Surgical site infection and development of antimicrobial sutures: a review


1Department of Medical Microbiology, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia
2Nanotechnology and Catalysis Research Centre, Universiti Malaya, Kuala Lumpur, Malaysia
3Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Universiti Malaya, Kuala Lumpur, Malaysia
4Department of Pharmacology, Faculty of Medicine, Universiti Malaya, Kuala Lumpur, Malaysia
5Institute of Biological Sciences, Faculty of Science, Universiti Malaya, Kuala Lumpur, Malaysia

R.A.H.W. Chua and S.K. Lim equally contributed to this work

Introduction

Surgical site infections (SSIs) are surgery-related infections that occur within 30 days after a surgical intervention, or within one year after the introduction of a medical implant. Depending on the anatomic sites where the infections take place, SSIs can present as either (i) superficial infection that affects the skin and subcutaneous tissues; (ii) deep incisional infection that affects deeper tissues, for instance, fascial and muscle; (iii) organ and/or space infection that affects any site of the body, other than the surgical site. Patients with SSIs often have a higher risk of hospital re-admittance, longer ICU stay, and postoperative complications. Not surprisingly, SSIs also end up with financial and emotional burdens due to the high medical cost and poor healthcare quality. Penel et al reported an additional length of hospital stay (16 days) and increased direct medical costs (17000 Euros) due to SSI after head and neck cancer surgery. MRSA SSI was reported to prolong hospital stay by 19.3 days and increased medical expenditure by $7015 after colorectal surgery. Tuon et al reported a mortality rate of 5.4% due to SSIs related to orthopedic trauma.

The incidences of SSI ranged from 1.2 to 5.2% in developed countries. Ling et al described a reduction in the incidence of SSI, with the cumulative rates ranging from 0.9% in the United States of America (USA) to 2.6% and 2.8% in Italy and Australia, respectively. The reduced incidence of SSIs may be attributed to the recent progress in medical practice; in particular, the introduction of minimally invasive surgery with smaller incision size and faster mobilization, better safeguarding of patient’s immunity, and reduced utilization of central venous catheters for parenteral nutrition. However, SSI is still amongst the most common type of hospital-acquired infection (HAI) in Europe and the USA.

While data on the incidence of SSI in developed countries is comprehensive, such data is lacking in Asia and low middle-income countries (LMIC). In Asia, the incidence of SSI ranged between 2.0% and 9.7% in Koreas, while in Japan, the cumulative incidence of SSI was 15.0%
Surgical site infection and development of antimicrobial sutures: a review

(6691/44 751 procedures) and 17.8% (3230/18 187 procedures) for colon and rectal surgery, respectively. The overall incidences of SSI were 7.8% in South East Asia (SEA) and 6.1% in LMICs. SSI was reported as the most common HAI in LMICs, with significantly higher risk than in developed countries.

Risk Factors of SSI

Multiple procedure- and patient-related risk factors are known to cause the initiation and progress of SSI. The procedure-related risk factors are associated with the nature of the surgical intervention such as the surgical site, conditions of wound contamination, and quality of pre- and postoperative care. For instance, colon, gastrointestinal and urinary tract surgeries are associated with a high risk of SSI due to a heavier bacterial load at the surgical site; hence, a higher chance of developing intraoperative contaminations. A correlation between wound category and incidence of SSI had been reported whereby the risk of SSIs increased from clean to dirty/infected wound.

Additionally, the type of surgery (elective/emergency), duration of surgery, the complexity of surgical procedures and length of pre-operative hospital stays are also correlated with SSIs. A surveillance study in Europe (2010-2011) showed that the highest cumulative incidence of SSI in patients is colon surgery (9.5% episodes per 100 operations), followed by coronary artery bypass graft (3.5%), and caesarean section (2.9%). Other procedure-related risk factors include degree of wound contamination and patients’ clinical condition.

The age, sex, lifestyle, body mass index, pre-existing infection, diabetes, comorbidities, and surgical history are among the patient-related risk factors contributing to SSI. Aga et al. reported that 22.1% of patients undergoing abdominal surgery developed SSIs up to 30 days post-surgery. Orthopedic SSIs require a multifaceted approach as patients experience a substantial loss of physical function and an overall poorer quality of life. Li et al. observed that diabetes mellitus, smoking, operations for >3 hours, absence of antibiotic prophylaxis, and a history of previous surgery had each contributed to a significant increase in the risk of SSIs. Additional factors that have been reported include movement and number of hospital staff, structural features of operating theatre, high body mass index, and severe scores based on US National Nosocomial Infections Surveillance (NNIS) risk index.

Figure 1. Several mechanisms have been associated with the increased antimicrobial resistance of biofilm-embedded bacteria: (i) inefficient antimicrobial infiltration through biofilm matrix, (ii) altered physiological responses of microbes to the heterogeneous environment of biofilm, (iii) emergence of persister or dormant cells, and (iv) presence of polymicrobial communities in the biofilm environment (i.e. co-infection of bacteria and fungi), which impede the selection of appropriate antimicrobial therapy for multidrug-resistant bacteria (Image courtesy of Amelia Low CY).
Sutures also provide a conducive surface for bacterial adherence, colonization, and biofilm formation\(^\text{30-32}\) (Figure 1). The presence of foreign materials (suture or medical implants) in a wound incision provides an anchoring surface for biofilm formation and a reservoir for shielding exogenous bacteria from the host-defense mechanism. The surface conformation of the multifilament suture is known to harbor a higher density of bacterial cells than monofilament suture\(^\text{31}\), while the interstices on suture knots provide a large surface area for bacterial propagation and colonization\(^\text{33}\). A study\(^\text{34}\) comparing absorbable and non-absorbable sutures during dento-alveolar surgery showed that non-absorbable sutures were more prone to biofilm formation. Since sutures under different host/environments can initiate SSI, the use of appropriate sutures for surgical procedures plays an important role in preventing SSI\(^\text{35}\).

**Common Microorganisms Associated with SSI**

Wound contamination and insufficient disinfection prior to surgical closure are the main reasons for SSI. Local microflora or environmental contaminants are frequently associated with the initiation of SSIs. *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Acinetobacter* species and *Enterococcus* species are common organisms isolated from patients with SSI\(^\text{36}\). *S. aureus*, which is present on the skin or anterior nares of almost 80% healthy individuals, represents the most predominant organism in causing SSIs during surgical intervention\(^\text{36,37}\).

The microbiological profiles of SSI vary with the type and site of surgical manipulations. *S. aureus* is more likely to be implicated among patients undergoing cardiac, neurosurgery, breast, and orthopedic surgeries, as well as patients receiving grafts, prostheses, or implants, while infections caused by Gram-negative bacilli are more frequently associated with patients receiving appendectomy, colorectal, urologic, obstetric and gynecologic procedures\(^\text{3}\). Strict compliances to infection control measures including decolonization of *S. aureus* prior to surgery, good hygienic practice of healthcare professionals and patients, as well as the usage of proper antiseptics for disinfection are recommended to reduce the rate of SSIs effectively\(^\text{38-40}\).

**Antimicrobial Resistance and SSIs**

The injudicious use of antibiotics has been identified as a cause for the emergence of antibiotic-resistant bacteria in healthcare facilities worldwide. The World Health Organization (WHO) warned that antibiotic-resistant bacteria may pose severe threats to human health if the situation is left uncontrolled\(^\text{41}\). Bacteria acquire antibiotic resistance traits through intrinsic, acquired, and adaptive mechanisms\(^\text{42,43}\). Intrinsic antibiotic resistance refers to the natural characteristics of bacteria in conferring resistance towards certain classes of antibiotics\(^\text{43,44}\). For instance, Gram-negative bacteria are relatively less sensitive to β-lactam antibiotics as compared to Gram-positive bacteria. The lipopolysaccharide cell wall, present only in Gram-negative bacteria, acts as a physical barrier to prevent the entry of hydrophilic β-lactam antibiotics, thus conferring intrinsic resistance towards antibiotics\(^\text{44}\). Acquired antibiotic resistance, on the other hand, occurs when microbes attain resistance to antibiotics previously susceptible due to mutations in the drug targets, changes of cellular physiology or adoption of foreign genes encoding antibiotic resistance via horizontal gene transfer\(^\text{43}\). Bacteria exhibit adaptive antibiotic resistance in a reversible, temporal manner in response to the alteration of environmental stress in the presence of antibiotics\(^\text{45}\), and as a result of metabolic alterations and changes on gene/protein expression profiles\(^\text{44,46}\).

The antibiotics used for the treatment of staphylococcal SSI depend on the location and depth of the infection site, adequate removal of damaged tissue or foreign object from surgical wound, and the occurrence of MRSA SSI\(^\text{47}\). Commonly employed antimicrobial treatment for methicillin-sensitive *S. aureus* (MSSA) SSI are first-generation cephalosporins and antistaphylococcal penicillins\(^\text{47,48}\), while for MRSA SSI, the conventional antibiotic employed is vancomycin\(^\text{47,49}\). Although vancomycin-containing antibiotic prophylaxis has resulted in decreased SSI rates\(^\text{50}\), the use of vancomycin alone has been associated with a higher risk of MSSA in MRSA-negative patients\(^\text{51}\). Hence, routine administration of vancomycin antibiotic prophylaxis in MRSA-negative patients is not recommended\(^\text{52}\). According to published guidelines, supportive data are still required for local and topical antibiotic therapy including antibiotic irrigations, antimicrobial-impregnated dressings, and wound sealants, in reducing SSI risk\(^\text{52,55}\).

Since the emergence of MRSA, the proportion of SSIs due to the superbug has increased from 9.2% to 63.5%\(^\text{54}\), depending on postoperative
antibiotic policy and surveillance programs at various clinical settings. Limited choices of drug are available for the treatment of MRSA infections. Multidrug-resistant (MDR) strains of *E. coli* and *P. aeruginosa* are also frequently reported in SSI. About 68.6% of bacteria isolated from orthopedic-related SSIs were resistant to cefuroxime a major teaching hospital in China. A systematic review of 41 studies published between 1994 and 2016 revealed the predominance of MRSA (23 studies), vancomycin-resistant enterococci (VRE), extended-spectrum β-lactamase (ESBL)–producing organisms, MDR *A. baumannii*, MDR *P. aeruginosa*, and MDR *Klebsiella pneumoniae*.

SSIs caused by MDR bacteria often result in longer hospital stays, higher rates of readmissions and mortality, increased financial cost and treatment complexity. Due to the use of more extensive drug regimens and aggressive treatment strategies, it has been estimated that an additional treatment complexity would be required for treating MDR bacterial infections. High incidences of SSIs caused by MDR bacteria have been reported to pose a serious threat to patients and the healthcare system.

**Biofilm-Associated Infections**

Biofilm is a multi-layered structure of microbial communities embedded in extracellular polymeric matrixes which are composed of polysaccharides, extracellular DNA, protein, lipid, and other biopolymers. The microbial communities in the biofilm show higher resistance (up to 1000-fold) to antimicrobial therapy in comparison to the planktonic counterparts. Several mechanisms have been associated with the increased antimicrobial resistance of biofilm-embedded bacteria, as shown in Figure 1. These include (i) inefficient antimicrobial infiltration through biofilm matrix, (ii) altered physiological responses of microbes to heterogeneous environment of biofilm, (iii) emergence of persister or dormant cells, and (iv) the presence of polymicrobial communities in a biofilm (i.e., co-infection of bacteria and fungi), which impede the selection of appropriate antimicrobial therapy for MDR bacteria. Additionally, as biofilms can host different species of bacteria in close contact with each other, this may facilitate the dissemination of genes encoding drug resistance or plasmid exchange in the microbial communities.

Biofilms on implanted medical devices (e.g., catheters, implants and surgical sutures) are difficult to be eradicated with the administration of systemic antibiotics. Surgical intervention is essential for the management of infected tissues and implanted medical devices. As biofilm-associated infections are one of the main factors behind the onset of recurrent and chronic infections, special care and appropriate strategies should be instituted for the prevention and eradication of the infections.

**Staphylococcus aureus** displays a high capacity to colonize new surfaces and is recognized as a major cause of biofilm-associated infections in medical devices. Begun et al. showed that *S. aureus* strains producing excessive biofilm killed *Caenorhabditis elegans* worms quicker than the strains with less biofilm production, suggesting that staphylococcal biofilm is an important virulence factor. Biofilm formation, a process involving bacterial adherence, accumulation, maturation, and dispersion, is determined by quorum sensing and various genetic factors. The density of biofilm is determined by bacterial species, availability of nutrients, and surface charges of the cells. The emergence of antibiotic resistance in clinical settings worldwide has led to limited options for the treatment of *S. aureus* biofilm-associated infections. As conventional approaches target bacterial viability, selection for resistant subpopulations frequently occurs in clinical settings. On the other hand, suppression of *S. aureus* virulence presumably exerts less selective pressure for antibiotic resistance, and thus, may serve as a promising approach for combating *S. aureus* biofilm-associated infection.

**Antimicrobial Sutures**

Several organizations have recommended the use of antimicrobial-coated sutures as a preventive measure against SSI. The Centers for Disease Control and Prevention (CDC) and WHO guidelines on reducing the risk of SSI provide recommendations on the use of triclosan-coated sutures, regardless of the type of the surgery. The National Institute for Health and Care Excellence (NICE) stated that the overall evidence favored triclosan-coated sutures over standard sutures; and a clear benefit has been shown by the triclosan-coated sutures in pediatric surgery. The triclosan-coated suture is also recommended by the American College of Surgeons & Surgical Infection Society (ACS/SIS) for wound closure in clean and clean-contaminated abdominal cases.
A series of clinical studies and meta-analyses\textsuperscript{80-82,84} indicated the superior efficacy of triclosan-coated sutures to prevent SSI in comparison to non-antimicrobial sutures. However, there have been conflicting opinions on the use of triclosan-coated sutures to reduce SSI risk and more evidence on the benefits of using triclosan-coated suture for the dressings of different wounds are required to draw a firm conclusion\textsuperscript{85}. As the impact of antiseptic-impregnated sutures on the development of resistance to antiseptics is not clear, the Society for Healthcare Epidemiology of America/Infectious Diseases Society of America (SHEA/IDSA) guidelines do not recommend antiseptic-impregnated sutures for routine use as a strategy to prevent SSI\textsuperscript{86}. Meanwhile, the Asia Pacific Society of Infection Control (APSIC) recommends the use of antimicrobial-coated sutures in settings with high SSI rates in clean surgeries\textsuperscript{9}. Table I shows antimicrobial sutures that have been marketed for medical and veterinary use. Braided polyglactin 910 coated with triclosan (Vicryl Plus) was the first antimicrobial suture to receive approval for clinical use by the US Food and Drug Administration (US FDA). To date, other triclosan-coated sutures, i.e., monofilament poliglecaprone (Monocryl Plus), monofilament polydioxanone (PDS Plus) and multifilament polyglactin 910 (Petcryl Plus) are commercially available. Several types of chlorhexidine-based sutures have also been marketed for veterinary use (Table I).

### Antimicrobial Agents and Sutting Technology

The physical, biological, and handling characteristics of sutures are essential to facilitate wound healing\textsuperscript{87}. There are two types of synthetic sutures based on the feature of absorption into the body. Absorbable sutures are made of polydioxanone, polyglycolic acid (PGA), monocryl polymer, and poly(lactic acid), while non-absorbable sutures are made of nylon, polyester, and polypropylene (PP) etc. Poly (lactic-co-glycolic acid) (PLGA)\textsuperscript{88}, polyvinyl alcohol (PVA) and poly-L-lactic acid (PLLA) are increasingly used in the manufacturing of modern sutures. Table II summarizes the characteristics (antimicrobial compounds, suture materials and technique) of antimicrobial sutures that have been reported from 1990-2020, besides triclosan-coated sutures.

The approaches used for incorporation of antimicrobial compounds on sutures (as illustrated in Figure 2) include (i) dip-coating, whereby sutures are dipped in a solution containing the antimicrobial agents and the polymeric coating agents (i.e., PLGA, PVA, and PLLA) for a predefined period for physical adsorption onto the sutures, (ii) surface modification and compound immobilization; whereby the suture surface is modified either by plasma treatment, radiation, or chemical grafting for introduction of a functional group to facilitate antimicrobial immobilization via formation of covalent bonding, and (iii) blending and compounding, whereby antimicrobial agents are blended with suture materials followed by synthesis of the antimicrobial suture. In this approach, electrospinning technique has been used to produce very thin fibers (micro or nano scales)\textsuperscript{89}. Amongst these methods, dip-coating approach is the most common method for incorporation of bioactive molecules onto suture as it is less expensive and technically less demanding compared to other drug-elution/fabrication methods and does not affect the mechanical properties of sutures\textsuperscript{89,90}.

| Table I. Antimicrobial sutures that have been commercialized. |
|---|---|---|---|
| Suture type | Brand name | Properties | Manufacturer |
| Medical use | Triclosan-based suture | VICRYL Plus | Multifilament, absorbable polyglactin 910 | Ethicon Inc. |
| | | MONOCRYL Plus | Monofilament, absorbable poliglecaprone | |
| | | PDS Plus | Monofilament, absorbable polydioxanone | Futura Surgicare Pvt Ltd |
| | | Petcryl Plus | Multifilament, absorbable polyglactin 910 | SamYang |
| | Chlorhexidine-based suture | Trisorb Plus | Multifilament, absorbable poly(glycolic acid) | Biopharmaceuticals Corp |
| | | Neosorb Plus | Multifilament, absorbable poly(glycolic co-lactic acid) (90:10) | |
| | | Monosorb Plus | Monofilament, absorbable polydioxanone | |
| Veterinary use | Chlorhexidine-based suture | Mono-Dox Plus | Monofilament, absorbable polydioxanone | CP Medical Inc. |
| | | Visorb Plus | Monofilament, absorbable poly(glycolic acid) | |
| | | Monoswift Plus | Monofilament, absorbable poly(glycolide-co-caprolactone) 25 | |
Table II. A summary of the studies conducted on the development of antimicrobial sutures (1990-2020).

<table>
<thead>
<tr>
<th>Antimicrobial sutures</th>
<th>Main suturing technology</th>
<th>Type of suture investigated</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiseptics-based sutures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorhexidine and octenidine</td>
<td>Dip-coating</td>
<td>Braided, absorbable PGA acid suture (Gunze PGA)</td>
<td>73</td>
</tr>
<tr>
<td>Iodine</td>
<td>Dip-coating</td>
<td>Nylon fibers (Modipon (India) Ltd., Modinagar-India)</td>
<td>109</td>
</tr>
<tr>
<td>2,5-dimethoxy-2,5-dihydrofuran (DMDF)--iodine</td>
<td>Cross-linking</td>
<td>Raw silk from Bombyx mori (Safia Silk Industries, Kolkata)</td>
<td>110</td>
</tr>
<tr>
<td>Octenidine hydrochloride, chlorhexidine dipalmitate, chlorhexidine dilaurate</td>
<td>Dip-coating</td>
<td>Synthetic absorbable PGA suture (PGA Resorba)</td>
<td>111</td>
</tr>
<tr>
<td>Octenidine</td>
<td>Dip-coating</td>
<td>PGA suture (PGA Resorba, USP 1.0), Vicryl and Vicryl Plus (Ethicon)</td>
<td>112</td>
</tr>
<tr>
<td>Povidone-iodine, chlorhexidine</td>
<td>Dip-coating</td>
<td>Braided nylon, non-braided nylon, silk, and Vicryl (Ethicon, USP 3-0) sutures</td>
<td>114</td>
</tr>
<tr>
<td>Chlorhexidine-functionalized polyelectrolyte films</td>
<td>Dip-coating</td>
<td>Silk, polyester, and copolymer of glycolide and L-lactide sutures</td>
<td>120</td>
</tr>
<tr>
<td>Chlorhexidine and poly (hexamethylene biguanide) (PHMB)</td>
<td>Dip-coating</td>
<td>Monofilament sutures of polyglycolide-b-poly(glycolide-co-trimethylene carbonate-co-c-caprolactone)-b-polyglycolide suture (Monosyn)</td>
<td>121</td>
</tr>
<tr>
<td>Chlorhexidine</td>
<td>Blending</td>
<td>PCL monofilament</td>
<td>122</td>
</tr>
<tr>
<td>K21</td>
<td>Dip-coating</td>
<td>Chromic gut, polyester suture, silk, and nylon suture</td>
<td>128</td>
</tr>
<tr>
<td>Natural product-based sutures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chitosan</td>
<td>Dip-coating</td>
<td>B. mori silk filaments</td>
<td>90</td>
</tr>
<tr>
<td>Aloe vera gel and silver (Ag)</td>
<td>Plasma functionalisation</td>
<td>Poly (ethylene terephthalate) (PET, Reliance Industries Ltd. India)</td>
<td>91</td>
</tr>
<tr>
<td>Grapefruit seed extract</td>
<td>Dip-coating</td>
<td>PLGA synthetic absorbable braided suture (Meta Biomed Co., Ltd.)</td>
<td>129</td>
</tr>
<tr>
<td>Aloe vera gel</td>
<td>Dip-coating</td>
<td>Braided, nonabsorbable silk sutures (1.5 metric, size 4-0)</td>
<td>130</td>
</tr>
<tr>
<td>Aloe vera ethanolic extract and ciprofloxacin</td>
<td>Dip-coating</td>
<td>Silk sutures (USP 3-0)</td>
<td>131</td>
</tr>
<tr>
<td>Chitosan</td>
<td>Dip-coating</td>
<td>Cotton yarn</td>
<td>133</td>
</tr>
<tr>
<td>Chlorinated high molecular weight chitosan (N-halamine)</td>
<td>Coating by layer-by-layer assembly</td>
<td>PGA suture (Jinhuan Medical Products, China)</td>
<td>134</td>
</tr>
<tr>
<td>Hydrolyzed chitosan, turmeric, and clove oil</td>
<td>Dip-coating</td>
<td>Multifilament polyethylene terephthalate (PET; linear densities 540) and polyamide (nylon 6) (1260 denier) threads</td>
<td>135</td>
</tr>
<tr>
<td>Totarol</td>
<td>Spray coating</td>
<td>Monofilament suture (Resonlon®, 75 cm USP 3/0) and the multifilament sutures (Ethibond Excel, 75 cm, USP 3-0)</td>
<td>136</td>
</tr>
<tr>
<td>Eugenol</td>
<td>Dip-coating</td>
<td>Cotton sutures (Techna 3-0/30 mm, São Paulo, Brazil)</td>
<td>137</td>
</tr>
<tr>
<td>Chitosan and ethanolic extracts of C. dactylon</td>
<td>Dip-coating</td>
<td>Silk filament (20 denier, Sarvodhya Sangam, Coimbatore)</td>
<td>138</td>
</tr>
<tr>
<td>Trans-resveratrol and rifampicin</td>
<td>Dip-coating</td>
<td>Braided, non-absorbable, nylon sutures (USP 0)</td>
<td>139</td>
</tr>
</tbody>
</table>

Continued
Table II (Continued). A summary of the studies conducted on the development of antimicrobial sutures (1990-2020).

<table>
<thead>
<tr>
<th>Antimicrobial sutures</th>
<th>Main suturing technology</th>
<th>Type of suture investigated</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nanoparticle-based sutures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium alginate-Ag nanoparticles</td>
<td>Dip-coating</td>
<td>Supramid polyamide sutures</td>
<td>140</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(ref SD208000, Serag-Wiessner)</td>
<td></td>
</tr>
<tr>
<td>Sodium alginate-Ag nanoparticles</td>
<td>Dip-coating</td>
<td>Surgical gut plain suture (Ethicon Inc.)</td>
<td>141</td>
</tr>
<tr>
<td>Ag nanoparticles encapsulated in hyperbranched polylsine</td>
<td>Dip-coating</td>
<td>Multifilament PGA sutures (Aesculap AG)</td>
<td>142</td>
</tr>
<tr>
<td>Ag nanoparticles (synthesized using hot water extract of H. inuloides)</td>
<td>Dip-coating</td>
<td>Catgut suture (Atramat, USP 3-0)</td>
<td>143</td>
</tr>
<tr>
<td>Bio-silver nanoparticles (AgNP)</td>
<td>Dip-coating</td>
<td>Nonabsorbable silk sutures</td>
<td>144</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Dogsan, Turkey, USP 3-0)</td>
<td></td>
</tr>
<tr>
<td>Bio-silver nanoparticles (AgNP)-propolis</td>
<td>Dip-coating</td>
<td>Nonabsorbable silk sutures</td>
<td>145</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Doğsan, Istanbul, Turkey, USP 4-0)</td>
<td></td>
</tr>
<tr>
<td>Zinc oxide nanoparticles</td>
<td>Dip-coating</td>
<td>Degummed silk fibers</td>
<td>146</td>
</tr>
<tr>
<td>Curcumin PEGylated gold nanoparticles</td>
<td>Dip-coating</td>
<td>TRUGLYDE FAST absorbable PGA suture</td>
<td>147</td>
</tr>
<tr>
<td>Silver nanoparticles conjugated with trans-cinnamic acid and povidone–iodine</td>
<td>Dip-coating</td>
<td>Multifilament, braided and absorbable PGA sutures (DAMACRYL, USP 3-0)</td>
<td>148</td>
</tr>
<tr>
<td>Antibiotic-based sutures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gentamicin and silver (Ag)</td>
<td>Blending</td>
<td>PCL suture</td>
<td>149</td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>Dip-coating</td>
<td>Silk suture (Jiangsu Medical Supplies Co., Ltd.)</td>
<td>150</td>
</tr>
<tr>
<td>Ciprofloxacin-PCL/PGA</td>
<td>Dip-padding</td>
<td>PLA suture (Zhejiang Gaoxin Company, Jiaxing, China)</td>
<td>151</td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>Electrospinning</td>
<td>PCL suture</td>
<td>152</td>
</tr>
<tr>
<td>Kanamycin, gentamicin, monomycin, and doxycycline</td>
<td>Graft polymerization</td>
<td>PCA and PP twisted suture</td>
<td>153</td>
</tr>
<tr>
<td>Tetracycline hydrochloride</td>
<td>Radiation grafting</td>
<td>PP suture</td>
<td>154</td>
</tr>
<tr>
<td>Tetracycline hydrochloride, chitosan, and silver nanoparticles, Vancomycin</td>
<td>Plasma functionalization</td>
<td>PP suture</td>
<td>155</td>
</tr>
<tr>
<td></td>
<td>Covalent immobilization</td>
<td>PP monofilament suture</td>
<td>156</td>
</tr>
<tr>
<td>Other antimicrobial-based sutures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spider silk protein linked with human neutrophil defensin-l(HNPI)</td>
<td>Dip-coating</td>
<td>Non-absorbable, multifilament silk sutures (USP 3-0; Perma-Hand, Ethicon, USA)</td>
<td>157</td>
</tr>
<tr>
<td>Poly[[aminoethyl methacrylate]-co-(butyl methacrylate)] (PAMBM)</td>
<td>Dip-coating</td>
<td>Vycril Plus sutures (VCP259, Ethicon Inc)</td>
<td>158</td>
</tr>
<tr>
<td>Poly(N-methylvinylimidazolium) iodide</td>
<td>Surface functionalization</td>
<td>PP monofilaments (Atramat suture threads)</td>
<td>159</td>
</tr>
<tr>
<td>Poly(2-methacryloyloxyethyl phosphorylcholine (MPC)-co-n-butyl methacrylate) (PMB)</td>
<td>Dip-coating</td>
<td>Absorbable polyglactin sutures (KRAYON Plus, KEISEI Medical Industrial Ltd., Tokyo, Japan)</td>
<td>160</td>
</tr>
</tbody>
</table>

Silver (Ag), nanoparticle (NP), polycaprolactone (PCL), polyglycolic acid (PGA), polypropylene (PP), poly-L-lactic acid (PLLA), polyacaproamide (PCA).
Surgical site infection and development of antimicrobial sutures: a review

Although the delivery of many bioactive molecules via sutures can be facilitated using melt spinning, electrospinning, and radiation, the mechanical properties of sutures may be affected during fabrication. Currently, plasma functionalization of the suture and subsequent conjugation with bioactive molecules are recognized as an effective strategy as both the mechanical and infection prevention features are not likely to be affected during the fabrication process. A variety of antimicrobial compounds including antiseptics, natural products, antibiotics, nanoparticles, and biotechnological products have been applied for the development of antimicrobial sutures (Table II). The evaluation of antimicrobial activities of sutures is often performed using zone of inhibition (ZOI) assays against both Gram-positive and Gram-negative bacteria (Figure 2). Antimicrobial activities are confirmed when inhibition zones are observed surrounding sutures on agar plates lawn with SSI organisms. Additionally, bacterial adherence assays are performed to determine the effectiveness of antimicrobial suture in resisting bacterial adherence and colonization. A review of the development of antimicrobial sutures over the last 30 years (1990-2020) is provided in Table II.

**Antisepetic-Based Sutures**

Triclosan (5-chloro-2-(2,4-dichlorophenoxy) phenol) is one of the antiseptics used in the early stage of antimicrobial suture development. It is a broad-spectrum, non-cationic, lipid-soluble chlorinated phenoxypheonl compound used in the formulation of personal care products including hand soap, toothpaste, antiperspirants shower gel, dishwashing liquid and toothpaste. It is also used as a topical decontamination agent for hospital patients colonized with MRSA. Triclosan exhibits antibacterial activity against various Gram-positive and Gram-negative bacteria, as well as some antifungal, anti-mycobacterial and antiparasitic activities. It interferes with bacterial fatty acid formation through direct binding to the FabI protein (enoyl-acyl carrier protein reductase) and displays bacteriostatic activity at low concentrations (0.025 to 1.000 μg/ml), and bactericidal at high concentrations (7.5 to 8.0 μg/ml). Several studies have reported the development of triclosan resistance in bacteria because of the high usage of triclosan in personal and healthcare products. Triclosan resistance is frequently reported in *S. aureus*. Bacterial strains with triclosan minimum inhibitory con-
centrations (MICs) between 0.025 and 1 µg/ml have been found resistant to multiple antibiotics. Pseudomonas aeruginosa is inherently resistant to triclosan due to the presence of the FabV gene (encoding an isozyme of Fabl protein). Hence, triclosan-coated surgical sutures are not suitable for surgical procedures associated with P. aeruginosa infections.

Iodine and povidone-iodine (PVP-I) are broad-spectrum antiseptics that act by oxidation of the reactive moieties on bacterial membranes and inactivation of bacterial enzymes in the respiratory electron transport system. Iodine has been incorporated either alone or with other antiseptics onto sutures to produce promising antimicrobial results. In a study by Francis et al., radio-antimicrobial sutures were developed by stepwise 2,5-dimethoxy-2,5-dihydro-furan (DMDF)–iodine cross-linking reaction for fabrication of silk fibers. The sutures inhibited S. aureus and E. coli and were non-cytotoxic against 3T3-fibroblast cells.

Chlorhexidine is an oral antiseptic with proven safety and efficacy that has been used for the development of antimicrobial sutures. Chlorhexidine exhibits broad-spectrum bac­tericidal activity against S. epidermis, MRSA, methicillin-resistant S. epidermis (MRSE) and E. coli through interaction with the phosphate moieties of bacterial membrane. Walker et al. demonstrated antimicrobial activities of nylon, silk and polyglactin (Vicryl) sutures coated with chlorhexidine against S. aureus, MRSA and S. epidermis. Sutures functionalized with chlorhexidine, poly(ethyleneimine), poly(sodium-4-styrene sulfonate), poly(allylamine hydrochloride), poly(L-glutamic acid), and poly(L-lysine) were demonstrated to inhibit E. coli up to 7 days. The inhibition against S. epidermis and E. coli has been shown by monofilament sutures coated with a combination of chlorhexidine, lactide, trimethylene, carbonate, and poly-hexamethylene biguanide (PHMB). Scaffaro et al. explored a novel coating method by incorporating chlorhexidine dicacetate (CHX) onto polycaprolactone (PCL) monofilament suture via a single-step approach during melt processing. Antimicrobial activities against E. coli, Micrococcus luteus and Bacillus subtilis strains were observed at a low CHX concentration without affecting the tensile properties of the sutures.

Oc­tenidine is an antiseptic that has been identified as a replacement compound for triclosan. The compound interacts with membrane cardiolipin, causes interference on the bilayer structure, and cytoplasmic leakage. The cationic surfactant has a broad-spectrum activity against MDR bacteria. A study by Obermeier et al. reported high biocompatibility, slow drug release and antimicrobial effect for up to 9 days of octenidine (11, 22 and 33 µg/cm) coatings on sutures using palmitic acid.

A series of antimicrobial sutures coated either with chlorhexidine or octenidine on PGA sutures using laurate or palmitate as drug carriers exhibited excellent antimicrobial activities. Obermeier et al. reported higher inhibition (1.7 log reduction) of S. aureus adherence on sutures coated with chlorhexidine/laurate, in comparison to Vicryl Plus sutures. Recently, K21, a new class of quaternary ammonium silane (SiQAS) disinfectant has been introduced as a coating agent for different sutures. K21-coated sutures demonstrated dose-dependent inhibitory activity against oral microorganisms (Porphyromonas gingivalis and Enterococcus faecalis).

Natural Product-Based Sutures

Natural products including plant extracts have been recognized as a potential source of antimicrobial coatings on sutures. Various natural products including grapefruit seed extract, aloe vera, chitosan, turmeric, clove oil, and eugenol have been explored for coating on sutures (Table II). Lee et al. showed the feasibility of incorporating grapefruit seed extracts on sutures for wound healing applications. Ghafour et al. investigated the efficacy of aloe vera-based antimicrobial su­tures against bacteria (E. coli and P. aeruginosa) and filamentous fungi (Aspergillus flavus and Aspergillus tubingensis). In their study, aloe vera gel was incorporated with PVA using a dip-coating approach. Silk sutures coated with 5% aloe vera/PVA demonstrated the best inhibition against target organisms and reduced bacterial colony counts at the incision sites of Balb/c mice.

In another approach undertaken by Ravishankar et al., silk suture was dipped in an ethanolic extract of aloe vera, dried, and challenged with E. coli (ATCC 25922) using ZOI assays. The suture demonstrated inhibitory activity to E. coli but did not outperform suture pre-treated with ciprofloxacin. A new approach of antimicrobial polyethylene terephthalate (PET) suture development using plasma functionalization followed by immobilization of aloe vera and silver (Ag) has been recently described by Anjum et al. The antimicrobial sutures demonstrated superior...
bacteriostatic and bactericidal activities against *E. coli* and *S. aureus* and improved the wound healing process of Swiss albino mice.

Chitosan is a natural antimicrobial agent well recognized for its low toxicity, biodegradability, and biocompatibility. It binds to bacterial teichoic acids, and disrupts cell morphology and division. Chitosan-coated surgical sutures have been reported to exhibit good antimicrobial activity and prevent bacterial adherence. The amino group of chitosan can be functionalized with other antimicrobial agents to enhance its antimicrobial property. Umair et al. developed novel N-halamine-based antibacterial sutures by coating PGA suture with chitosan-poly-sodium-p-styrenesulfonate (PSS) via a layer-by-layer assembly technique to attain a linear relationship between the number of layers and chlorine (released by N-halamine for its antimicrobial activity) loadings. Nine layers of chlorinated high molecular weight chitosan were found to give the most potent antibacterial effects, killing *E. coli* and *S. aureus* within 15 minutes of contact.

In a study by Masood et al., multifilament nonabsorbable PET and polyamide (Nylon 6) sutures coated with varying ratios of hydrolyzed chitosan, clove oil and turmeric, and corn starch showed inhibition against *S. aureus* and improved tensile and knot strength. Reinbold et al. incorporated totarol, a plant-derived diterpenoid and PLGA into non-absorbable monofilament and multifilament sutures. The totarol/PLGA-coated sutures demonstrated inhibition against *S. aureus* and improved tensile and knot strength. Reinbold et al. incorporated totarol, a plant-derived diterpenoid and PLGA onto non-absorbable monofilament and multifilament sutures. The totarol/PLGA-coated sutures showed inhibition against *S. aureus* for over 15 days without causing cytotoxicity to L929 murine fibroblast cells. Cotton sutures coated with eugenol, an aromatic constituent of clove, have been demonstrated to prevent Streptococcus mutans adherence. Additionally, silk suture coated with chitosan and Cynodon dactylon, a herbal drug, also demonstrated inhibition against *S. aureus* and *E. coli*. Recently, a polymerized β-cyclodextrin-based coating of trans-resveratrol (a plant antimicrobial) and rifampicin has been reported to show 24-day long antimicrobial effects towards *S. aureus* and 14-day long anti-inflammatory effects.

**Nanoparticle-Based Sutures**

The potential application of nanoparticles against infectious agents is well recognized in the medical field. Dubas et al. were amongst the first to use a layer-by-layer approach for coating Ag nanoparticles onto polyamide sutures. Taking the advantage of the negative charges of Ag nanoparticle binding to the cationic PDADMAC, Ag nanoparticles were rapidly adsorbed to pre-coated PDADMAC layer on sutures. The resulting suture showed a 76.82% reduction in *S. aureus* colony counts. In a study conducted by Augustine and Rajarathinam et al., surgical gut plain suture coated with Ag nanoparticles and sodium alginate demonstrated inhibition against *S. aureus* and *E. coli* for up to 72 hours. A hyperbranched-polylysine-based PGA suture was developed by Ho et al. to ensure long-term release of Ag nanoparticles. The coating agent was made up of a hydrophilic core (polylysine) and a hydrophobic shell (stearoyl/palmitoyl chloride or glycidyl hexadecyl ether) and encapsulated with at least 10 µg/cm of Ag nanoparticles. The suture reduced more than 99.5% of bacterial adherence in comparison to the uncoated control and exhibited a stable release of Ag ions for up to 30 days.

Biogenic Ag nanoparticles have attracted considerable attention as antimicrobial agents, largely due to their safety and high biocompatibility, as compared to synthetic nanoparticles. Biogenic Ag nanoparticles are made from plant extracts or biological materials, thus bypassing the need for reducing agents such as hydrazine, dimethylformamide, and sodium borohydride. Guadarrama Reyes et al. reported the use of a medicinal plant (Heterotheca inuloides) extract to circumvent the harmful effect of chemical-based reducing agents. After immersion in the nanoparticle solution, Ag nanoparticle-based catgut suture threads showed inhibitory activities against *S. aureus* and *E. coli*. Using a similar approach, Baygar et al. reported the synthesis of Ag nanoparticles using Streptomyces sp. AU2 cell-free extract as a reducing agent. The resulting silk sutures demonstrated inhibitory activities against Candida albicans, *E. coli* and *S. aureus* with minimal cytotoxicity towards 3T3 fibroblasts.

Antimicrobial sutures have been developed by coating propolis extract with Ag nanoparticles on silk sutures. Besides Ag nanoparticles, zinc oxide (ZnO) nanoparticles have also been explored for coating on silk sutures. The nanoparticles, synthesized using honey as a bio-reductant, were incubated with silk sutures for adsorption. The sutures demonstrated inhibition against *S. aureus* (MTCC 6908) for up to 6 days. By conjugating curcumin with PEGylated-gold nanoparticles, the solubility and metabolic stability of curcumin for coating on PGA sutures have been improved.
Antibiotic-Based Sutures

Bacterial colonization is less likely to occur on suture in the presence of antibiotics (Table II). The development of antibiotic-based sutures is dependent on the biocompatibility, retention of antibiotic activity, and the target organisms. Sustained co-delivery of gentamicin and silver on PCL sutures using blending approach has been described\textsuperscript{149}. Pre-treatment of braided-silk sutures with 0.1N sodium hydroxide solution, followed by coating of sulfaethoxazole/trimethoprim using PCL produced a longer duration (5 days) of antimicrobial activities against \textit{S. aureus} and \textit{E. coli}, in comparison to the untreated suture (4 days)\textsuperscript{150}. Liu et al\textsuperscript{151} reported synergistic effects generated by PGA and PCL after incorporation with ciprofloxacin. Using a rat model of bacterial keratitis, Parikh et al\textsuperscript{152} reported the development of nanofiber-based sutures loaded with a variety of drugs, including levofloxacin for the prevention of rat ocular infection.

A method to introduce ion-exchange properties to polycaproamide (PCA) and PP fibers has been described for the development of antimicrobial sutures\textsuperscript{153}. Methacrylic acid-grafted PCA and sulfo- nated styrene-grafted PP sutures facilitated the adsorption of antibiotics including kanamycin, gentamicin, monomycin, and doxycycline, resulting in long-term \textit{in vivo} antimicrobial efficacy (45 and 78 days on gentamicin-immobilized PCA and PP sutures, respectively) and good shelf-life for storage (more than 3 years). A radiation grafting approach described by Gupta et al\textsuperscript{154} was used to immobilize tetracycline hydrochloride onto PP suture. The suture surface was first activated using radiation followed by grafting of acrylonitrile to introduce extra carboxyl groups for immobilization of tetracycline. The resulting sutures demonstrated antimicrobial activity against \textit{E. coli} and \textit{S. aureus} with drug release duration of 4 to 5 days, and anti-infective activity in albino rats. Additionally, graft polymerization of acrylic acid via plasma-induction followed by chitosan binding for immobilization of tetracycline hydrochloride and Ag nanoparticles showed promising \textit{in vitro} and \textit{in vivo} antimicrobial and drug release properties\textsuperscript{155}. A new approach has been recently described by Garcia-Vargas et al\textsuperscript{156} using grafting followed by covalent immobilization of vancomycin on polypropylene (PP) monofilament sutures pre-irradiated using a \((^{60}\text{Co})\gamma\)-source. The resulting suture showed a reduced number of \textit{S. aureus} colonizing the suture.

Other Antimicrobial-Based Sutures

Biotechnological products such as synthetic peptides and recombinant proteins have been explored for the development of antimicrobial sutures. The coating of silk suture with a chimeric recombinant protein consisting of spider silk protein and alpha-defensin using dip-coating approach was reported by Franco et al\textsuperscript{157}. The antimicrobial suture showed a reduction in the viability, adherence, and biofilm formation of MRSA and \textit{E. coli}, and high bio- and hemocompatibility.

Amphiphilic polymers have been investigated for development of antimicrobial suture. Poly[(aminoethyl methacrylate)-co-(butylmethacrylate)] (PAMB)-coated suture demonstrated a higher reduction in bacterial viability as compared to the triclosan-coated (Vicryl Plus) sutures\textsuperscript{158}. Technological-wise, a novel method for grafting of bacteriostatic polymer, polyvinylimidazole (PNVIm), onto PP suture has been described by López-Saucedo et al\textsuperscript{159}. In that study, suture exposed to gamma-ray treatment followed by acrylic monomers formed 2-hydroxyethyl methacrylate (HEMA) or N-isopropylacrylamide (NIPAAm) brushes for grafting of methyl iodide and methylimidazolium iodide which were inhibitory to \textit{S. aureus} and \textit{E. coli}. In a recent study\textsuperscript{160}, polyglactin sutures coated with poly (2-methacryloyloxyethyl phosphorylcholine (MPC)-co-n-butyl methacrylate) (PMB) were reported to exhibit significant inhibition against adhesion and biofilm formation of MRSA and MSSA.

Conclusions and Future Perspectives

In line with the current advances in human and veterinary medicine, there has been an increasing demand for surgical sutures for various procedures and wound management. This review presents a summary of a variety of novel antimicrobial sutures that have been developed over the last three decades. The enthusiasm of scientific research and innovation has led to the discovery of novel antimicrobial compounds, new formulations, and improvements in suturing technology.

Achieving a zero SSI rate is the goal for all healthcare providers. An ideal surgical suture should be non-toxic, does not cause host inflam-
Surgical site infection and development of antimicrobial sutures: a review

Conflict of Interest
The Authors declare that they have no conflict of interests.

Acknowledgements
This study is funded by IIRG 003C-19FNW and ST029-2020 provided by Universiti Malaya, Malaysia.

References


Surgical site infection and development of antimicrobial sutures: a review

102) Kampf G. Biocidal agents used for disinfection can enhance antibiotic resistance in Gram-negative species. Antibiotics (Basel) 2018; 7: 110.
123) Hübner NO, Siebert J, Kramer A. Octenidine dihydrochloride, a modern antiseptic for skin, mucous membranes and wounds. Skin Pharmacol Physiol 2010; 23: 244-258.


Masood R, Hussain T, Umar M, Azemullah, Areeb T, Riaz S. In situ development and application of natural coatings on non-absorbable sutures to reduce incision site infections. J Wound Care 2017; 26: 115-120.


Surgical site infection and development of antimicrobial sutures: a review


