. Agurto, Searching for the best polypropylene mesh to be used in bowel contamination, Hernia 15 (2011) 173–179.
[35] L. Prieto-Borja, R. Perez-Tanoira, D.C. Levano-Linares, A. Celdran, I. Mahillo-Fernandez, J. Esteban, Sonication of abdominal drains: clinical implications of quantitative cultures for the diagnosis of surgical site infection, Surg. Infect. 17 (2016) 459–464.
[36] B.R. Swenson, T.R. Camp, D.P. Mulloy, R.G. Sawyer, Antimicrobial-impregnated surgical incise drapes in the prevention of mesh infection after ventral hernia repair, Surg. Infect. 9 (2008) 23–32.
[37] D. Alston, S. Parnell, B. Hoonjan, A. Sebastian, A. Howard, Conservative management of an infected laparoscopic hernia mesh: a case study, Int J Surg Case Rep. 4 (2013) 1035–1037.
[38] M.E. Falagas, S.K. Kasiakou, Mesh-related infections after hernia repair surgery, Clin. Microbiol. Infect. 11 (2005) 3–8.
[39] M.A. Yerdel, E.B. Akin, S. Dolalan, A.G. Turkcapar, M. Pehlivan, I.E. Gecim, et al., Effect of single-dose prophylactic ampicillin and sulbactam on wound infection after tension-free inguinal hernia repair with polypropylene mesh: the randomized, double-blind, prospective trial, Ann. Surg. 233 (2001) 26–33.
[40] E.W. Taylor, K. Duffy, K. Lee, R. Hill, A. Noone, I. Macintyre, et al., Surgical site infection after groin hernia repair, Br. J. Surg. 91 (2004) 105–111.
[41] I.S. Bailey, S.E. Karran, K. Toyn, P. Brough, C. Ranaboldo, S.J. Karran, Community surveillance of complications after hernia surgery, BMJ 304 (1992) 469–471.
[42] S. Kathju, L. Nistico, L.A. Lasko, P. Stoodley, Bacterial biofilm on monofilament suture and porcine xenograft after inguinal herniorrhaphy, FEMS Immunol. Med. Microbiol. 59 (2010) 405–409.
[43] H. Kulacoglu, Current options in inguinal hernia repair in adult patients, Hippokratia 15 (2011) 223–231.
[44] H. Kulacoglu, Hernia, mesh, and topical antibiotics, especially gentamycin: seeking the evidence for the perfect outcome, Front Surg. 1 (2014) 53.
[45] J.R. Andersen, F. Burcharth, H.W. Larsen, O. Roder, B. Andersen, Polyglycolic acid, silk, and topical ampicillin. Their use in hernia repair and cholecystectomy, Arch. Surg. 115 (1980) 293–295.
[46] F. Lazorthes, P. Chiotasso, P. Massip, J.P. Materre, M. Sarkissian, Local antibiotic prophylaxis in inguinal hernia repair, Surg. Gynecol. Obstet. 175 (1992) 569–570.
[47] M. Deysine, Infection control in a hernia clinic: 24 year results of aseptic and antiseptic measure implementation in 4,620 "clean cases, Hernia 10 (2006) 25–29.
[48] G.-J.A. ter Boo, D.W. Grijpma, T.F. Moriarty, R.G. Richards, D. Eglin, Antimicrobial delivery systems for local infection prophylaxis in orthopedic- and trauma surgery, Biomaterials 52 (2015) 113–125.
[49] M. Musella, A. Guido, S. Musella, Collagen tampons as aminoglycoside carriers to reduce postoperative infection rate in prosthetic repair of groin hernias, Eur. J. Surg. 167 (2001) 130–132.
[50] C. Frangou, Study Reveals Staggering Costs of Ventral Hernia Repair Complication Mesh Infection General Surgery News, 2014.
[51] J.T. Jenkins, P.J. O'Dwyer, Inguinal hernias, Bmj 336 (2008) 269–272.
[52] M. Deysine, Pathophysiology, prevention, and management of prosthetic infections in hernia surgery, Surg Clin North Am. 78 (1998) 1105–1115.
[53] M.S. Cohen, J.M. Stern, A.J. Vanni, R.S. Kelley, E. Baumgart, D. Field, et al., In vitro analysis of a nanocrystalline silver-coated surgical mesh, Surg. Infect. 8 (2007) 397–403.
[54] T.A. Santora, J.J. Roslyn, Incisional hernia, Surg Clin North Am. 73 (1993) 557–570.
[55] D. Alston, S. Parnell, B. Hoonjan, A. Sebastian, A. Howard, Comment on: conservative management of an infected laparoscopic hernia mesh: a case study, Int J Surg Case Rep 5 (2014) 306.
[56] S. Petersen, G. Henke, M. Freitag, A. Faulhaber, K. Ludwig, Deep prosthesis infection in incisional hernia repair: predictive factors and clinical outcome, Eur. J. Surg. 167 (2001) 453–457.
[57] B. Aguilar, A.B. Chapital, J.A. Madura 2nd, K.L. Harold, Conservative management of mesh-site infection in hernia repair, J. Laparoendosc. Adv. Surg. Tech. 20 (2010) 249–252.
[58] U. Klinge, K. Junge, B. Spellerberg, C. Piroth, B. Klosterhalfen, V. Schumpelick, Do multifilament alloplastic meshes increase the infection rate? Analysis of the polymeric surface, the bacteria adherence, and the in vivo consequences in a rat model, J. Biomed. Mater. Res. 63 (2002) 765–771.
[59] N.W. Kugler, M. Bobbs, T. Webb, T.W. Carver, D. Milia, J.S. Paul, A dual-stage approach to contaminated, high-risk ventral hernia repairs, J. Surg. Res. 204 (2016) 200–204.
[60] A.H. Petter-Puchner, R.H. Fortelny, The heart of darkness, Hernia 19 (2015) 195–196.

[61] W.C. Cole, E.M. Balent, P.C. Masella, L.N. Kajiura, K.W. Matsumoto, L.M. Pierce, An experimental comparison of the effects of bacterial colonization on biologic and synthetic meshes, Hernia 19 (2015) 197–205.

[62] C.F. Bellows, B.M. Wheatley, K. Moroz, S.C. Rosales, L.A. Morici, The effect of bacterial infection on the biomechanical properties of biological mesh in a rat model, PLoS One 6 (2011) e21228.

[63] R. Garcia-Pumarino, G. Pascual, M. Rodriguez, B. Perez-Kohler, J.M. Bellon, Do collagen meshes offer any benefits over preclude (R) ePTFE implants in contaminated surgical fields? A comparative in vitro and in vivo study, J. Biomed. Mater. Res. B Appl. Biomater. 102 (2014) 366–375.

[64] J. Chamieh, W.H. Tan, R. Ramirez, E. Nohra, C. Apakama, W. Symons, Synthetic versus biologic mesh in single-stage repair of complex abdominal wall defects in a contaminated field, Surg. Infect. 18 (2017) 112–118.

[65] R. Ott, T. Hartwig, A. Tannapfel, R. Blatz, A.C. Rodloff, P. Madaj-Sterba, et al., Biocompatibility of bacterial contaminated prosthetic meshes and porcine dermal collagen used to repair abdominal wall defects, Langenbeck's Arch. Surg. 392 (2007) 473–478.

[66] C. Sabbagh, P. Verhaeghe, O. Brehant, F. Browet, B. Garriot, J.M. Regimbeau, Partial removal of infected parietal meshes is a safe procedure, Hernia 16 (2012) 445–449.

[67] D. Le, C.W. Deveney, N.L. Reaven, S.E. Funk, K.J. McGaughey, R.G. Martindale, Mesh choice in ventral hernia repair: so many choices, so little time, Am. J. Surg. 205 (2013) 602–607.

[68] C.N. Brown, J.G. Finch, Which mesh for hernia repair? Ann. R. Coll. Surg. Engl. 92 (2010) 272–278.

[69] A.F. Engelsman, H.C. van der Mei, H.J. Busscher, R.J. Ploeg, Morphological aspects of surgical meshes as a risk factor for bacterial colonization, Br. J. Surg. 95 (2008) 1051–1059.

[70] J.M. Bellon, G.H. N, F. Jurado, A. Carranza, J. Bujan, In vitro interaction of bacteria with polypropylene/ePTFE prostheses, Biomaterials 22 (2001) 2021–2024.

[71] J.M. Bellon, A. Garcia-Carranza, N. Garcia-Honduvilla, A. Carrera-San Martin, J. Bujan, Tissue integration and biomechanical behaviour of contaminated experimental polypropylene and expanded polytetrafluoroethylene implants, Br. J. Surg. 91 (2004) 489–494.

[72] N.W. Law, H. Ellis, A comparison of polypropylene mesh and expanded polytetrafluoroethylene patch for the repair of contaminated abdominal wall defects-an experimental study, Surgery 109 (1991) 652–655.

[73] N.F.N. Stoikes, J.R. Scott, A. Badhwar, C.R. Deeken, G.R. Voeller, Characterization of host response, resorption, and strength properties, and performance in the presence of bacteria for fully absorbable biomaterials for soft tissue repair, Hernia 21 (2017) 771–782.

[74] A.F. Engelsman, G.M. van Dam, H.C. van der Mei, H.J. Busscher, R.J. Ploeg, In vivo evaluation of bacterial infection involving morphologically different surgical meshes, Ann. Surg. 251 (2010) 133–137.

[75] J.A. Blatnik, D.M. Krpata, M.R. Jacobs, Y. Gao, Y.W. Novitsky, M.J. Rosen, In vivo analysis of the morphologic characteristics of synthetic mesh to resist MRSA adherence, J. Gastrointest. Surg. 16 (2012) 2139–2144.

[76] B. Perez-Kohler, S. Sotomayor, M. Rodriguez, M.I. Gegundez, G. Pascual, J.M. Bellon, Bacterial adhesion to biological versus polymer prosthetic materials used in abdominal wall defect repair: do these meshes show any differences in vitro? Hernia 19 (2015) 965–973.

[77] S. Bhende, T. Barbolt, S. Rothenburger, L. Piccoli, Infection potentiation study of synthetic and naturally derived surgical mesh in mice, Surg. Infect. 8 (2007) 405–414.

[78] H.Y. Zhou, J. Zhang, R.L. Yan, Q. Wang, L.Y. Fan, Q. Zhang, et al., Improving the antibacterial property of porcine small intestinal submucosa by nano-silver supplementation: a promising biological material to address the need for contaminated defect repair, Ann. Surg. 253 (2011) 1033–1041.

[79] J.F. Buell, D. Sigmon, C. Ducoin, M. Shapiro, N. Teja, E. Wynter, et al., Initial experience with biologic polymer scaffold (Poly-4-hydroxybuturate) in complex abdominal wall reconstruction, Ann. Surg. 266 (2017) 185–188.

[80] A. Majumder, J.S. Winder, Y. Wen, E.M. Pauli, I. Belyansky, Y.W. Novitsky, Comparative analysis of biologic versus synthetic mesh outcomes in contaminated hernia repairs, Surgery 160 (2016) 828–838.

[81] O. Goeau-Brissonniere, V. Leflon, M. Letort, M.H. Nicolas, Resistance of antibiotic-bonded gelatin-coated polymer meshes to Staphylococcus aureus in a rabbit subcutaneous pouch model, Biomaterials 20 (1999) 229–232.

[82] J.A. Inzana, E.M. Schwarz, S.L. Kates, H.A. Awad, Biomaterials approaches to treating implant-associated osteomyelitis, Biomaterials 81 (2016) 58–71.

[83] G.D. Neeta, Q.S. Mohiuddin, Recent trend of aminoglycoside resistance among Staphylococcus aureus isolates in tertiary care hospital, J. Microbiol. Antimicrob. 6 (2014) 94–96.

[84] K. Junge, R. Rosch, U. Klinge, C. Krones, B. Klosterhalfen, P.R. Mertens, et al., Gentamicin supplementation of polyvinylidenfluoride mesh materials for infection prophylaxis, Biomaterials 26 (2005) 787–793.

[85] M. Fernandez-Gutierrez, E. Olivares, G. Pascual, J.M. Bellon, J. San Roman, Low-density polypropylene meshes coated with resorbable and biocompatible hydrophilic polymers as controlled release agents of antibiotics, Acta Biomater. 9 (2013) 6006–6018.

[86] K.T. Grafmiller, S.T. Zuckerman, C. Petro, L. Liu, H.A. von Recum, M.J. Rosen, et al., Antibiotic-releasing microspheres prevent mesh infection in vivo, J. Surg. Res. 206 (2016) 41–47.

[87] K.C. Harth, M.J. Rosen, T.R. Thatiparti, M.R. Jacobs, I. Halaweish, S. Bajaksouzian, et al., Antibiotic-releasing mesh coating to reduce prosthetic sepsis: an in vivo study, J. Surg. Res. 163 (2010) 337–343.

[88] E.E. Sadava, D.M. Krpata, Y. Gao, Y.W. Novitsky, M.J. Rosen, Does presoaking synthetic mesh in antibiotic solution reduce mesh Infections? An experimental study, J. Gastrointest. Surg. 17 (2013) 562–568.

[89] J.A. Blatnik, T.R. Thatiparti, D.M. Krpata, S.T. Zuckerman, M.J. Rosen, H.A. von Recum, Infection prevention using affinity polymer-coated, synthetic meshes in a pig hernia model, J. Surg. Res. 219 (2017) 5–10.

[90] V. Letouzey, J.P. Lavigne, X. Garric, J. Coudane, R. de Tayrac, D.O. Callaghan, Is degradable antibiotic coating for synthetic meshes provide protection against experimental animal infection after fascia repair? J. Biomed. Mater. Res. B Appl. Biomater. 100 (2012) 471–479.

[91] T. Laurent, I. Kacem, N. Blanchemain, F. Cazaux, C. Neut, H.F. Hildebrand, et al., Cyclodextrin and maltodextrin finishing of a polypropylene abdominal wall implant for the prolonged delivery of ciprofloxacin, Acta Biomater. 7 (2011) 3141–3149.

[92] N. Harnett, S. Brown, C. Krishnan, Emergence of quinolone resistance among clinical isolates of methicillin-resistant Staphylococcus aureus in Ontario, Canada, Antimicrob. Agents Chemother. 35 (1991) 1911–1913.

[93] O. Guillaume, X. Garric, J.P. Lavigne, H. Van Den Berghe, J. Coudane, Multilayer, degradable coating as a Carrier for the sustained release of antibiotics: preparation and antimicrobial efficacy in vitro, J. Contr. Release 162 (2012) 492–501.

[94] A. Majumder, J.R. Scott, Y.W. Novitsky, Evaluation of the antimicrobial efficacy of a novel rifampin/minocycline-coated, noncrosslinked porcine acellular dermal matrix compared with uncoated scaffolds for soft tissue repair, Surg Innov 23 (2016) 442–455.

[95] C.D. Klink, M. Binnebosel, A. Lambertz, H.P. Alizai, A. Roeth, J. Otto, et al., In vitro and in vivo characteristics of gentamicin-supplemented polyvinylidenfluoride mesh materials, J. Biomed. Mater. Res. 100 (2012) 1195–1202.

[96] A. Wiegering, B. Sinha, L. Spor, U. Klinge, U. Steger, C.T. Germer, et al., Gentamicin for prevention of intraoperative mesh contamination: demonstration of high bactericide effect (in vitro) and low systemic bioavailability (in vivo), Hernia 18 (2014) 691–700.

[97] C. Labay, J.M. Canal, M. Modic, U. Cvelbar, M. Quiles, M. Armengol, et al., Antibiotic-loaded polypropylene surgical meshes with suitable biological behaviour by plasma functionalization and polymerization, Biomaterials 71 (2015) 132–144.

[98] Y. Hong, K. Fujimoto, R. Hashizume, J. Guan, J.J. Stankus, K. Tobita, et al., Generating elastic, biodegradable polyurethane/poly(lactide-co-glycolide) fibrous sheets with controlled antibiotic release via two-stream electrospinning, Biomacromolecules 9 (2008) 1200–1207.

[99] O. Guillaume, J.P. Lavigne, O. Lefranc, B. Nottelet, J. Coudane, X. Garric, New antibiotic-eluting mesh used for soft tissue reinforcement, Acta Biomater. 7 (2011) 3390–3397.

[100] J.M. Suárez-Grau, S. Morales-Conde, V. González Galán, J.A. Martín Cartes, F. Docobo Durantez, F.J. Padillo Ruiz, Antibiotic embedded absorbable prosthesis for prevention of surgical mesh infection: experimental study in rats, Hernia 19 (2015) 187–194.

[101] P. Avetta, R. Nistico, M.G. Faga, D. D'Angelo, E.A. Boot, R. Lamberti, et al., Hernia-repair prosthetic devices functionalised with chitosan and ciprofloxacin coating: controlled release and antibacterial activity, J. Mater. Chem. B 2 (2014) 5287–5294.

[102] A. Cakmak, Y. Cirpanli, E. Bilensoy, K. Yorganci, S. Calis, Z. Saribas, et al., Antibacterial activity of triclosan chitosan coated graft on hernia graft infection model, Int. J. Pharm. 381 (2009) 214–219.

[103] B. Perez-Kohler, F. Garcia-Moreno, T. Brune, G. Pascual, J.M. Bellon, Preclinical bioassay of a polypropylene mesh for hernia repair pretreated with antibacterial solutions of chlorhexidine and allicin: an in vivo study, PLoS One 10 (2015) e0142768.

[104] https://www.ethicon.com/, Triclosan-coated Sutures Now Recommended by World Health Organization, 2017.

[105] S. Ankri, D. Mirelman, Antimicrobial properties of allicin from garlic, Microb. Infect. 1 (1999) 125–129.

[106] C.A. dos Santos, M.M. Seckler, A.P. Ingle, I. Gupta, S. Galdiero, M. Galdiero, et al., Silver nanoparticles: therapeutical uses, toxicity, and safety issues, J Pharm Sci. 103 (2014) 1931–1944.

[107] K. Kalishwaralal, S. BarathManiKanth, S.R. Pandian, V. Deepak, S. Gurunathan, Silver nanoparticles impede the biofilm formation by Pseudomonas aeruginosa and Staphylococcus epidermidis, Colloids Surf B Biointerfaces 79 (2010) 340–344.

[108] W. Badiou, J.P. Lavigne, P.J. Bousquet, D. O'Callaghan, P. Mares, R. de Tayrac, In vitro and in vivo assessment of silver-coated polypropylene mesh to prevent infection in a rat model, Int Urogynecol J 22 (2011) 265–272.

[109] O. Saygun, C. Agalar, K. Aydinuraz, F. Agalar, C. Daphan, M. Saygun, et al., Gold and gold-palladium coated polypropylene grafts in a S. epidermidis wound infection model, J. Surg. Res. 131 (2006) 73–79.

[110] V. Kumar, C. Jolivalt, J. Pulpytel, R. Jafari, F. Arefi-Khonsari, Development of silver nanoparticle loaded antibacterial polymer mesh using plasma polymerization process, J. Biomed. Mater. Res. 101 (2013) 1121–1132.

[111] S. Zhang, K. Xu, L. Ge, M.A. Darabi, F. Xie, S. Derakhshanfar, et al., A novel nano-silver coated and hydrogel-impregnated polyurethane nanofibrous mesh for ventral hernia repair, RSC Adv. 6 (2016) 90571–90578.

[112] R. Satishkumar, S. Sankar, Y. Yurko, A. Lincourt, J. Shipp, B.T. Heniford, et al., Evaluation of the antimicrobial activity of lysostaphin-coated hernia repair

meshes, Antimicrob. Agents Chemother. 55 (2011) 4379–4385.
[113] J.F. Kokai-Kun, T. Chanturiya, J.J. Mond, Lysostaphin eradicates established Staphylococcus aureus biofilms in jugular vein catheterized mice, J. Antimicrob. Chemother. 64 (2009) 94–100.
[114] W.A. Zygmunt, P.A. Tavormina, Lysostaphin: model for a specific enzymatic approach to infectious disease, Prog. Drug Res. 16 (1972) 309–333.
[115] J. Miao, R.C. Pangule, E.E. Paskaleva, E.E. Hwang, R.S. Kane, R.J. Linhardt, et al., Lysostaphin-functionalized cellulose fibers with antistaphylococcal activity for wound healing applications, Biomaterials 32 (2011) 9557–9567.
[116] Y. Yurko, K. McDeavitt, R.S. Kumar, T. Martin, A. Prabhu, A.E. Lincourt, et al., Antibacterial mesh: a novel technique involving naturally occurring cellular proteins, Surg Innov 19 (2012) 20–26.
[117] I. Belyansky, V.B. Tsirline, T.R. Martin, D.A. Klima, J. Heath, A.E. Lincourt, et al., The addition of lysostaphin dramatically improves survival, protects porcine biomesh from infection, and improves graft tensile shear strength, J. Surg. Res. 171 (2011) 409–415.
[118] I. Belyansky, V.B. Tsirline, P.N. Montero, R. Satishkumar, T.R. Martin, A.E. Lincourt, et al., Lysostaphin-coated mesh prevents staphylococcal infection and significantly improves survival in a contaminated surgical field, Am. Surg. 77 (2011) 1025–1031.
[119] K. Ehlert, W. Schroder, H. Labischinski, Specificities of FemA and FemB for different glycine residues: FemB cannot substitute for FemA in staphylococcal peptidoglycan pentaglycine side chain formation, J. Bacteriol. 179 (1997) 7573–7576.
[120] K.A. Poelstra, N.A. Barekzi, A.M. Rediske, A.G. Felts, J.B. Slunt, D.W. Grainger, Prophylactic treatment of gram-positive and gram-negative abdominal implant infections using locally delivered polyclonal antibodies, J. Biomed. Mater. Res. 60 (2002) 206–215.
[121] H.R. Ibrahim, T. Matsuzaki, T. Aoki, Genetic evidence that antibacterial activity of lysozyme is independent of its catalytic function, FEBS Lett. 506 (2001) 27–32.
[122] L. Hammarstrom, C.I. Smith, New and old aspects of immunoglobulin application. The use of intravenous IgG as prophylaxis and for treatment of infections, Infection 18 (1990) 314–324.
[123] B. Perez-Kohler, M. Fernandez-Gutierrez, G. Pascual, F. Garcia-Moreno, J. San Roman, J.M. Bellon, In vitro assessment of an antibacterial quaternary ammonium-based polymer loaded with chlorhexidine for the coating of polypropylene prosthetic meshes, Hernia (2016).
[124] O. Guillaume, A.H. Teuschl, S. Gruber-Blum, R.H. Fortelny, H. Redl, A. Petter-Puchner, Emerging trends in abdominal wall reinforcement: bringing biofunctionality to meshes, Adv. Healthc. Mater. 4 (2015) 1763–1789.
[125] K. Junge, U. Klinge, R. Rosch, P. Lynen, M. Binnebosel, J. Conze, et al., Improved collagen type I/III ratio at the interface of gentamicin-supplemented polyvinylidenfluoride mesh materials, Langenbeck's Arch. Surg. 392 (2007) 465–471.
[126] J. Huang, H. Murata, R.R. Koepsel, A.J. Russell, K. Matyjaszewski, Antibacterial polypropylene via surface-initiated atom transfer radical polymerization, Biomacromolecules 8 (2007) 1396–1399.
[127] A.E. Ozcam, K.E. Roskov, R.J. Spontak, J. Genzer, Generation of functional PET microfibers through surface-initiated polymerization, J. Mater. Chem. 22 (2012) 5855–5864.
[128] G. Zhai, Z.L. Shi, E.T. Kang, K.G. Neoh, Surface-Initiated atom transfer radical polymerization on poly(vinylidene fluoride) membrane for antibacterial ability, Macromol. Biosci. 5 (2005) 974–982.
[129] S. El Habnouni, J.P. Lavigne, V. Darcos, B. Porsio, X. Garric, J. Coudane, et al., Toward potent antibiofilm degradable medical devices: a generic method for the antibacterial surface modification of polylactide, Acta Biomater. 9 (2013) 7709–7718.
[130] S. Oh, M. Tandukar, S.G. Pavlostathis, P.S. Chain, K.T. Konstantinidis, Microbial community adaptation to quaternary ammonium biocides as revealed by metagenomics, Environ. Microbiol. 15 (2013) 2850–2864.
[131] K.D. Park, Y.S. Kim, D.K. Han, Y.H. Kim, E.H.B. Lee, H. Suh, et al., Bacterial adhesion on PEG modified polyurethane surfaces, Biomaterials 19 (1998) 851–859.
[132] R. Bos, H.C. van der Mei, J. Gold, H.J. Busscher, Retention of bacteria on a substratum surface with micro-patterned hydrophobicity, FEMS Microbiol. Lett. 189 (2006) 311–315.
[133] J. Chen, C. Howell, C.A. Haller, M.S. Patel, P. Ayala, K.A. Moravec, et al., An immobilized liquid interface prevents device associated bacterial infection in vivo, Biomaterials 113 (2017) 80–92.
[134] G.J. Ter Boo, D. Arens, W.J. Metsemakers, S. Zeiter, R.G. Richards, D.W. Grijpma, et al., Injectable gentamicin-loaded thermo-responsive hyaluronic acid derivative prevents infection in a rabbit model, Acta Biomater. 43 (2016) 185–194.
[135] E. Gallazzi, M. Bortolin, D. Romano, L. Drago, C.L. Romano, Anti-adhesive properties of a fast-resorbable, hydrogel anti-bacterial implant coating, Orthopaedic Proc. (2018), 99-B:90.
[136] C.L. Romano, K. Malizos, N. Capuano, R. Mezzoprete, M. D'Arienzo, C. Van Der Straeten, et al., Does an antibiotic-loaded hydrogel coating reduce early post-surgical infection after joint arthroplasty? J. Bone Joint Infect. 1 (2016) 34–41.
[137] J.R. DeBord, J.J. Bauer, D.M. Grischkan, K.A. LeBlanc, R.T. Smoot, G.R. Voeller, et al., Short-term study on the safety of antimicrobial-agent-impregnated ePTFE patches for hernia repair, Hernia 3 (1999) 189–193.
[138] A.M. Carbonell, B.D. Matthews, D. Dreau, M. Foster, C.E. Austin, K.W. Kercher, et al., The susceptibility of prosthetic biomaterials to infection, Surg. Endosc. 19 (2005) 430–435.
[139] Y.W. Novitsky, T. Ryan, J.R. Scott, Antimicrobial Efficacy of a Novel Minocycline/rifampin Composite Mesh Coating in a Rabbit Model of Open Ventral Hernia Repair, Society of American Gastrointestinal and Endoscopic Surgeons, San Antonio, TX, USA, 2011.
[140] M. Fontanazza, New Ventral Hernia Mesh Shoots to Kill Bacteria, MedTechIntelligence: Innovative Publishing Co, 2016.
[141] W.S. Cobb, B.L. Paton, Y.W. Novitsky, M.J. Rosen, K.W. Kercher, T.S. Kuwada, et al., Intra-abdominal placement of antimicrobial-impregnated mesh is associated with noninfectious fever, Am. Surg. 72 (2006) 1205–1208.
[142] E.H. Baker, D. Lepere, M.P. Lundgren, P.J. Greaney, D.A. Ehrlich, S.E. Copit, et al., Early clinical outcomes of a novel antibiotic-coated, non-crosslinked porcine acellular dermal graft after complex abdominal wall reconstruction, J. Am. Coll. Surg. 223 (2016) 581–586.