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# Prosthetic meshes for hernia repair: state of art, classification, antimicrobial approaches, and fabrication methods

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## Abstract

Worldwide, hernia repair represents one of the most frequent surgical procedures encompassing a global market valued at several billion dollars. This type of surgery usually requires the implantation of a mesh that needs the appropriate chemical, physical and biological properties for the type of repair. This review thus presents a description of the types of hernias, current hernia repair methods, and the state of the art of prosthetic meshes for hernia repair providing the most important meshes used in clinical practice by surgeons working in this area classified according to their biological or chemical nature, morphology and whether bioabsorbable or not. We emphasise the importance of surgical site infection in herniatology, how to deal with this microbial problem, and we go further into the future research lines on the production of advanced antimicrobial meshes to improve hernia repair and prevent microbial infections, including multidrug-resistant strains. A great deal of progress has been made in this biomedical field in the last decade. However, we are still far from an ideal antimicrobial mesh that can also provide excellent integration to the abdominal wall, mechanical performance, low visceral adhesion and minimal inflammatory or foreign body reactions, among many other problems.

**Keywords:** meshes, hernia, biomaterials, antimicrobials, surgery, abdominal wall

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## 1. Introduction

Hernia repair is one of the most frequent surgical procedures with more than 20 million interventions per year worldwide [1,2]. In 2019, the global hernia repair market was valued at $4.75billion, and it is estimated to rise to $6.3 billion by 2027 [3]. Hernias of the abdominal wall are classified into primary hernias (inguinal, femoral, umbilical, epigastric, Spiegel and lumbar) and secondary or incisional hernias, which are produced after incision of the abdominal wall [4]. Ventral hernia is an inclusive term for incisional, umbilical, epigastric, Spiegel and lumbar hernias, that is, those that are not inguinal nor femoral hernias [5]. Hernias are mainly formed due to obesity, other co-morbidities, wound infections, immunosuppression, and prostatism [5–7]. After abdominal surgery, incisional hernia presents an incidence ranging from 11 to 20 % [8–10]. Surgeries performed for inguinal hernia repair is among the most common interventions [11–13] in both adults and children [14–16]. Inguinal hernias are usually symptomatic and their only cure is surgery [1]. However, even a watchful waiting approach in the asymptomatic group results in surgery in most cases [17]. Prior to the use of prosthetic meshes for inguinal hernia repair, suture repair methods, such as Bassini's, were the most common techniques employed in this type of intervention [18,19]. However, improvements in the surgical technique [20,21], along with the development of new advanced biomaterials have made prosthetic meshes important in hernia repair [22]. These meshes render easier closure, tension-free, and ensure high wound strength [23]**.** The main inguinal hernia repair methods include the *Lichtenstein onlay patch*, the *Plug and patch method*, *Kugel's technique* and the *Laparoscopic approach* [24]. The *Lichtenstein* tension-free repair is considered the *gold standard* [25]. This method approaches the inguinal canal [25] and reinforces the floor with a piece of flat prosthetic mesh [24]. The *plug and patch method* (Rutkow-Robbins technique and other similar methods) involves placing a prosthetic mesh plug through the defect in the inguinal canal [24]. Complications are rare; however, there is a possibility of patient discomfort, given the geometry of the plug [26]. This method is more expensive than the Lichtenstein technique [27]. The international guide to the management of inguinal hernia (HerniaSurge) recommends not using the plug because it adds a high amount of prosthetic biomaterial, it is necessary to enter the anterior and posterior plane and the additional cost [1]. *Kugel's technique* [28] uses a bilayer patch placed in the preperitoneal area and has achieved a recurrence rate of 0.4% [29]. The *laparoscopic approach* includes two different techniques: total extraperitoneal (TEP) and transabdominal preperitoneal (TAPP) repairs [30]. Both TAPP and TEP techniques obtain similar results [1]. The laparoscopic approaches for hernia repair cost more and take longer [31] and can produce several complications such as intestine, bladder and vascular injury or nerve entrapment [32]. However, laparoscopic methods show a faster recovery and present a low risk of chronic postoperative pain [1].

The laparoscopic technique has been well accepted for the treatment of incisional hernia but the ideal mesh produced with the ideal biomaterials has not yet been found [33]. There is consensus on its indication in bilateral inguinal hernias, recurrent hernias of the anterior pathway or in women, but although this type of approach is also recommended, due to the advantages described above, in unilateral male hernias its implementation has not been generalized in routine clinical practice [1]. The repair of primary umbilical or epigastric hernias involves the placement of preperitoneal prosthetic materials except if the size of the hernial defect is small (0 - 1 cm) [34]. Hernias classified as incisional and parastomal usually require the placement of one or more prostheses since otherwise the recurrence rate is very high. The site of the placement of this prosthesis (*onlay*, *sublay*, etc.) is variable according to the characteristics of the incision, location,

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type, size, preferences of the surgeon, etc. Complex incisional hernias may require abdominal preparation before surgery with infiltration of botulinum toxin and sometimes also with the creation of a progressive pneumoperitoneum [35,36].
Hernia repair is thus characterized by the increasing use of prosthetic meshes made of pure or different hybrid biomaterials, depending on the type of surgery [37]. Figure 1 provides an example of a large incisional hernia which required the use a polyvinylidene difluoride (PVDF) prosthetic mesh.

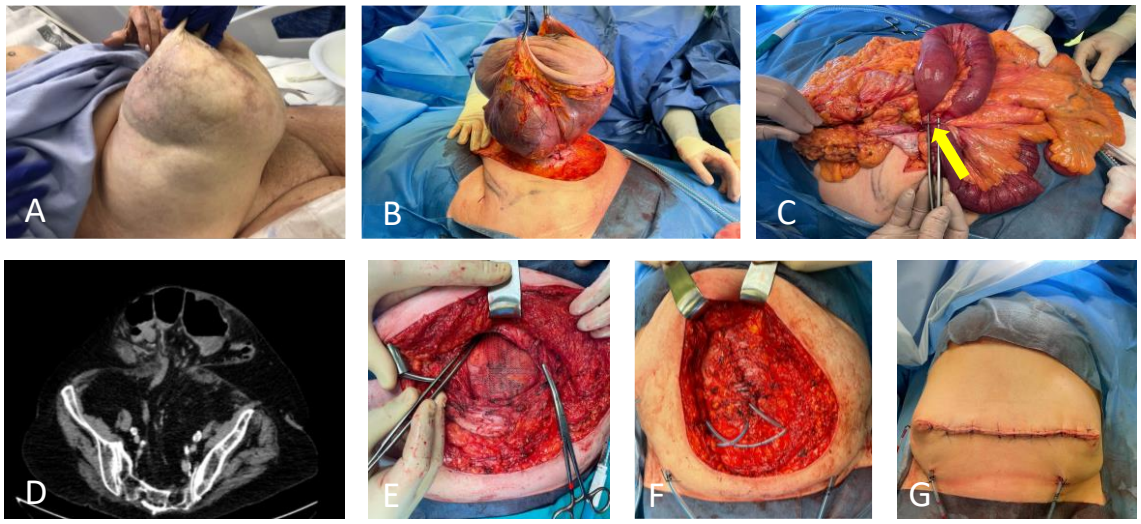


**Figure 1.** Example of large incisional hernia (A). Hernia M3M4W2according to the classification of the European Hernia Society [4] (22x9.7x25 cm transversal x anteroposterior x craniocaudal) with an 8 x 12 cm hernial defect (transverse x craniocaudal) that produces obstruction in handle closed by fibrous bands (yellow arrow in C) (B & C). Image of the hernial defect in axial tomography section (D). Wall repair with placement of a retromuscular PVDF prosthesis and final result (E, F and G).

After the insertion of a foreign material into the human body, such as a prosthetic mesh, the immune system produces a reaction whose intensity and chronicity depend on the chemical nature and morphology of the mesh [38], so that serious problems such as shrinkage, seroma, erosion, encapsulation, and pain can occur [39]. In fact, common biomaterials, such as polypropylene (PP), have been broadly used in clinics due to their good biocompatibility and may trigger a cascade of histopathological mechanisms and immune reactions in the patient in the long term. The level of inflammatory cytokines and pro-angiogenic factors depends on the nature of the implanted meshes (biological or synthetic) [40]. A method of avoiding the post-implantation inflammatory response is to load the meshes with various anti-inflammatory drugs such as cortisone [41], ibuprofen [42,43], or tetracycline [44,45]. For example, local cortisone release was found to limit the inflammatory reaction, reduce the size of the granuloma, and improve neovascularization. Insertion of a medical device is known to increase the susceptibility to infection 10,000 to 100,000 times [46], and bacterial contamination has been reported in a high percentage of the total implanted prosthetic meshes during surgery and after years of implantation [47,48]. Some authors have used mesh prophylaxis before the operation and reported a significant reduction of mesh infection [49]. For example, gentamicin was able to reduce mesh infections [50]. Another alternative antibacterial strategy consists of antibiotic prophylaxis for open mesh repair in high-risk patients and low-risk settings [1]. However, the current international guidelines do not recommend antibiotic prophylaxis in open surgery for medium-risk patients in low-risk settings [1], and it is not recommended in any case of laparoscopic repair. In high-risk settings, however, it is recommended in all cases except laparoscopic interventions. In this regard,

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the development of antimicrobial meshes, or meshes made with biomaterials able to impede microbial infections is gaining importance in the field of hernia repair [51]. Due to the inappropriate use of antibiotics, bacterial resistance levels have increased and become a serious health problem that could produce more deaths than cancer by the year 2050, according to the World Health Organization [52]. The next generation of prosthetic meshes therefore must be engineered with biomaterials able to impede infection, including those that are multidrug-resistant.

## 2. Meshes for hernia repair

Open non-mesh herniorrhaphy has been successfully performed by surgeons for many decades. However, the surgeon's experience played a very important role in the recurrence rate, which varies considerably. The introduction of meshes for hernia repair achieved *tension-free* hernioplasties and provided a new solution to produce relatively similar results that do not depend on the surgeon [53]. For this reason, several clinical trials have been carried out to find the optimal prosthetic mesh [54–56] and the best technique for implantation[57,58]. In this regard, biocompatibility and mesh-related complication issues such as pain, seroma and persisting infection (chronic infection or biofilm) are the most important factors [59]. According to the experience of the authors of this review, the ideal or perfect mesh would be made of a material that achieves good integration with the abdominal wall and possesses wide pores, low density, high elasticity, mechanical functionality, low incidence of visceral adhesions, good resistance to infection in contaminated areas, and minimal inflammatory or foreign body reaction. From the currently available meshes, the PP mesh fulfils all these requirements with the exception that it fails in the incidence of visceral adhesions because it is not possible to place the mesh in contact with the viscera. Furthermore, the PP mesh does not involve antimicrobial activity and usually requires the addition of antibiotics, silver ions or alternative antimicrobial approaches. However, the increasing microbial resistance to antibiotics [52] and metals such as silver ions [60] is demanding the development of new alternative antimicrobial meshes that could provide long-lasting solutions. Several classifications of meshes for hernia repair have been proposed so far. The first classification defined four types of prostheses mainly according to the porosity and chemical nature of the materials employed in their production [61]. A classification was reported according to physical and biological properties such as porous and non-porous, pore size, 3D morphology, biological origin, and additional features [62]. However, here we provide an updated classification of meshes based on Bellón's classification [63] showing the most frequently employed meshes in clinical practice and considering the chemical nature of their materials, application site, biodegradability and biological origin (see Table 1).

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| MESH TYPE | MESH SUBTYPE | BIOMATERIAL TRADEMARK | INTEGRATION | NEOPERITONEUM |
|---|---|---|---|---|
| NON-BIOABSORBIBLE | RETICULAR | POLYPROPYLENE (PP) Optilene® Prolene ® Herniamesh® | ***** | * |
| | | POLYESTER (PE) Parietex® | ***** | * |
| | | POLYTETRAFLUOROETYLENE (cPTFE) Infinit® PTFE mesh | **** | * |
| | | POLYVINYLIDENE FLUORIDE (PVDF) Dynamesh® | **** | * |
| | | PP + TITANIUM TiMesh® | **** | *** |
| | | PP WITH SILVER IONS Optilene Siver Mesh ® | ***** | * |
| | LAMINAR | ePTFE (EXPANDED) Gore-Tex® DualMesh® | ** | ***** |
| | HYBRID | PP/ePTFE Ventralex ™ Hernia Patch | ***** | ***** |
| | | PP/PVDF Dynamesh®IPOM | ***** | ***** |
| PARTIALLY BIOABSORBABLE | COMPOSITE | PP/POLIGLECAPRONE-25 Ultrapro™ | ***** | ***** |
| | | PP/POLIDIOXANONE/OXIDATED REGENERATED CELULLOSE Proceed™ Ventral Patch | ***** | ***** |
| | | PP/HYALURONIC ACID+CARBOXYMETHYLCELLULOSE+ POLYETYLENE GLYCOL Sepramesh ® | ***** | ***** |
| | | PP/ ∘ Sepra® Hydrogel Barrier Ventralex ST® Ventrio ST ® Ventralight ST® | ***** | ***** |
| | | POLYGLYCOLIC ACID (PGA)+ POLY(TRIMETHYLENE CARBONATE) (PTMC) /PTFE/PGA+PTMC Gore® Synecor | ***** | ***** |
| | AUTOADHESIVE COMPOSITE | PP/POLYETHYLENE GLYCOL+POLYVINYLPYRROLIDONE Adhesix® | ***** | * |
| | | PP/POLILACTIC ACID Parietene™ ProGrip™ | ***** | * |
| | | PE/POLILACTIC ACID Parietex™ ProGrip™ | ***** | * |
| BIOABSORBIBLE | BIOLOGICAL | PORCINE DERMIS Permacol™ Strattice™ | ** | ***** |
| | | PORCINE INTESTINAL SUBMUCOSE Surgisis® | ** | ***** |
| | | BOVINE PERICARDIUM Veritas® | ** | ***** |
| | | HUMAN DERMIS Alloderm® FlexHD® AlloMax™ | ** | ***** |
| | BIOSYNTHETIC | BACTERIAL POLYMER MESHES (P4HB) Phasix™ and Phasix™ ST (∘ Sepra® Hydrogel Barrier) | ***** | * & ***** |
| | SYNTHETIC | POLYGLACTIN 910 Vicryl ™ | ***** | *** |
| | | PGA + PTMC Gore® BIO-A® | **** | **** |
| | | POLYLACTIC ACID + PGA + PTMC TIGR - matrix ® | **** | **** |

**Table 1.** Classification of prosthetic meshes for hernia repair most used in clinical practice. ∘ Sepra® Hydrogel Barrier: Sodium hyaluronate hydrogel, carboxymethylcellulose and polyethylene glycol. Bonded to polypropylene by polyglycolic acid fibres. Trademarks most used in clinical practice are indicated in blue letters. The meshes that allow intraperitoneal placement are highlighted in green. The mesh tissue integration and capacity to create neoperitoneum is indicated (ranging from excellent ***** to very poor *)

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This new classification was designed with the goal of being useful to surgeons when deciding the type of mesh to be used in different interventions. The abundant number of biomaterials available for abdominal wall repair calls for a practical classification that attempts to answer the questions that a surgeon may ask himself when using them. The first important question is to know if the prosthesis is permanent and if it will be partially or completely absorbed. The second question consists of knowing whether the type of mesh is reticular, laminar, or composite. The last, but not the least, question is to know whether the mesh can be placed intra-abdominally. Integration is related to the capacity of the mesh to allow the growth of cells between its fibres so that the reticular usually allow better integration than the laminar types [64]. Connective tissue surrounds the filaments, forming spirals over them, and there is a major angiogenesis [65]. Lamellar prostheses are mainly represented by expanded PTFE (ePTFE) and their integration is cellular, the cells from the tissue receptor invading the outermost thirds of the material. The vessels do not penetrate the interstices of the ePTFE, and the prosthesis-receptor tissue interface is weak from a mechanical point of view [66]. The integration of the mesh also correlates with the mechanical resistance (the greater the integration, the greater the resistance) [67]. Regarding the neoperitoneum formation capacity, the structure of a biomaterial influences this behaviour rather than its chemical composition [68]. Lamellar prostheses allow a good development of the neoperitoneum. In experimental studies an early network of collagen fibres has already been observed covered with typical mesothelial cells [64]. These fibres are placed parallel to the prosthetic surface and are accompanied by a large number of cells, especially fibroblasts and some foreign body reaction cells. After this time, the neoperitoneum is remodelled, and most cells that react to foreign bodies disappear (index of good tolerance of the prosthesis), and fibroblasts are the dominant ones. The collagen fibres are parallel to the prosthetic surface and the mesothelium is outside these, in contact with the visceral peritoneum. The genesis of this perfectly shaped neoperitoneum avoids the formation of adhesions, which is one of the complications that can appear after the placement of a prosthesis in contact with the visceral peritoneum. On the other hand, as PP-type reticular prostheses generate a neoperitoneum with a disorganized structure, rough in texture, with some areas of hemorrhage and necrosis that facilitate adhesions [69], the reticular structure of the prosthesis probably conditions an inappropriate arrangement of the mesothelial cells on it.
For all these reasons, we present here a classification of the most important meshes used in clinical practice with all their information regarding biomaterials, trademarks, tissue integration and capacity to create neoperitoneum (Table 1). The manufacturing materials of 3D prostheses with special designs for specific situations such as meshes designed for laparoscopic repair of inguinal hernias are also included in this table.

The pore size of the most common biomaterials used for hernia surgery can range from very large (>2000 μm) to micropores (<100 μm) [70]. Larger pores render it easier to increase vascularization, enhance wound healing, among the many other required properties for hernia repair [71–73]. However, the problem of using meshes with large pores is the increased risk of adhesion to internal viscera [61,74]. The weight (in $g/m^2$) is another parameter usually employed to classify meshes from heavyweight (< 90) to ultra-lightweight (<35) [70]. High weight meshes are associated with chronic pain from profound foreign body response and fibrosis, among other complications [71,75]. Therefore, it is important to reduce the weight of meshes, while retaining the mechanical resistance required for abdominal wall repair [60,61]. Mono-filaments are the most frequent mesh morphology used for inguinal hernia [76], or several braided fibres such as multi-filaments by polymer extrusion [77]. The filament structure affects several properties of the prosthetic mesh such as molecular permeability, pliability and mechanical performance [76]. Multifilament meshes are commonly associated with a higher risk of infection due to the interstices formed between the braided fibres [39,76]. However, new multifilament meshes have been developed with partially biodegradable filaments that provide enhanced physical and biological properties [37]. The manufacturing process (knitted, foil, woven, non-woven, etc.) also affects their properties [78]. Some techniques used in the production of porous polymers like scaffolds include polymerization using solvents [79–83], the porogen technique [84–86], electrospinning [87–89], and 3D printing [90–92], among others. Table 2 provides several examples of the wide range of pore sizes, weights, and morphology available in the market for the same and different types of meshes.

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**Table 2.** Examples of prosthetic meshes with different pore size, weight, and morphology.

| **Biomaterials** Trademark/Manufacturer | **Pore size** | **Weight (g/m$^2$)** | **Morphology** |
|---|---|---|---|
| PP (Optilene) Optilene® | 1.0 mm[93] – 2.8 [94] | 36[93,95] - 48[96] | Monofilament[97] |
| PVDF Dynamesh® | 1.1-1.3 mm [98] | 45 - 73 [99] | Monofilament [98] |
| PP/PVDF Dynamesh®IPOM | 0.6 mm [94] | 60 [94] - 108 [100] | Two-layered mesh [100] |
| PE Parietex® | 1.0 - 1.6 mm[101] /1.5 x 1.8 mm[102] | 38[101] - 78[102] | Multifilament[101] |
| PP coated with plasma Ti TiMesh® | > 1 mm [103] | 16/35/65 [103] | Monofilament [103] |
| PP coated with $TiO_2$$TiO_2$Mesh® | 3 mm [103] | 45 [103] | Monofilament [103] |
| ePTFE Gore-Tex® DualMesh® | 0.003-0.022 μm [104] | 320[105] | Foil[106] |
| PP/Poliglecaprone-25 Ultrapro ™ | 2.0 - 4.0 mm[102] | 28[102] | Monofilament[107] |
| PP/PLA Parietene™ ProGrip™ | 1.1–1.7 mm [108] | 41 [108] | Monofilament [108] |
| Polyester/PLA Parietex™ ProGrip™ | 1.5 mm [109] | 38 [109] | Knitted [109] |
| Silk fiber-based meshes Allergan | 1 mm$^2$[110] | 50 [111] | Multifilament [111](woven) [110] |
| Bacterial polymer meshes (P4HB)Phasix™ | 0.258 mm$^2$[112] | 182[112] | Monofilament (knitted)[112] |
| PLGA-based meshesVicryl Rapide™(Polyglactin 910) | 0.5 mm[107] | 50[107] | Multifilament (woven or knitted)[107] |
| PLA-based meshes Ethicon | 0.2 – 1.4 mm[113] | 50[113] | Multifilament[113] |

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*2.1.Non-bioabsorbable meshes*

Non-bioabsorbable meshes can be classified into reticular, laminar or combined structures (see Table 1). Thus, reticular meshes include polypropylene meshes that are excellent to close major hernia defects and can be used by surgeons for very complicated hernias due to the material requiring less general dissection [114]. A PP mesh hernioplasty requires a minimum operating time and its simplicity reduces surgical deficiencies leading to an insignificant recurrence rate, which exceeded 12 months in 95% of the cases and occasionally reached 5 years [115]. One of the most common prosthetics used in clinical practice is the Optilene® lightweight PP mesh. This mesh was compared with a large-pore knitted polytetrafluoroethylene (PTFE) mesh and both meshes showed comparable biocompatibility regarding chronic inflammatory reaction [116]. Its good tissue integration and good tissue adhesion characteristics ,make PP meshes suitable for hernia repair surgery. However, the highly non-reactive thermoplasticreticula PVDF is used to produce suitable meshes named Dynamesh® for laparoscopic incisional and parastomal hernia interventions [117]. Long-term animal model experiments have shown a reduced foreign-body reaction to PVDF meshes [118]. A hybrid polypropylene-based reticula mesh is Dynamesh®-IPOM that contains PVDF and compared with the non-biodegradable reticular Parietex® polyester mesh, produces a reduced incidence of recurrence, seroma and haematoma, although an increased incidence of adhesion-related bowel obstruction [119]. Parietex® meshes are commonly used as synthetic prosthetic with a long track record of clinical efficacy for tension-free hernia repair [38,120] and offer enhanced compliance, excellent laparoscopic handling, and good local tolerance [121]. On the other hand, titanium-coated polypropylene reticular meshes have shown lower postoperative pain (short term), less analgesic use and faster recovery than the Parietex® mesh in the laparoscopic intraperitoneal onlay mesh (IPOM) technique [103]. This study analysed the most common titanium-coated PP meshes including TiMesh produced by plasma coating of atomic titanium and BioCer with a coating of $TiO_2$. Reticular meshes made of PP with a coating of nano-crystalline silver (Optilene Silver Mesh® from Braun) provide the only antimicrobial mesh currently used in clinics [122]. Regarding the laminar meshes, in a prospective study with 86 patients having incisional or ventral hernias who used laminar Gore-Tex® mesh in laparoscopic repairs, an average hospital stay of 4.8 days was achieved [123]. Gore-Tex® meshes thus proved to be effective as they reduce pain, complications, hospital stays, and recurrence [123].The use of Gore-Tex® for congenital diaphragmatic hernia repair was compared to Surgisis®, a biological mesh composed of porcine small intestinal submucosa (SIS) and showed no significant difference in recurrent herniation rates between Surgisis® (44%) and Gore-Tex® (38%)[124]. Furthermore, both groups showed similar recurrence times and most of these recurrences occurred after the first year [125]. The use of a laminar expanded polytetrafluoroethylene (ePTFE) Dual Mesh® (Gore) showed no significant avascular visceral adhesions 2-weeks after implantation in 91% of the patients with intraabdominal hernia repairs [126].
Ventralex™ hernia patch hybrid meshes made of polypropylene and ePTFE offer a valuable alternative for several hernia repair types: epigastric, umbilical, and small incisional hernias [127]. However, Ventralex™ Hernia Patch showed minimal postoperative morbidity (2 patients of 101) and a low recurrence rate (2%) in a long-term follow-up (range 6–55) in a small ventral abdominal wall by intraperitoneal mesh repair [128].

*2.2. Partially bioabsorbable meshes*

Partially bioabsorbable meshes can be classified according to composite and autoadhesive composite material structure (see Table 1). Partially bioabsorbable composite meshes include PP-based meshes with PEG, Polyester meshes with PEG, PP-based meshes with poliglecaprone (Ultrapro™ Mesh), PP-based meshes with polydioxanone (PDO) and oxidated regenerated cellulose (Proceed™ Ventral Patch), PP-based meshes with hydrophilic layer of HA and carboxymethylcellulose (CMC) such as Sepramesh® and PP-based meshes with PGA fiber with a coating of hyaluronic acid (HA), CMC, and polyethylene glycol (PEG) (Ventralight ST®). Ultrapro™ is a lightweight mesh that has shown disadvantages regarding chronic postoperative pain, recurrence and is more expensive than standard heavyweight meshes in TEP laparoscopic inguinal hernia repair [129]. A conventional heavyweight standard polypropylene 10 x 15 mesh is thus more suitable for laparoscopic inguinal hernia repair and has good biocompatibility [130]. Proceed Ventral meshes are used for ventral and incisional hernia repair [131]. This mesh is safe and effective and its performance is comparable with that of the Ventralex™ Hernia Patch (PP/ePTFE) [131]. Sepramesh® is a composite mesh made of PP monofilaments and is coated on one side with Seprafilm, a hydrogel safety coating composed of sodium

hyaluronate (HA) and CMC, which biodegrades at a speed that allows visceral protection during the critical healing process [132] and has been shown to be effective in reducing the likelihood of adhesions to surgical incisions [133,134]. The Ventralight ST® mesh is a complex composite that minimizes adhesion by placing the PGA-coated side towards viscera [37].
On the other hand, PP/PEG/PVP (Adhesix®), PP/PLA (Parietene™ Progrip™) and PE/PLA (Parietex™ Progrip™) are partially biodegradable autoadhesive meshes. Two self-adhering meshes (Parietene™ProGrip™ and Adhesix®) were studied in a rat model and showed minimal foreign body reaction in both groups but better mechanical grip fixation for the Parietene™ ProGrip™ for hernia repair [135]. The role of mesh fixation is important in the endoscopic technique because penetrating techniques offer a good chance of developing a post-herniotomy pain syndrome. Self-adhering thus meshes play a fundamental role today. The recovery after inguinal hernia interventions with Parietex™ Progrip™ showed that this type of mesh is able to significantly reduce the surgery time [136]. A new innovative line of research is the manufacture of self-adhesive meshes based on a biodegradable gelatin layer (LifeMesh™) and PP with large-pores and lightweight for hernia repair[137]. In a comparative study between the composite LifeMesh™ and PP meshes, LifeMesh™ showed good tolerance and its implantation did not lead to any adverse local reaction. Its adhesive layer degraded during the 4 weeks after implantation and a histopathological examination revealed that the presence of the adhesive contributed to a uniform thickness of the granulation tissue surrounding the mesh, suggesting that the mesh will better integrate with the abdominal wall. The use of this type of mesh resulted in less adherence to the internal organs, which is very important in preventing adverse effects [137].

### *2.3. Bioabsorbable meshes*

Biodegradable meshes provides the advantage of being bioabsorbable and thus can repair hernias avoiding a second surgery procedure [138]. Biodegradable meshes can be produced from biological tissues as biological meshes, by degradable biosynthetic polymers and by biodegradable synthetic polymers [139]. However, synthetic or biosynthetic bioabsorbable meshes are more economic than biological meshes [138]. Nonetheless, it is important to underline that all these bioabsorbable meshes are much more expensive than the permanent non-bioabsorbable PP mesh such as Optilene®.

#### *2.3.1. Biological bioabsorbable meshes*

Biological grafts were introduced for hernia repair applications as alternative biomaterial to synthetic meshes with the goal of reducing post-operative complications [140]. Biologically derived meshes are matrices produced by tissue decellularization [141] to reduce the risk of infections and foreign body reaction, although there is still some controversy in this regard [141,142]. These collagen-based structures can positively influence wound healing due to their intrinsic biological properties by fast angiogenesis and tissue regeneration [143,144]. Porcine derived tissues isolated from the dermis (Permacol™ from Tissue Science Laboratories [145] and Strattice™) or from the SIS (Surgisis® from Cook Surgical) [146] have been the most extensively implanted matrices. Although Permacol™ is safe and feasible, Surgisis® in a comparative study showed improved strength of incorporation and enhanced collagen deposition and neovascularization after 60 days [145]. Permacol™ meshes are seldom used for abdominal wall hernia repair due to their price and because there are better alternatives. Thus, SIS mesh has been applied successfully for inguinal and paraesophageal hernia repair and for enterocutaneous fistula and bile duct repairs in recent years [147–150]. SIS mesh has also been found to be a good option for the repair of potentially contaminated ventral hernias [151,152] and is also used in other biomedical fields such as bladder regeneration [153]. Other common meshes produced from acellular derived tissues are those obtained from bovine pericardium (Veritas®) and from human cadaver skin (Alloderm® LifeCell/Flex HD®/Allomax™). Human acellular dermis is safe and more effective for ventral hernias on contaminated welds [154,155].
Biological meshes are especially useful for the reconstruction of trunk defects when infection of the wound or mesh can lead to a hernia after reconstruction of the abdominal wall [156]. However, biological meshes have very high costs, which means that they cannot be used for routine reconstruction of the abdominal wall [157]. As such, some surgeons only use this type of mesh for the repair of complex defects of the abdominal wall [157–159]. In addition, acellular dermal meshes may produce infection, seroma, wound dehiscence in the short-term and mesh infection and recurrence complications in the long-term, as well as hernia recurrences

[160,161]. Therefore, although this type of repair can produce satisfactory results in some cases, it is far from being a definitive method of hernia repair. To tailor the degradation speed of the mesh and increase its stability to enzymatic decomposition, chemical crosslinking reactions can be carried out, using hexamethylene diisocyanate (HMDI), 1-ethyl-3- (3-dimethylaminopropyl) carbodiimide hydrochloride (EDAC) or genipin [162–164]. However, crosslinking density may limit tissue growth and hinder or reduce the pore size, providing a suitable housing for bacteria and may even promote fibrotic encapsulation [165,166]. These types of meshes are not used for inguinal hernia. In abdominal wall repair they are used less and less due their high price and the existence of better alternative options.

*2.3.2. Biosynthetic bioabsorbable meshes*

Biosynthetic biodegradable meshes mainly include those based on silk fibre, gelatin, polyhydroxyalkanoates (PHAs) and plant fibre-based materials. Thus, insect-based protein-based products such as silk fibre extracted from silkworms, Bombyx mori, with remarkable mechanical properties and reabsorption time of 2 years have gained attention to compete with biological matrices [167]. Recent research has focused on the use of natural biopolymers such as silk fibre [168–172]. Other biosynthetic polymers such as bacterial poly(4-hydroxybutyrate) (P4HB) have been used to developed bioabsorbable meshes such as Phasix™. This type of mesh is a fully resorbable monofilament scaffold for rapid tissue incorporation that have shown an *in vitro* and *in vivo* degradation with 80% and 18% greater strength than native abdominal wall at 8 and 72 weeks post-implantation, respectively, despite the significant biopolymer degradation [112]. P4HB reabsorbable meshes are showing promising results in the management of chronic mesh infection [173–175]. The electrospun silk fibroin (SF) in combination with other PHA with excellent biological properties, poly (3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV) [176,177], to produce hybrid scaffolds have showed high efficiency and biocompatibility to repair abdominal wall defects [178]. The use of plant-derived fibers as mesh materials for abdominal wall repair is also being studied [179]. These meshes showed biosecurity both *in vitro* and *in vivo*, but only in those where intensive purification steps were applied after various chemical treatments. The silk fibre, gelatin and plant-fibee-based meshes are not yet being used in clinics. However, bacterial Phasix meshes are currently used in hospitals such as La Fe in Valencia, Spain. This prosthesis, like the bioabsorbable synthetic BIO-A described below, has been used in cases of complex eventrations with contaminated or dirty surgeries (grade III and IV of the Centers for Disease Control (CDC) classification) or in cases of chronic infection of the mesh (biofilm). There is no consensus on the use of this type of material in contaminated fields since there are working groups that defend the use of permanent synthetic materials [180].

*2.3.3. Synthetic bioabsorbable meshes*

Synthetic biodegradable meshes include those based on biodegradables synthetic polymers such as poly-ε-caprolactone (PCL), polyglicolic acid (PGA), polylactic acid (PLA) and the copolymer poly(lactic-co-glycolic) (PLGA). Although initially widely used, PGA meshes are not used any more because they degrade too fast [181]. Since PLA degrades slower than PGA, a mesh named POLYGLACTIN 910 (Vicryl™) was developed by Ethicon. This mesh is composed of 92% glycolide copolymerized with 8% lactide [151]. However, this type of mesh also has some complications such as the fact that it does not prevent post-operative recurrence of herniation, probably because of an inappropriate degradation rate [113,182]. Synthetic biodegradable scaffolds of 67% PGA copolymerized with 33% trimethylene carbonate (TMC) such as PGA-PTMC (BIO-A®) from Gore, also known as Gore® BIO-A, have shown significantly better tissue integration and resistance than that obtained with biological matrices such as Strattice™ and Veritas®, and the native abdominal wall [40,183]. BIO-A® meshes have also shown improved properties in comparison with common biological meshes. Complex open bioabsorbable reconstruction of the abdominal wall (COBRA) studied the results of BIO-A® in contaminated fields II and III of the CDC classification and concluded that it showed efficacy in terms of long-term recurrence and quality of life for complex ventral hernia repair and offers an alternative to biological and permanent synthetic meshes in these complex situations [184]. Prospective multicentre studies have also described its usefulness in repairing complex herniations [185]. PLA-based meshes from Ethicon composed of 95% Lactide and 5% glycolide provide further improved mechanical properties for more than 9 months [113]. However, PLA-based meshes also present complications such as foreign body granuloma and giant cell formation.

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## 3. Mesh adhesion problem

Due to their good performance in abdominal wall hernia repair and lower cost than those of other available options, PP mesh is the most broadly used [186]. However, this type of mesh frequently induces dense adhesions due to fibrovascular infiltration when there is direct contact between the mesh and the viscera [187] and if the mesh is placed directly over the intestine and other visceral organs [134,188]. Mesh adhesion may cause obstruction and perforation of the bowel and thus is one of the main problems that arise after the treatment of hernias and can cause discomfort and generate adverse reactions [189]. Difficult reoperation, intestinal obstruction, or enteric fistula may be led by mesh adhesions [187]. Intestinal and omentum tissue have exhibited severe adhesions to common meshes such as PP, which may cause many serious complications [190]. To try to solve these problems, ePTFE meshes, like Gore-Tex® were used since they cause less adhesion to the intestine due to their microporous surface morphology. However, the tensile strength in their interface is lower than in the PP mesh or composite mesh made of PP and ePTFE [191]. In addition, when the ePTFE mesh becomes infected, recovery is very difficult, and the mesh usually requires removal [192,193]. Research on the development of new materials and coatings as strategies to prevent adhesion is therefore essential in this field. The adhesion problem has promoted the development of a composite mesh that combines two or more materials made of a non-absorbable material such as polypropylene, polyester or PVDF on one face and a non-adhering biodegradable material on the face in contact with handles or viscera, such as ePTFE, PLA, etc [37].

## 4. Chronic mesh infection problem

Prosthetic materials for hernia repair often present infection by bacteria on the material surface that results in failure of the implanted meshes [194–197]. Two examples of chronic bacterial infections (biofilm) are shown in Figure 2.

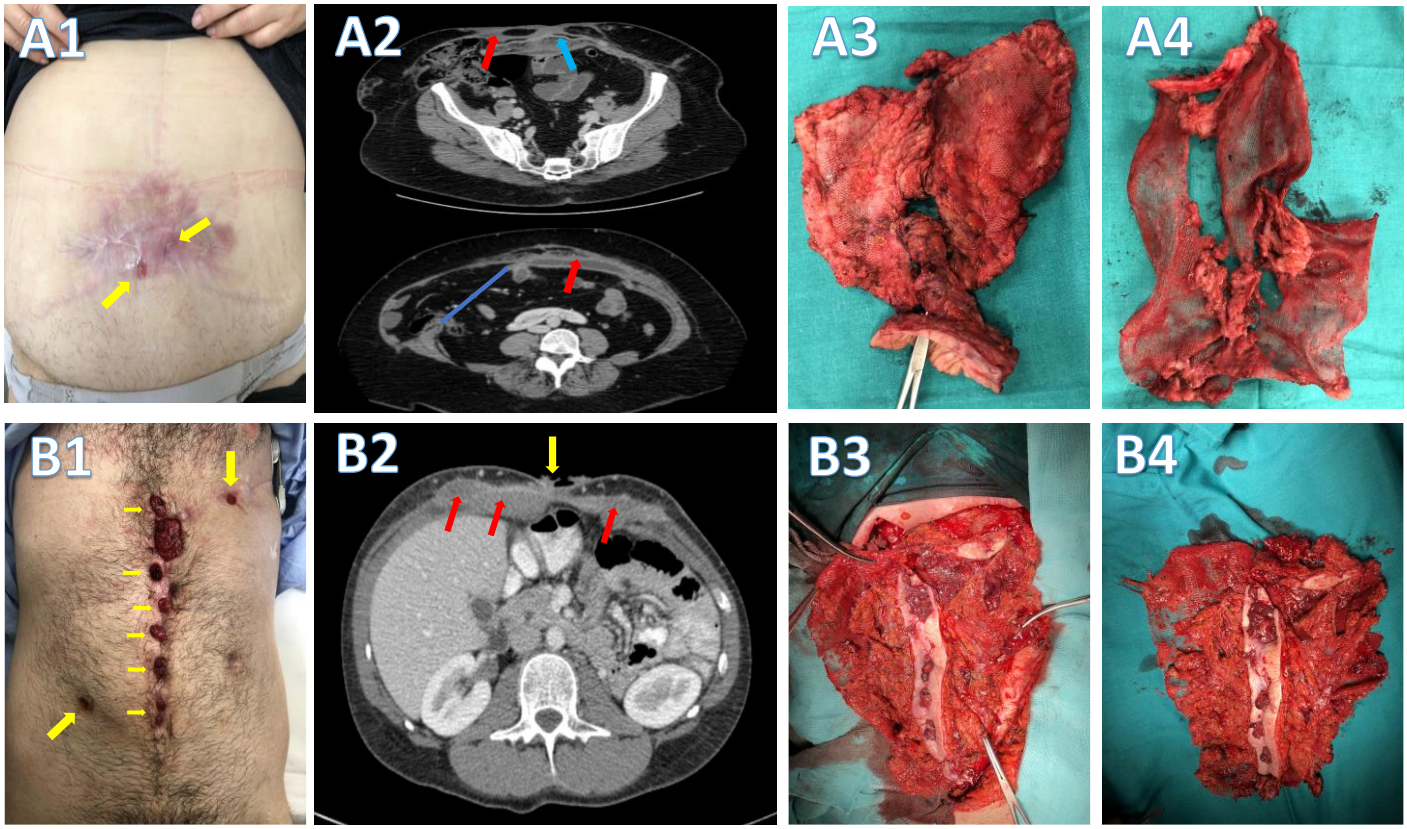


**Figure 2.** Examples of meshchronic infections. Biofilm case **A**: 50-year-old woman with recurrent incisional hernia (10 previous interventions with placement of several prosthesis). She presented two fistulous orifices with chronic suppuration (yellow arrows) (A1). The microbiological analysis showed infection by *Staphylococcus aureus*. The tomography (A2) shows a large lateral incisional hernia (blue line), postsurgical changes in the anterior abdominal wall associating collection of 15 x 13 x 1.2 cm (transverse / craniocaudal / anteroposterior) (red arrows) and one of the prostheses previously placed (blue arrow). Removal of 2

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previous prostheses (A3 placed onlay and A4 preperitoneal) and reconstruction of wall with placement of a 4 PHB prosthesis (Phasix ST) was required. Biofilm case **B**: 26-year-old man who needed several laparotomies due to traffic accident with placement of PVDF prosthesis. Four months later he presented multiple fistulous orifices with chronic suppuration (yellow arrows) (B1). The microbiological analysis showed infection by *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The tomography shows an anfractuous collection on the prosthesis (red arrows) and fistulous orifices (yellow arrows) (B2). Complete removal of the PDVF prosthesis was required (B3 and B4).

Figure 2 shows two examples of the problem of chronic mesh infections where bacterial biofilm was formed and complicated the search for a satisfactory solution. The microbiological cultured in these two cases showed infection by *Staphylococcus aureus* and by *Pseudomonas aeruginosa*also in the second case.
*S. aureus* [198] and *Staphylococcus epidermidis* [199] are the most common microorganisms related to mesh infection (approximately 90%), *S. aureus* (MRSA) [200], involved in up to 63% of surgical site mesh-related infections [201–203], being methicillin-resistant. Other microorganisms related to mesh infection include *Streptococcus pyogenes* [204], *Enterococcus faecalis* [205,206], *Pseudomonas sp.*[204], *Escherichia coli*, *Klebsiella pneumonia* [207,208], *Propionibacterium acnes* and *Candida albicans* [209–211].

## 5. Antimicrobial meshes and their fabrication methods

Most common prosthetic meshes used for hernia repair (Table 1) are made of materials that do not possess antimicrobial activity. However, surgical infections have an increasing clinical, economic and socioeconomic impact due to the cost of managing infectious complications in digestive surgery, triple the total direct cost of surgery and the patients' reduced quality of life of patients and affect waiting lists [212,213]. In this regard, the coating of biomaterials with antimicrobial compounds is the most common technique to provide antimicrobial properties to the surface and thus prevent microbial colonization and attachment [214,215]. Antimicrobial meshes can be made by dipping/soaking, plasma surface functionalization, plasma-induced graft polymerization [216] (see Figure 3).

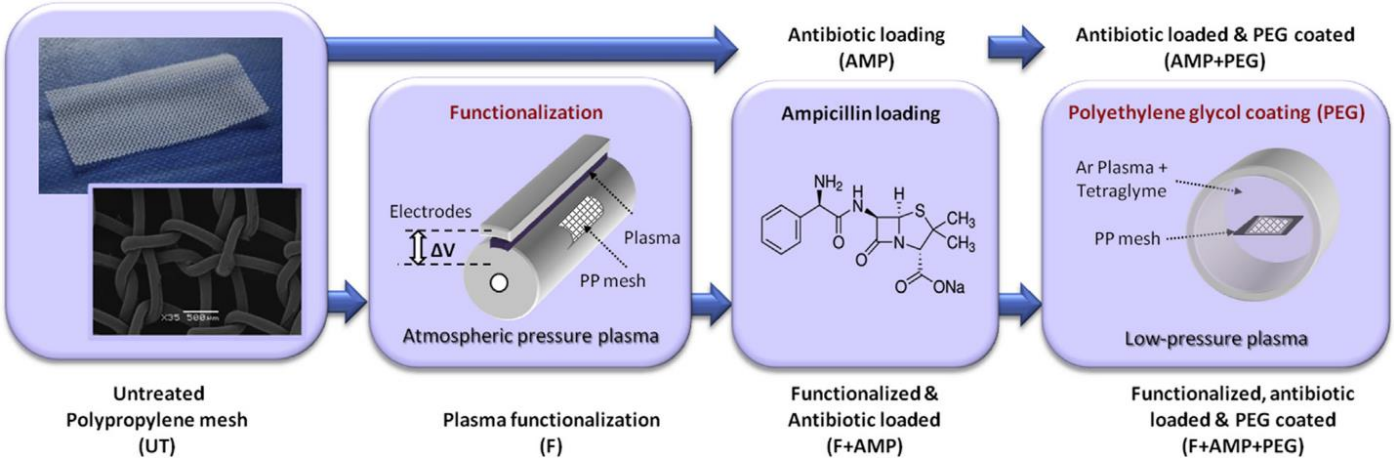


**Figure3.** Manufacturing scheme of PP meshes with enhanced biological properties through plasma functionalization, antibiotic load and plasma polymerization of a polyethylene glycol coating. *Reprinted with permission from Elsevier* [216].

The antibiotic dipping/soaking method [217–220], antiseptics [221] and enzymes [222,223] dissolved in a liquid solution (usually aqueous) that are physically adsorbed onto the mesh. This technique, while useful, has not demonstrated clinical superiority over systemic antibiotic therapy. In addition, it presents the limitation of providing a short-term period of infection prevention. Plasma treatment of the matrices triggers the formation of intermediate reactive species and functional groups on the mesh surfaces that enhance the interaction between the drug and the surface [216]. Plasma can also be used to produce anchor points on the mesh surface for monomer polymerization as plasma-induced graft polymerization [224–227]. The plasma treatment and plasma-induced graft polymerization provide longer-lasting antimicrobial options [216,225,228,229]. 3D printing is another available method of producing antimicrobial meshes selected by some researchers, also referred to as rapid prototyping or additive manufacturing, by different 3D printing mechanisms: stereo lithography, selective laser sintering, injection printing, or fused deposition modelling (FDM) [230]. FDM consists of extruding a polymer filament after heating to its melting temperature and is the most promising technique due to its lower-cost and the possibility of producing personalized hernial meshes [230].

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All of the antimicrobial meshes shown in this section are currently under research and only the silver-coated polypropylene mesh (Optilene Silver Mesh® from Braun) shown in Table 1 has recently started to be used on a limited number of patients with ventral hernias in hospitals such as the Spanish Hospital La Fe. However, these meshes are only being applied in special cases such as patients with incisional hernias who are at risk of infection, i.e. contaminated grade III or clean contaminated II of the CDC classification. The manufacturer of this type of mesh would like to broaden the application to the rest of the grades but further scientific research is required to achieve this goal. Although there are really no tests with a high degree of recommendation that determine the type of mesh to be used in each case and surgeons must decide according to their own experience. According to the manufacturer, silver ions ($Ag^+$) provide a broad spectrum antimicrobial action, the release of the silver ion is gradual and sustained over time, which allows better prevention of infection, and their use is safe in the long term, does not present toxicity or generate resistance [231]. However, many scientific studies have demonstrated that silver ions can be highly toxic for mammalian cells [232,233] and induce microbial resistance [234,235]. Further research is therefore necessary in this field to find a solution to avoid microbial infections, including those strains that are multidrug-resistant. The optimal hernia repair mesh would be ideally made of a material able to deal with microbial resistance to provide a long-lasting solution. In this regard, a broad range of antimicrobial meshes have been proposed so far (see Table 3).

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**Table 3. Promising antimicrobial meshes for hernia repair.**

| Mesh material | Antimicrobial agent | Microorganism tested | Antimicrobial activity | Cytotoxic effect | In vivo tested (animal model) | Year | Ref. |
|---|---|---|---|---|---|---|---|
| **Meshes with antibiotics** | | | | | | | |
| Polyester | Coating with CD-PEGDGE and vancomycin | *S. aureus* | Yes, against *S. aureus* | Not tested | Yes (mouse) | 2010 | [236] |
| PGA-TMC | Cefazolin | *S. aureus* | Yes, against *S. aureus* | Not tested | Yes (rats) | 2015 | [220] |
| Porcine acellular dermal matrix | Rifampin/minocycline | *E. coli* and MRSA | Yes, against *E. coli* and MRSA | No | Yes (rabbit) | 2016 | [237] |
| Polyester (Parietex®) | Cyclodextrin-based polymer loading Vancomycin | MRSA | Yes, against MRSA | Not tested | Yes (pig) | 2017 | [238] |
| PLLA | Ciprofloxacin | *S. aureus* and *E. coli* | Yes, against S. aureus and *E. coli* | No | No | 2017 | [239] |
| PP | Coating with PLGA-rifampicin microspheres | *S. aureus* | Yes, against *S. aureus* | No (human fibroblasts from foreskin) | Yes (mouse) | 2017 | [240] |
| PP grafted with HDI-CD | Levofloxacin | *S. aureus* and *E. coli* | Yes, against *S. aureus* and *E.coli* | Not tested | No | 2018 | [241] |
| PBSA | Levofloxacin | *S. aureus* and *E. coli* | Yes, against *S. aureus* and *E. coli* | No (Mouse fibroblast L929) | Yes (mouse) | 2019 | [242] |
| Different meshes | HApN with gentamicin/ rifampicin | *S. aureus*, MRSA, *S. epidermidis*, *E. coli* | Yes, aginst *S. aureus*, MRSA, *S. epidermidis* and less against *E. coli* | No | No | 2019 | [243] |
| PVA and PP | Ciprofloxacin hydrochloride | Not tested | Not tested | No | Yes (rabbit) | 2019 | [90] |
| **Meshes with antimicrobial metals** | | | | | | | |
| PP | Ag/Silica | *S. aureus* | Yes, against *S. aureus* | No | No | 2016 | [244] |
| PP (Optilene Silver Mesh®) | Nano-crystalline silver coating | MRSA | Yes | Not tested | Yes (rats) | 2018 | [122] |
| PP | Zinc | *In vivo* | Yes (*In vivo*) | No tested | Yes | 2020 | [245] |
| **Meshes with antimicrobial polymers** | | | | | | | |
| Silk fibroin | Blended with Chitosan | Not tested | Not tested | Not tested | Yes (guinea pigs) | 2006 | [246] |
| Chitin | Chitin | Not tested | Not tested | Not tested | Yes (rats) | 2017 | [247] |
| Chitin | Chitin | Not tested | Not tested | Not tested | Yes (rats) | 2018 | [248] |
| **Meshes with antiseptics** | | | | | | | |
| PP | Chlorhexidine and Allicin | *S. aureus* | Yes, against *S. aureus* | Yes (rabbit skin fibroblasts) | No | 2015 | [249] |
| PP | Chlorhexidine and Allicin | *S. aureus* | Yes, against *S. aureus* | Not tested | Yes (rabbit) | 2015 | [221] |
| PP (Optilene®) | QA-based polymer loaded with chlorhexidine | *S. aureus*, *E.coli* and *S. epidermidis* | Yes, against *S. aureus*, *E.coli* and *S. epidermidis* | Yes (rabbit skin fibroblasts) | No | 2016 | [250] |
| PP grafted with HDI-CD | Triclosan | *S. aureus* and *E. coli* | Yes, against *S. aureus* and *E.coli* | Not tested | No | 2018 | [251] |
| PP (Optilene®) | Chlorhexidine-loaded carboxymethylcellulose gel | *S. aureus* | Yes, against *S. aureus* | Low (rabbit skin fibroblasts) | Yes (rabbit) | 2019 | [252] |
| **Meshes with antimicrobial peptides** | | | | | | | |
| PP with PCL | AMPs in gellan gum | *S. aureus* and *E. coli* | Yes, against *S. aureus* and *E.coli* | No (HDFs) | No | 2019 | [253] |
| PP | AMP (PEP-1) in PCL | *E. coli* and *S. aureus* | Yes, against *E. coli* | No (HDFs) | No | 2019 | [254] |
| **Meshes produced by combined strategies** | | | | | | | |
| PP | Triclosan-chitosan coating | *S. aureus* | Yes, against *S. aureus* | Not tested | Yes (rats) | 2009 | [255] |
| ePTFE | silver carbonate and chlorhexidine diacetate | S. aureus | Yes, against S. aureus | Not tested | Yes (rabbit) | 2015 | [221] |
| PLLA | MSN of levofloxacin and silver | MRSA | Yes, against MRSA | No | Yes (rat) | 2017 | [256] |
| PCL | Levofloxacin and irgasan | *S. aureus* and *E. coli* | Yes, against *S. aureus* and *E. coli* | Not tested | No | 2017 | [257] |
| PCL | Alginate and gentamicin | *E. coli* | Yes, against *E. coli* | Not tested | Yes (rats) | 2019 | [258] |
| Polyester | Coating of chitosan-phenytoin-pluronic nanomicelles and ciprofloxacin-alginate | *S. aureus* and *P. aeruginosa* | Yes, against *S. aureus* and *P. aeruginosa* | Not tested | Yes (dog) | 2019 | [259] |
| Nylon-6 (core) with poly(hexanide) | Chitosan/Polyethylene oxide (shell) with 5-chloro-8-quinolinol | *S. aureus* and *P. aeruginosa* | Yes, against *S. aureus* and *P. aeruginosa* | Not tested | No | 2020 | [260] |
| PP (Optilene®) | Chlorhexidine fixed with cyanoacrylate adhesive | *S. aureus* | Yes, against *S. aureus* | Not tested | Yes (rabbit) | 2021 | [261] |

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Nevertheless, none of these meshes have been successful in clinical practice or have not yet been tested. They are classified according to their antimicrobial agents such as antibiotics, silver, antimicrobial polymers, antiseptics, antimicrobial peptides and by combined antimicrobial strategies.

*5.1. Meshes with antibiotics*

A polyester mesh was coated with *β*-cyclodextrin-Polyethylene glycol diglycidyl ether loaded with vancomycin and showed effective prevention of *S. aureus* mesh infection two and four weeks after implantation *in vivo* in a mouse animal model [236]. Prior to the clinical translation of these meshes, further studies including long-term evaluation and biocompatibility studies are needed. Other meshes that have already shown an evident decrease in bacterial colonization of the Gram-positive *S. aureus* are prostheses impregnated with the antibiotic cefazolin [220]. Although adhesions to the prosthesis were produced when it was placed in contact with intra-abdominal viscera, the antibiotic mesh reduced the formation of adhesions compared with the control group, besides inhibiting the inflammatory response to infection [220]. Another strategy proposed consisted of biological meshes to take advantage of their good compatibility, giving them antibacterial properties by charging them with antibiotics [237]. These researchers produced a porcine acellular dermal matrix mesh charged with minocycline and rifampin (XenMatrix AB) that showed antimicrobial activity both *in vitro* and *in vivo* against *E. coli* and the life-threatening multidrug-resistant MRSA. XenMatrix AB exhibited complete bacterial inhibition, no abscess formation, and a reduced inflammatory response in an *in vivo* rabbit model compared with the uncoated meshes [237].
A significant reduction of antibiotic dose (1.75 mg/cm$^2$) compared with systemic antibiotic administration was achieved in a pig model preventing a multifilament prosthetic mesh infection with a Parietex® polyester mesh with a crosslinked cyclodextrin-based polymer and incorporated vancomycin [238]. This small amount of vancomycin achieved complete elimination of the MRSA infection in the mesh implanted in six pigs without affecting tissue integration [238]. Another strategy consisted of thermofixating polycyclodextrin on a PLLA mesh [239]. This antimicrobial approach showed suitable release kinetics of ciprofloxacin to provide efficient antibacterial activity against *S. aureus* wand *E. coli* [239]. Polypropylene meshes coated with PLGA-rifampicin microspheres showed that this compound continuously releases over 60 days and provides potent antibacterial activity against *S. aureusin vitro* and *in vivo* and no adverse effects appeared against fibroblast cells for hernia repair [240]. The loading with levofloxacin and grafting of a PP mesh with hexamethylene diisocyanate (HDI) and cyclodexrins (CD) exhibited long-lasting antibacterial activity against *E. coli* and *S. aureus* [241]. Antibiotic (levofloxacin) surface modification of poly(butylene succinate-co-butylene aspartate) (PBSA2-*g*-Lv) meshes achieved *in vitro* antibacterial capacity against *S. aureus* and *E. coli* without affecting the viability of L929 fibroblast cells [242]. These PBSA2-*g*-Lv meshes prevented bacterial infection and promoted tissue regeneration in an *in vivo* wound-healing mouse model (Figure 4) [242].

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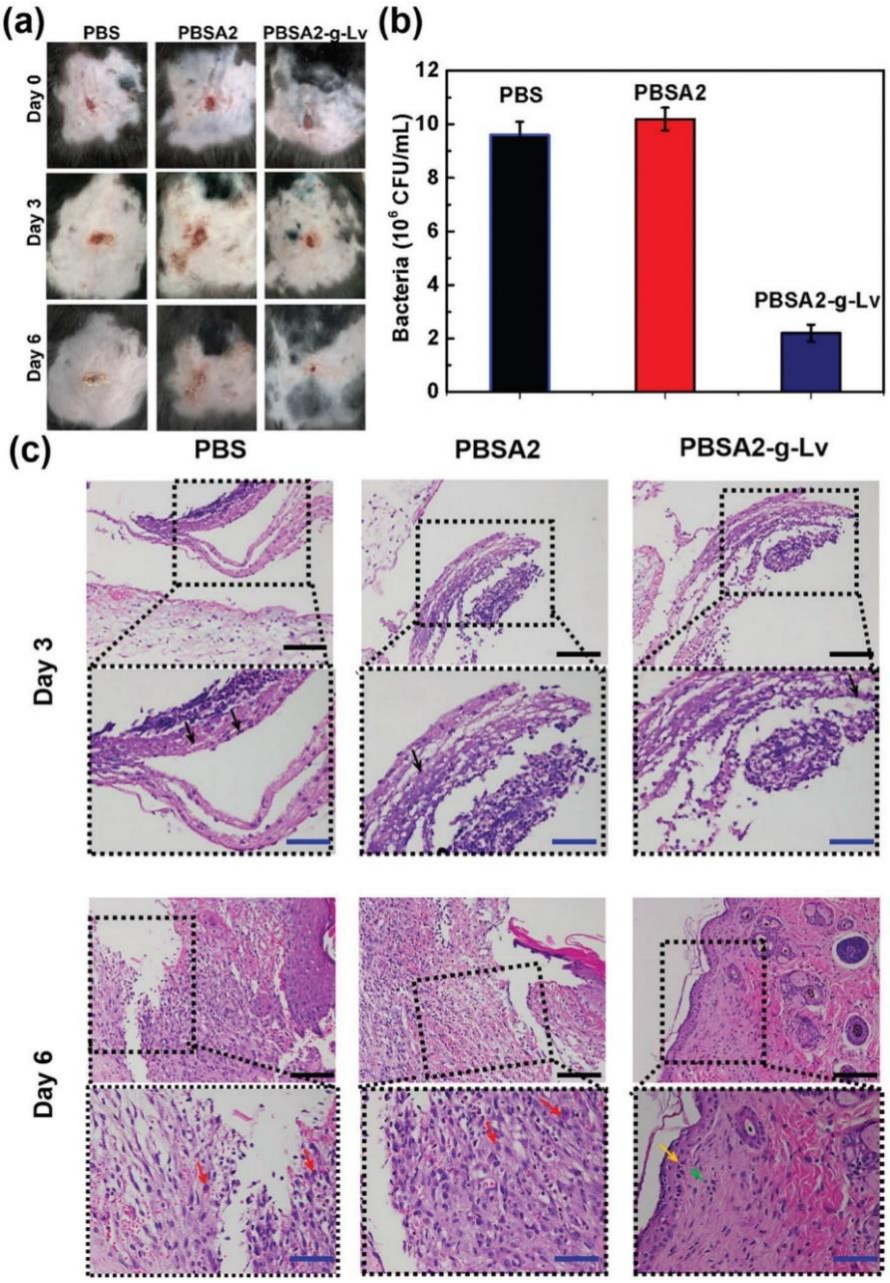


**Figure 4. (a)** Images of wounds treated with polyester electrospun nanofibre meshes of polybutylene succinate (PBS), poly(butylene succinate-co-butylene aspartate) (PBSA2) and poly(butylene succinate-co-butylene aspartate) with levofloxacin (PBSA2-*g*-Lv). **(b)** Bacterial concentrations measured in the wound tissue of a mouse animal model. **(c)** Hematoxylin and eosin staining after three and six days of treatment (the black and blue scale bars are 200 μm and 100 μm, respectively) - *Published by The Royal Society of Chemistry (RSC)*[242].

A polymer-based hyaluronic acid-poly(N-isopropylacrylamide)(HApN) hydrogel that can be used as drug-loaded coating of gentamicin and rifampicin applicable to different meshes to provide strong antimicrobial activity against *S. aureus*, MRSA, *S. epidermidis* and less against *E. coliin vitro* [243]. Polyvinyl alcohol (PVA) is another biomaterial hydrogel with excellent biocompatibility and water sorption properties [262]. Meshes with a broad range of porosities with pores of different shapes and sizes using different sized threads can be produced with PVA and PP loaded ciprofloxacin hydrochloride to minimize post hernioplasty infections by FDM 3D printing (see Figure 5) [90].

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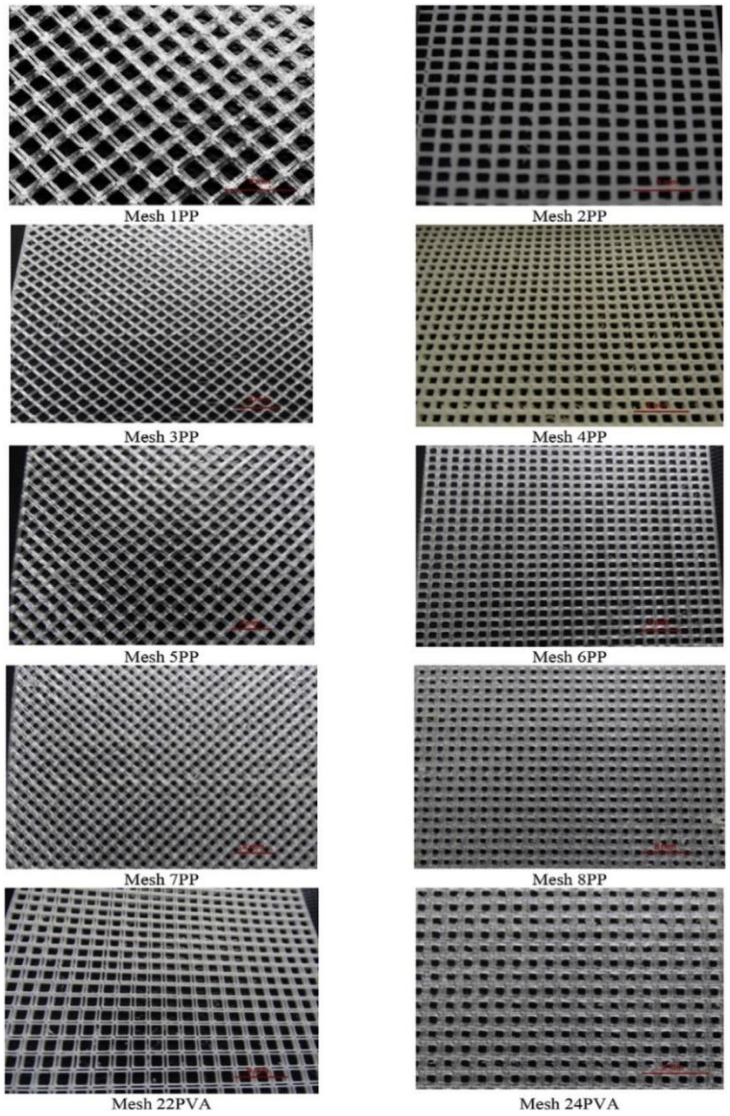


**Figure 5.** Pictures of different 3D printed antimicrobial meshes by FDM. *Reprinted with permission from Elsevier* [90].

All of the 3D printed antimicrobial meshes showed outstanding mechanical performance *in vivo* biocompatibility, adhesion capacity, mild-to-moderate appearance of adhesions to visceral tissue, and did not exhibit signs of implant rejection. However PVA-based meshes showed slightly faster drug release than PP-based meshes [90]. The development of new antimicrobial meshes against all types of microorganisms, including the multidrug-resistant strains, is becoming more important due to the global problem of the increasing antibiotics resistance repeatedly announced by the World Health Organization [52]. In this regard, many alternative antimicrobial meshes are currently under development by many international research groups.

### *5.2. Meshes with antimicrobial metals*

Polypropylene meshes with a silica/silver layer have been proposed for hernia repair and showed good biocompatibility in peritoneal mesothelial cells and tissue repair [244]. An antimicrobial mesh made of PP (Optilene Silver Mesh® from Braun) with a coating of nano-crystalline silver showed significantly better bactericidal effect than the normal PP meshes [122]. Other metal-based meshes impregnating with Zinc (ZnMesh) have recently been proposed for abdominal wall repair and showed significant reduction of infection in a rat animal peritonitis model [245]. However, a higher percentage of adhesions were reported in this type of mesh than in conventional PP meshes.

### *5.3. Meshes with antimicrobial polymers*

Natural materials such as chitosan with intrinsic antimicrobial activity combined with silk fibroin have been proposed to produce meshes for ventral hernia repair [246]. In this study, these meshes were tested in guinea

pigs and compared with biodegradable human acellular dermal matrix and a PP mesh, which showed extensive intestinal adhesions and scarring in contrast to the other two meshes that underwent tissue remodelling. Another promising biodegradable hernia patch for repairing rat abdominal wall full thickness defects was made with another antimicrobial material, chitin [247]. The chitin patch induced more abundant new blood vessels with less tissue inflammation and fibrosis compared to PP mesh. In a subsequent study performed by the same authors, chitin patches showed good biomechanical properties and satisfactory healing effects on the abdominal wall, which render them promising for clinical hernia treatment [248]. However, the antimicrobial characterization of these promising chitin and silk fibroin/chitosan meshes have not yet been explored.

*5.4. Meshes with antiseptics*

Another strategy proposed by Perez-Köhler et al. consisted of soaking a reticular heavyweight PP mesh with antiseptics such as a mixture of chlorhexidine and allicin to inhibit *Staphylococcus aureus* adhesion [249]. Inhibition zones and SEM micrographs were compared with each compound separately and with the vancomycin antibiotic. While allicin alone lost its effectiveness after 24 hours, when applied together with chlorhexidine the antibacterial activity was greater than that of vancomycin. However, allicin and chlorhexidine exerted high cytotoxicity against rabbit fibroblasts in contrast to vancomycin [249]. For this reason, the same authors performed an *in vivo* study with these meshes in New Zealand White rabbits and compared them with the performance of a commercial antimicrobial mesh (Gore Dual Mesh Plus mesh®)[221]. The chlorhexidine pre-soaked mesh displayed antimicrobial activity without interrupting tissue integration. However, although the meshes of the allicin-chlorhexidine group showed new tissue formation, they contained abscesses and bacterial infections (see Figure 6**)**.

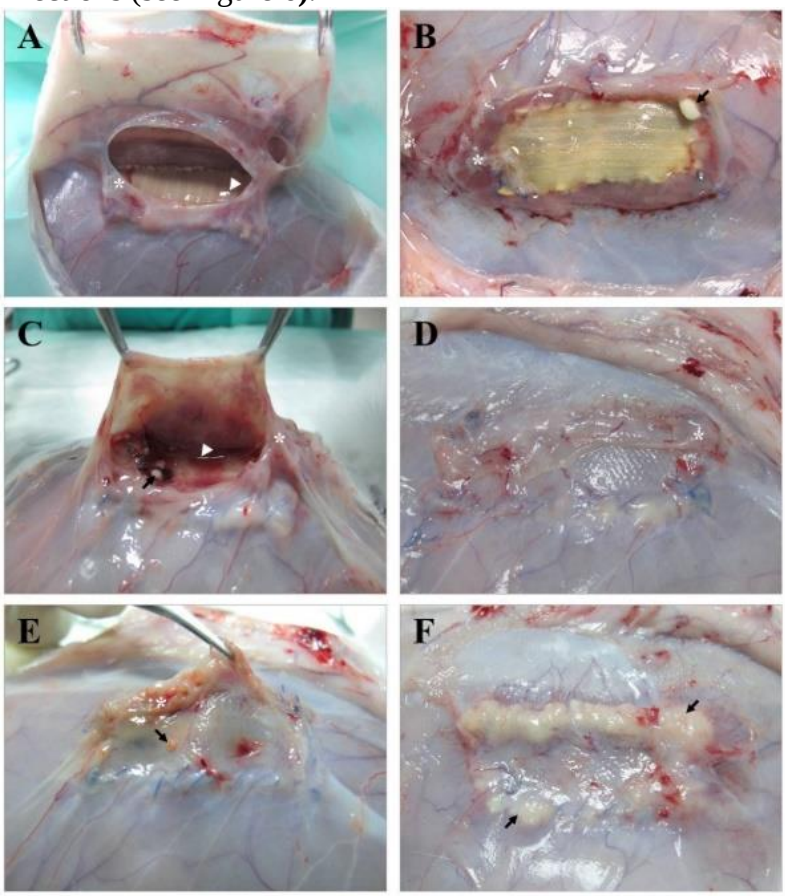


**Figure 6.** Prosthetic meshes for hernia repair after two weeks of surgery and *S. aureus* infection. **(A, B)** Laminar mesh of ePTFE with a coating of silver carbonate and chlorhexidine diacetate: clean main body, thick fibrous encapsulation (*), seroma formation (▶) and purulent material (→). **(C, D)** Polypropylene soaked with chlorhexidine implants showed more intense vascularization and a total mesh integration into the host tissue. **(E, F)** Polypropylene soaked with allicin-chlorhexidine meshes showed a high level of purulent material (→) on different parts of the mesh surface [221].

Soaking PP meshes with a low chlorhexidine concentration is thus a promising treatment to prevent and resist infection during hernia repair. In the same research line, the coating of polypropylene meshes (Optilene®) with antibacterial quaternary ammonium-based polymer loaded with chlorhexidine (POL–CHX) meshes also

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showed antimicrobial activity [250]. *In vitro* antimicrobial assays against *S. aureus*, *S. epidermis* and *E.coli* showed significant inhibition halos around these composite meshes with the three bacteria strains: Gram-negative *E. coli* and Gram-positive *S. aureus* and *S. epidermidis* ($p<0.01$). However, this compound turned out to have some toxicity against human fibroblasts, significantly reducing its viability. *In vivo* performance in rabbits with partial abdominal wall defects were carried out with this type of mesh and showed maintenance of antimicrobial action and no bacterial adhesion 14 days after surgery. A PP mesh grafted with HDI and CD and loaded with triclosan showed excellent long-lasting antibacterial properties against *S. aureus* and *E. coli* [251]. Another strategy proposed more recently consisted of coating Optilene®PP meshes with an antibacterial chlorhexidine-loaded carboxymethylcellulose gel [252].

### *5.5. Meshes with antimicrobial peptides*

Alternative solutions to the exponential increase of antibiotic resistance are based on producing antibacterial composite meshes charged with wide-spectrum antimicrobial peptides (AMPs) [253] (Figure 7).

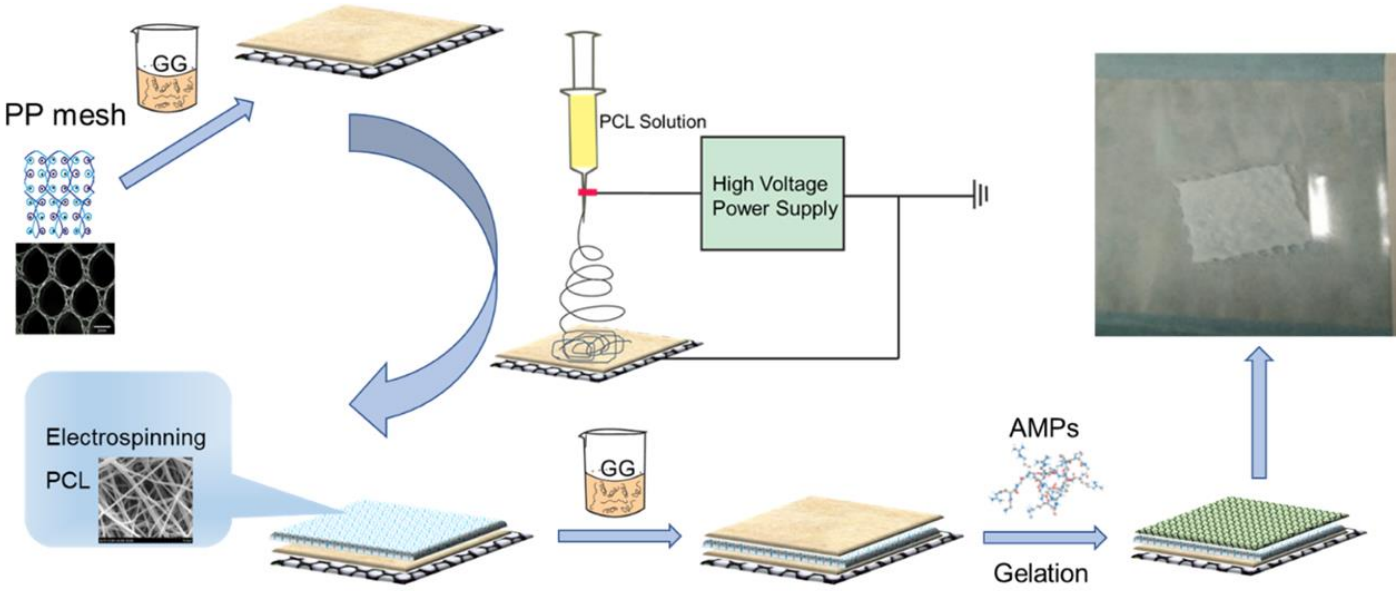


**Figure 7.** Manufacturing scheme of antimicrobial composite meshes made of a PP mesh and PCL electrospun nanosheets charged with wide-spectrum antimicrobial peptides (AMPs) incorporated in gellan gum. *Reprinted with permission from ACS* [253]. *Copyright (2019) American Chemical Society. Further permissions related to the material excerpted should be directed to the ACS.*

These novel antimicrobial meshes provided prolonged *in vitro* release of AMPs (< 60% in 10 days) and thus potent antibacterial action against *S. aureus* and *E. coli* bacteria, while they did not show any cytotoxic effect in human dermal fibroblasts (HDFs) even with an AMPs incorporation of 10 mg/cm$^2$ [253]. Another investigation used an antimicrobial peptide PEP-1 incorporated in a conventional PP mesh with large pores and showed adequate *in vitro* release of the peptide while maintaining a similar tensile strength to two commercial meshes and effective antibacterial activity against *E. coli* without inducing toxicity in HDFs [254].

### *5.6. Meshes produced by combined strategies*

PP meshes coated with triclosan-chitosan revealed a reduction of *S. aureus* adherence to polypropylene grafts in an *in vivo* rat model [255]. Another study of combined antimicrobial strategies showed that the main body of a laminar mesh of ePTFE with a coating of silver carbonate and chlorhexidine diacetate remained clean but thick fibrous encapsulation, seroma and purulent material were observed related to the mesh anchorage (see Figure 6) [221]. In the same research line, a mesoporous silica nanoplatform (MSN) composed of levofloxacin (Lev) and silver (Lev@MSN@Ag), and poly-L-lactide (PLLA) electrospun (Lev@MSN@Ag–PLLA) *via* blending electrospinning was proposed as an alternative antimicrobial option for hernia repair (see Figure 8) [256].

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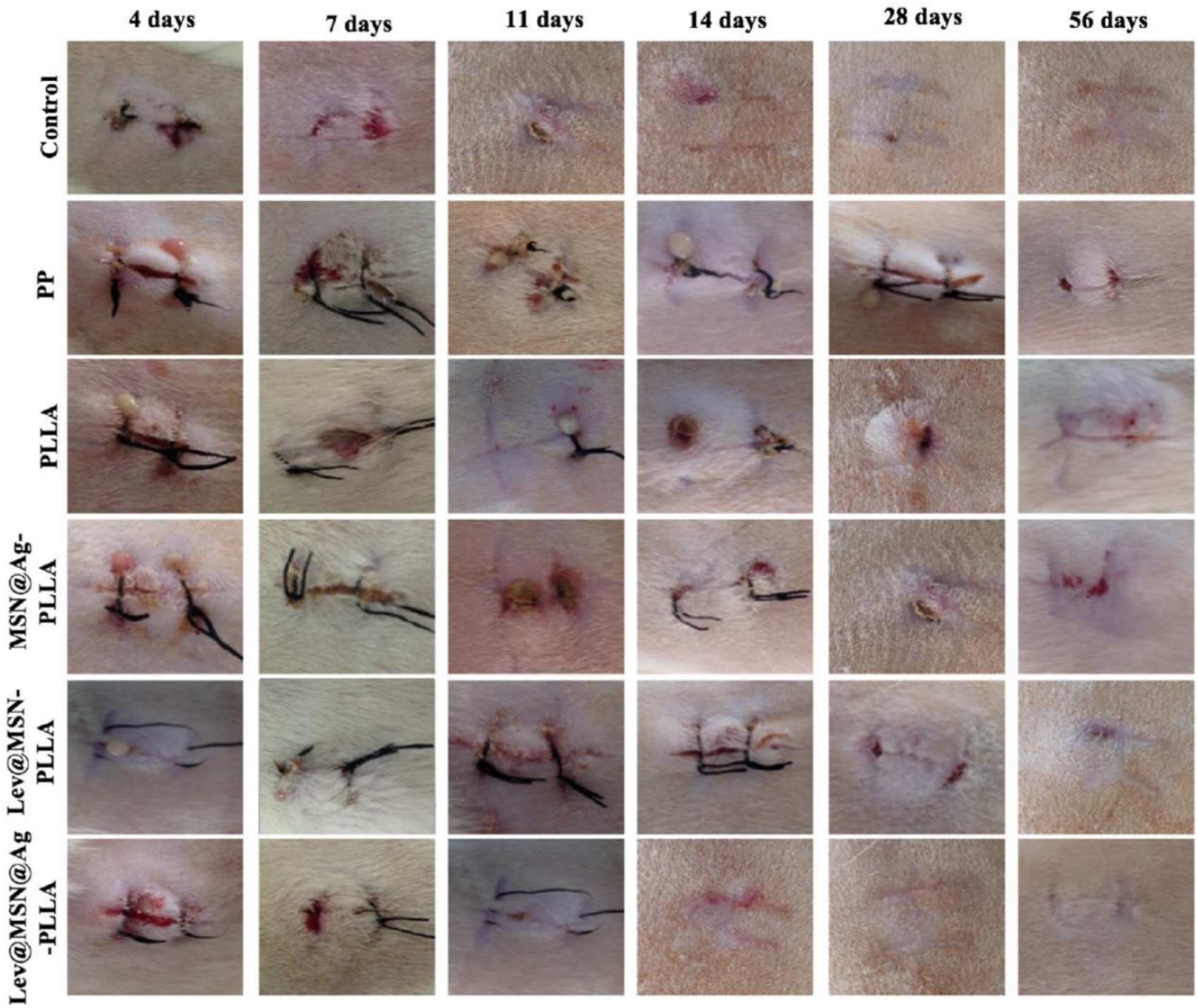


**Figure 8.** Macroscopic evaluation. Images indicating the wound healing status and scar formation. **(a)** control, **(b)** PP, **(c)** PLLA, **(d)** MSN@Ag-PLLA, **(e)** Lev@MSN-PLLA, **(f)** Lev@MSN@Ag-PLLA - *Published by The Royal Society of Chemistry (RSC)*[256].

The combined action of these compounds allows high inhibition of resistant bacteria without the need for applying high doses of antibiotics, which can be toxic for the human body. Another strategy for producing antimicrobial meshes consisted of loading electrospun PCL scaffolds with either an antibacterial agent, irgasan, which provides slow release, or a broad-spectrum antibiotic with burst release, levofloxacin [257]. Both advanced meshes were able to inhibit the growth of *E. coli* and *S. aureus* by the agar diffusion test [263]. The alginate biopolymer possesses excellent water sorption, biocompatibility, biodegradation, and is a renewable material with a wide range of biomedical applications [264–270]. 3D printed meshes made of PCL containing alginate and gentamicin were recently implanted in rats and showed bactericidal effects and good histopathological behaviour [258]. A multifunctional prosthetic polyester-based hybrid mesh for hernia repair has been developed by using commercial polyester as the backbone material to ensure mechanical integrity, coated with a complex antimicrobial and healing promoting coating made of chitosan with pluronic nanomicelles loaded with phenytoin and microparticles of ciprofloxacin-alginate polyelectrolyte complex [259]. These prostheses possess excellent antimicrobial activity against *S. aureus* and *P. aeruginosa* and efficient healing with excellent biocompatibility was achieved *in vivo* in dogs. More recently, the coaxial electrospinning technique was investigated in order to develop new core/shell nanofibres with mechanically stable structures consisting of a core made of Nylon-6 and a shell composed of chitosan/polyethylene oxide, which incorporates antimicrobial capacity against *S. aureus* and *P. aeruginosa* by dual drug release of poly (hexanide) from both the shell and the core [260]. The antimicrobial performance and tissue response of the

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PP meshes soaked with chlorhexidine (shown in Figure 6) have recently been improved by cyanoacrylate adhesive fixation [261] (see Figure 9).

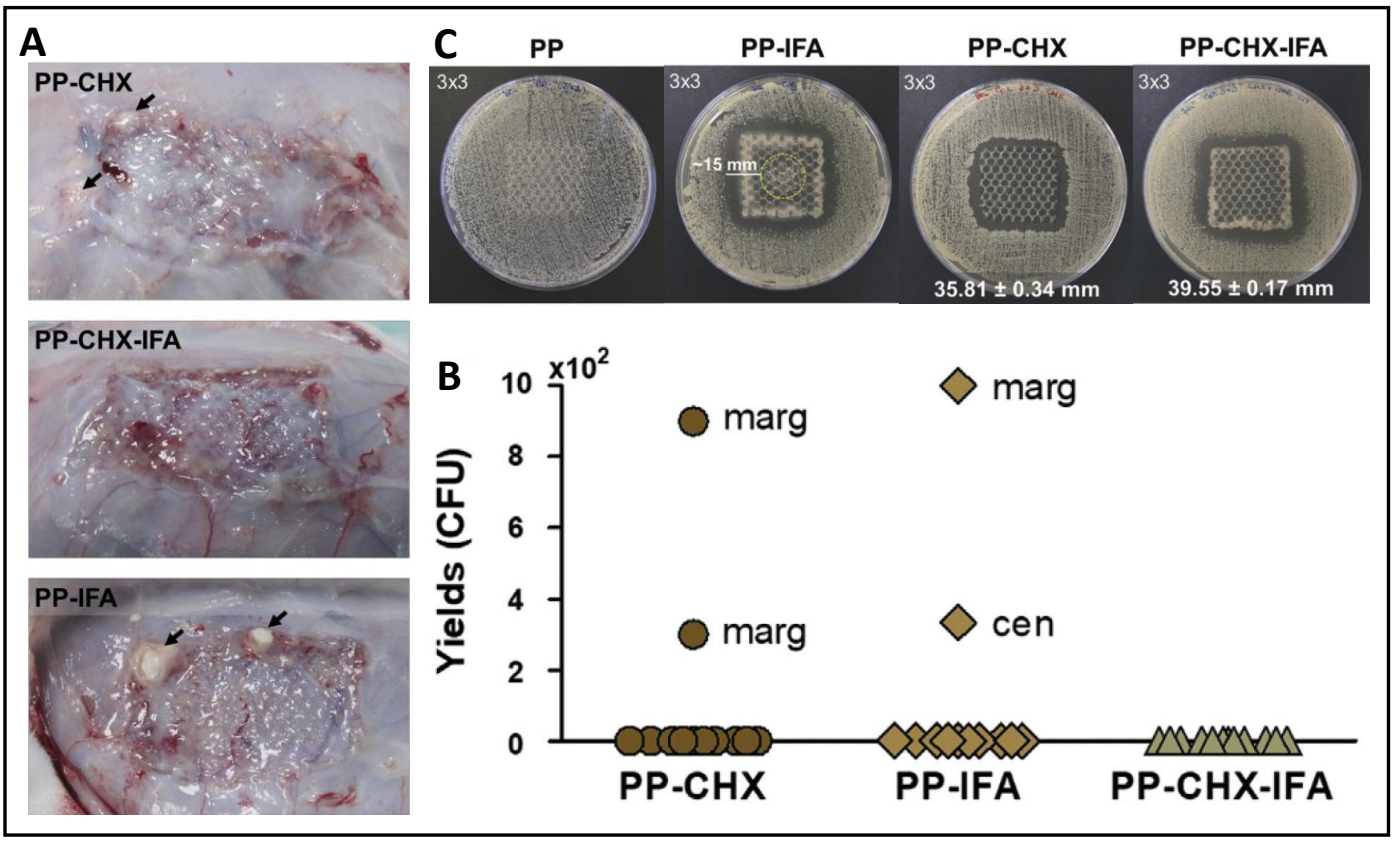


**Figure 9.** Macroscopic representative images at the time of rabbit euthanasia using PP meshes with chlorhexidine (PP-CHX), PP meshes with chlorhexidine fixed with cyanoacrylate adhesive (PP-CHX-IFA) and PP meshes fixed with cyanoacrylate adhesive (PP-IFA) (A). Purulent material, indicated by black arrows, only appeared on the surface of the PP-CHX and PP-IFA meshes. The bacterial adhesion was quantified (B) and showed no *S. aureus* adhered to the PP-CHX-IFA meshes. However, the PP-CHX and PP-IFA showed *S. aureus* adhesion in the marginal (marg) or central (cen) zones. The growth inhibition effect of the Optilene® meshes (PP), PP-IFA, PP-CHX and PP-CHX-IFA on the growth of *S. aureus* after more than 24 hours of culture (C). The PP-IFA meshes produced bacterial inhibition zones 15 mm in diameter (see dashed line). *Adapted with permission from Elsevier* [261].

This combined strategy of an antibacterial polymer (cyanoacrylate adhesive) [271] with an antiseptic (chlorhexidine) provides an enhanced solution that demonstrated in preclinical studies in a rabbit animal model to be capable of preventing Gram-positive *S. aureus* infections without affecting mesh integration. However, its performance against other clinically relevant bacterial strains and its long-term *in vivo* evaluation needs to be evaluated. A great deal of further research therefore needs to be performed in order to develop the ideal mesh that fulfils all the optimal requirements for hernia repair, such as good integration to the abdominal wall providing suitable mechanical functionality, low incidence of visceral adhesion, minimal inflammatory or foreign body reaction, and capable of preventing infections, including multidrug-resistant strains.

## 6. Conclusions

Polypropylene mesh is probably the most frequent porous polymer matrix used for hernia repair in clinical practice due to its good physical and biological properties, as well as its reasonable price. However, there are many other alternative options composed of a broad range of biomaterials that can be summarised to facilitate the available options when surgeons have to decide on the type of mesh to be used. The classification of the most important meshes used in clinical practice includes their capacity to be completely bioabsorbed or partially bioabsorbed. The structures of these meshes are also described, indicating whether they are reticular, laminar, hybrid, composite, autoadhesive, biological, biosynthetic or synthetic, with all the information regarding biomaterials, trademarks, tissue integration and capacity to create neoperitoneum. Even though we are still far from producing the ideal antimicrobial mesh for hernia repair, all the progress achieved so far and the advanced antimicrobial meshes developed during the last decade are included in this review. We therefore encourage researchers to keep on working on the development of an optimal mesh capable of providing

optimal integration to the abdominal wall, mechanical functionality, low visceral adhesion and minimal inflammatory or foreign body reaction, while simultaneously capable of dealing with the life-threatening problem of microbial infections, especially those that are multidrug-resistant.

**Abbreviation list**

| | |
|---|---|
| AMPs | Antimicrobial peptides |
| CD | *β*-Cyclodextrin prepolymer |
| CDC | Centers for Disease Control |
| CMC | Carboxymethylcellulose |
| cPTFE | Condensated polytetrafluoroethylene |
| ECM | Extracellular matrix |
| EDAC | 1-ethyl-3- (3-dimethylaminopropyl) carbodiimide hydrochloride |
| ePTFE | Expanded polytetrafluoroethylene |
| FDM | Fused deposition modelling |
| HA | Hyaluronic acid |
| HApN | Hyaluronic acid-poly(N-isopropylacrylamide) |
| HDFs | Human dermal fibroblasts |
| HDI | Hexamethylene diisocyanate |
| HMDI | Hexamethylene diisocyanate |
| IPOM | Intraperitoneal onlay mesh |
| Lev | Levofloxacin |
| Lev@MSN@Ag | Mesoporous silica nanoplatform consisting of levofloxacin and silver |
| Lev@MSN@Ag–PLLA | Mesoporous silica nanoplatform consisting of levofloxacin and silver with poly-L-lactide electrospun membranes |
| MSN | Mesoporous silica nanoplatform |
| PBS | Polybutylene succinate |
| PBSA | Poly(butylene succinate-co-butylene aspartate) |
| PBSA2-*g*-Lv | Poly(butylene succinate-co-butylene aspartate) with levofloxacin |
| PCL | Poly-ε-caprolactone |
| PDO | Polydioxanone |
| PE | Polyethylene |
| PEG | Polyethylene glycol |
| PEGDGE | Polyethylene glycol diglycidyl ether |
| PET | Polyethylene terephthalate |
| PGA | Polyglycolic acid |
| PGA-TMC | Polyglycolic acid-trimethylene carbonate |
| PGA-PTMC | PGA copolymerized with poly(trimethylene carbonate) |
| PHAs | Polyhydroxyalkanoates |
| PLA | Polylactic acid |
| PLA-PTMC | PLA copolymerized with poly(trimethylene carbonate) |
| PLGA | Poly(lactic-co-glycolic acid) |
| PLGA-PTMC | PLGA copolymerized with poly(trimethylene carbonate) |
| PLLA | Poly-L-lactide |
| PTFE | Polytetrafluoroethylene |
| PTMC | Poly(trimethylene carbonate) |
| PVDF | Polyvinylidene fluoride or polyvinylidene difluoride |
| PVP | Polyvinylpyrrolidone |
| PP | Polypropylene |
| PU | Polyurethane |
| 4PHB | Poly(4-hydroxybutyrate) |
| QA | Quaternary Ammonium |
| TAPP | Transabdominal preperitoneal repair |
| TEP | Total extraperitoneal repair |

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**Conflicts of Interest**

The authors declare no conflict of interest.

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