REVIEW

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Healthcare associated infection: novel strategies and antimicrobial implants to prevent surgical site infection

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ABSTRACT

This report is based on a Hygienist Panel Meeting held at St Anne's Manor, Wokingham on 24–25 June 2009. The panel agreed that greater use should be made of antiseptics to reduce reliance on antibiotics with their associated risk of antibiotic resistance. When choosing an antiseptic for clinical use, the Biocompatibility Index, which considers both the microbiocidal activity and any cytotoxic effects of an antiseptic agent, was considered to be a useful tool. The need for longer and more pro-active post-discharge surveillance of surgical patients was also agreed to be a priority, especially given the current growth of day-case surgery. The introduction of surgical safety checklists, such as the World Health Organization's *Safe Surgery Saves Lives* initiative, is a useful contribution to improving safety and prevention of SSIs and should be used universally. Considering sutures as 'implants', with a hard or non-shedding surface to which micro-organisms can form biofilm and cause surgical site infections, was felt to be a useful concept.

KEYWORDS

Surgical site infection – Antimicrobial sutures – Biofilms

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Healthcare associated infections (HCAIs) occur in all parts of the healthcare system. The change in nomenclature from nosocomial or hospital-acquired infections is important because the best methods to prevent HCAIs are those directed at many different levels. As the UK Department of Health *Winning Ways* report noted: 'there is seldom any quick fix'.[1]

HCAIs include urinary and respiratory tract infections, bacteraemias and intravascular catheter infections, surgical site infections (SSIs) and *Clostridium difficile* emergence. A contributory factor to the increase in HCAIs has been the mis-use of antibiotics in healthcare and food production which has driven: (i) the proliferation of extended spectrum β-lactamases and resistance related to urinary infections; (ii) the emergence of glycopeptide-resistant enterococci and ventilator-associated pneumonias; and (iii) multiple drug resistant, coagulase-negative staphylococci on vascular catheters and joint prostheses. Meticillin resistant *Staphylococcus aureus* (MRSA) bacteraemia is declining in the UK but resistance underscores the need for antibiotic stewardship, particularly of newer broad-spectrum agents.

The UK Department of Health advocates that antibiotics should be used for treatable infections, the choice being governed by information about antibiotic resistance patterns and sensitivities.[1] Antibiotics should be used for prophylaxis of infection only when there is proven benefit, preferably with narrow spectrum antibiotics over a prescribed period at the correct dose. Alternatives to antibiotic therapy, such as a greater use of antiseptics or novel antibacterial sutures, are attractive prospects for surgical practice.

Surgical site infection

SSIs occur frequently and their prevention and treatment, especially those involving prosthetics, is challenging. SSIs comprise up to 20% of all HCAIs in the UK. At least 5% of patients undergoing surgery develop an SSI, which has an effect on quality of life and is a financial burden to healthcare providers.[2] This is lamentable given that the majority of SSIs are preventable. Furthermore, whilst SSIs after clean-wound surgery have been reported as being as low as 1.4%,[3] this is an underestimation. If a trained and blinded observer is involved, using close and prolonged post-discharge surveillance (PDS) to at least 30 days postoperatively (and a year after major joint replacement surgery), with agreed definitions, the SSI rate is much higher. Surgical wounds are categorised as 'clean', 'clean–contaminated', 'contaminated' or 'dirty'. Scoring systems, such as the ASEPSIS score[4] (Additional treatment, Serous discharge, Erythema, Purulent exudates, Separation of deep tissues, Isolation of bacteria and Stay duration as in-patient) allow further evaluation with interval data. Other scores such as SENIC (Study on the Efficacy of Nosocomial Infection Control) and NNIS risk index can identify patients at high risk of SSI.[5]

Prevention

Several guidelines exist for prevention of surgical site infection, including those produced by the UK National Institute for Health and Clinical Excellence (NICE).

Pre-operative phase

1. Hair removal should not be undertaken to reduce the risk of SSI.
2. If hair has to be removed, use electric clippers with a single-use head on the day of surgery. Razors used for hair removal increase the risk of SSI.
3. Give antibiotic prophylaxis before clean prosthetic surgery, clean-contaminated surgery and contaminated surgery but not routinely for clean, non-prosthetic, uncomplicated surgery using local antibiotic formularies which consider potential adverse effects.
4. Consider a single dose intravenously on starting anaesthesia but give prophylaxis earlier when a tourniquet is used.

Intra-operative phase

1. Prepare the skin before the incision using antiseptics such as povidone iodine or chlorhexidine.
2. Cover surgical incisions with an interactive dressing.

Postoperative phase

1. Refer to a tissue viability nurse, or equivalent, for advice on appropriate dressings for surgical wounds which are healing by secondary intention after an infection.

Patient homeostasis

Tissues heal well with optimal oxygenation, perfusion and body temperature. Avoiding hypothermia is a component of care bundles and may help to reduce the overuse of antibiotics.[6] In hernia surgery, postoperative pain scores may be lowered after pre-warming with lower ASEPSIS wound scores.[7] A meta-analysis[8] concluded that hypothermia, averaging only 1.5ºC less than normal, results in adverse outcomes adding between US$2,500–7,000 for each surgical patient. Avoidance of hypothermia is also associated with fewer adverse outcomes and shorter hospital stay.

There are many causes of hypothermia (< 36ºC) in the cool, dry operating theatre environment, including cold intravenous fluids and anaesthetic gases, and vasodilatation (or inhibited vasoconstriction) which lead to increased BMR and oxygen requirements and poor oxygen delivery. The physiological complications of hypothermia include shivering, increasing oxygen demand, a shift in the oxygen dissociation curve, acidosis, relative organ ischaemia and myocardial infarction. Higher inspired oxygen concentrations in the peri-operative period may reduce SSI rates when compared with lower oxygen concentration.[9] However, peri-operative tissue oxygen tension in obese surgical patients, even with supplemented oxygen, can fall to levels associated with an increased infection risk.[10]

Checklist approach

An initiative to improve the safety of surgery has been the introduction of surgical safety checklists.[11] Deaths and complications were reduced by more than a third in a year-long study using the World Health Organization (WHO) *Safe Surgery Saves Lives* initiative, which involved hospitals in eight cities around the world. The checklist requires only minutes to complete: before anaesthesia; before skin incision; and before the patient is removed from the operating room. Safe delivery of anaesthesia, appropriate preventive measures and reduction of infection and effective teamwork are ensured.

Implants, bacterial adhesion and biofilms: their roles in surgical site infection

Around half of the two million cases of HCAIs which occur annually in the US are associated with in-dwelling devices. Infections associated with permanent implants are more likely to occur and are difficult to manage because they require long courses of antibiotics and repeated surgical procedures.[12] Surgical sutures may also be considered as implants and, when bacteria contaminate tissues, sutures increase the virulence of organisms responsible for SSIs. Coating implants and sutures with a wide-spectrum antibacterial agent, such as triclosan, has the potential to reduce SSIs, particularly after prosthetic and contaminated surgery, and be an adjunct to antibiotics and lessen their overuse.

Implants are used in orthopaedics; as cardiovascular/vascular stents, pacemakers, grafts and shunts; and in cosmetic and dental surgery. Sutures, like most other implants, have a non-shedding surface to which bacteria can adhere, form biofilms and potentiate SSIs. The adherence of bacteria to various sutures has been investigated,[13] and variations in adherence-affinity correlated with infection. Another study[14] examined the physical and chemical properties of suture materials on the adherence of *S. aureus* and *Escherichia coli*. Ten suture materials were tested (including catgut, Dexon, Vicryl, PolyDioaxanone Suture and Prolene); of the absorbable sutures, PDS exhibited the lowest adherence-affinity whereas Dexon sutures had the highest. Suture-related keratitis, following penetrating keratoplasty, has been reported[15] triggered by a suture allowing *Corynebacterium macginleyi* to migrate into the cornea and form a biofilm.

Biofilms: are they significant in SSI and how can they be managed?

Biofilms are ubiquitous and form whenever micro-organisms (bacteria, yeasts, algae, fungi, or protozoa) attach to surfaces. Once attached, planktonic (free-living) bacteria undergo a phenotypic change and, within minutes, deposit 'slime': extracellular polymeric material (EPS) or biofilm matrix. Implants have non-shedding surfaces which can be colonised by skin or other bacteria during surgery, to form a biofilm. Of all human infections, at least 60% are thought to involve biofilms.

The recognition that biofilms are the dominant mode of microbial growth, and that the majority of bacteria exist in biofilms, is relatively recent. Once established, in the environment or in infections, biofilm bacteria are difficult to treat because, shielded within the matrix, they are less susceptible to antibiotics and antiseptics. This recalcitrance is not reflected by laboratory susceptibility tests and a bacterium shown to be susceptible to antibiotics may be impossible to treat in a biofilm. Reasons for the reduced susceptibility of biofilm-embedded organisms, compared with planktonic counterparts, includes: (i) heterogeneity of growth rates; (ii) cells being in a stationary physiological phase, present as recalcitrant 'persister' cells or able to degrade antimicrobials; and (iii) reduced rates of penetration of the biofilm by antibiotics.[16] Biofilms can also shield their constituent micro-organisms from the body's immune system.[17]

Biofilms, implants and infection

Intravascular catheters and urinary catheters are the two most common causes of acquired bacteraemia. Biofilm formation on the surfaces of in-dwelling catheters is central to the pathogenesis of infection.[18] Biofilms have also been implicated in suture-related infection. Post-traumatic endophthalmitis, unresponsive to systemic, intra-ocular and topical antibiotic therapy has been described with slime-producing *Staphylococcus epidermidis* revealed on sutures by confocal microscopy. The planktonic form of the isolate was susceptible *in vitro* but in biofilm was resistant.[19]

Preventative strategies

Once a biofilm infection is established on an implant, it usually needs removal and antibiotic treatment. Preventative strategies include prophylactic antibiotics before the biofilm can form, or 'intelligent' surfaces that prevent colonisation or have antimicrobial properties. Potential antiseptics for coating surfaces include chlorhexidine, polyhexamethylene biguanide (PHMB), octenidine and triclosan. Compared with antibiotics, which generally have single pharmacological targets which select for resistance, antiseptics have several or multiple targets and true 'resistance' is rare. Antimicrobial-impregnated implants, which prevent bacterial adhesion and biofilm formation, can avoid long-term, ineffective, systemic antibiotics, reduce the risk of microbial resistance generation and need for implant removal.

Wound antisepsis and antiseptic sutures: antiseptics instead of antibiotics?

Antiseptics are topical antimicrobials which destroy or inhibit growth of micro-organisms in or on living tissue. Their use to prevent SSIs has shifted back and forth, being negative after the high toxicity of Lister's carbolic wound spray and the toxic side effects of other early antiseptics such as organic mercury compounds, dyes, sulphonamides, nitrofuranes, and quinolinols. The introduction of penicillin also down-played antiseptics but their current renaissance probably relates to increasing antibiotic resistance and new, better tolerated antiseptics.

Tolerability

Ideally, antiseptics should have a rapid, potent and broad microbiocidal spectrum with long-lasting effects and no risk of developing antimicrobial resistance. They should be biocompatible with medical products, not impair healing processes and be well tolerated in wounds with no toxicity or systemic absorption. The old surgical aphorism 'do not apply anything to a wound that you would not put in your eye' remains pertinent. Antiseptics should be not applied if absorption risks systemic side effects; the choice should be a balance between risk of damage by infection or toxicity. The Biocompatibility Index (BI) which considers microbiocidal activity and cytotoxic effects can inform this choice.[20]

Octenidine

Octenidine has a BI > 1, is rapidly effective, active against biofilms, not absorbed, has no association with resistance, does not interfere with wound healing and has no allergic or toxic risks. Phagocytosis and PDGF may be up-regulated, but it is toxic to some tissues.[21] However, after 3 weeks of treatment, octenidine eradicated *S. aureus*, *S. epidermidis*, and *Proteus mirabilis* in neoplastic ulcers.[22]

Polihexanide

Polihexanide has a BI > 1 and is also active against biofilms,[23] is not absorbed and has no allergic or toxic risks. Wound healing is stimulated but angiogenesis may be delayed. Polihexanide is suitable for second-degree burns because, in addition to its antiseptic and debriding action, it does not inhibit epithelialisation.[24,25]

PVP-iodine

PVP-iodine has a BI < 1, is microbiocidal, sporicidal and partially virucidal. It inhibits inflammatory mediators *in vitro*. PVP-iodine is absorbed with a risk of sensitisation, is cytotoxic, and may be incompatible for peritoneal lavage.

The role of antiseptic impregnated sutures for prevention of SSI

Implanted foreign materials, including sutures, increase the risk of SSI.[26,27] Sutures in contaminated tissues may enable micro-organisms to penetrate deeper[28] and the inoculum size of micro-organisms needed to cause an SSI is 10^5-times lower when foreign material is present.[29] Biofilms around a suture may protect micro-organisms from host defence mechanisms.[30,31] There have been trials of sutures containing cephalosporins[32] and neomycin-impregnated silk and Dacron implanted into tissues contaminated with *S. aureus*, *E. coli*, *P. mirabilis*, or *Pseudomonas aeruginosa* reduced bacterial numbers.[33] Antiseptics have also attracted interest for incorporation into sutures but iodine products have not been utilised because of their cytoxicity.[34]

Triclosan-coated poliglecaprone (Monocryl Plus) has been evaluated to inhibit bacterial colonization by *E. coli* and *S. aureus* in the mouse and guinea pig.[35] After 48 h, the triclosan-coated suture produced a 3.4-log reduction in *S. aureus* and a 2-log reduction in *E. coli* compared with control. Another *in vivo* study showed that triclosan-coated suture inhibited bacterial colonisation with a 20-mm protective zone, effective against *S. aureus* and *S. epidermidis*, which was effective for 5–7 days.[36] The efficacy of PDS, with and without triclosan impregnation, was evaluated against *S. aureus*, *S. epidermidis*, *Klebsiella pneumoniae*, and *E. coli* *in vitro* and *in vivo*.[37] PDS with triclosan demonstrated antibacterial activity which was maintained until the sutures dissolved.

Potential risks of triclosan-coated devices and implants

A review of 30 years of triclosan use showed there was no risk of resistance[38] and a toxicology database found no carcinogenic potential or genotoxicity.[39] There was no evidence of skin sensitisation and pharmacokinetic studies have shown that triclosan is rapidly absorbed, well distributed, metabolised in the liver, and excreted by the kidneys. No association between triclosan and antibiotic resistance and the susceptibility of bacteria isolated in the community has been found.[40]

Antimicrobial sutures: what are the benefits?

The patent application for antimicrobial sutures describes a multifilament suture with an antimicrobial coating on at least part of the surface.[41] These sutures offer advantages, including less SSIs with reductions in healthcare costs and improved quality of life for patients.

Triclosan-coated polyglactin (Vicryl Plus) sutures inhibited *in vitro* growth of *S. aureus*, including MRSA, and *S. epidermidis*, which did not diminish for up to 7 days.[42] In culture media, the bacteria-free zone surrounding knotted sutures had a volume of 14–18 cm^3 with zones of inhibition persisting after 5–10 passes through tissue. Cultures of *S. aureus*, MRSA, *S. epidermidis* (biofilm-positive) and *E. coli* were inoculated in another study with triclosan-coated and non-coated polyglactin and reductions in bacterial adherence were observed with antibacterial activity persisting for at least 96 h.[43]

A study of breast-reduction surgery found no antimicrobial effect of triclosan-coated sutures.[44] However, a high number of patients developed wound dehiscence and there were methodological inconsistencies. In another clinical study, the intra-operative handling and wound healing characteristics of triclosan-coated polyglactin sutures was addressed in paediatric surgery.[45] The primary end-point was the surgeon's assessment of intra-operative handling, including: (i) ease of passage through tissue; (ii) first-throw knot holding; (iii) knot tie-down smoothness; (iv) knot security; and (v) suture fraying. The triclosan-coated sutures received more 'excellent' scores (71% vs 59%; not significant). In a study of post-appendicectomy SSIs in children, conventional treatment was compared with the use of triclosan-coated sutures or gentamicin-impregnated sponges, inserted prior to wound closure.[46] The antimicrobial sutures and sponges significantly reduced SSIs.

In an animal model of prosthetic infection, triclosan-coated sutures reduced the number of positive cultures after surgery by two-thirds, compared with a braided suture.[47] In a clinical prosthetic study, which evaluated the incidence of CSF shunt infections following use of triclosan-coated or conventional sutures, the infection rate was significantly reduced in the triclosan-coated suture group (4.3% vs 21%).[48]

Table 1 Sensitivity analysis of suture with and without antiseptic

	1	2	3	4
Increase cost per intervention	€1.2	€1.2	€1.2	€1.2
Number of interventions	20,000	20,000	20,000	20,000
Total increase	24,000	24,000	24,000	24,000
Infection rate	5%	5%	5%	5%
Number of SSIs	1000	1000	1000	1000
Percentage reduction*	15	10	5	1
Number of avoided infections	150	100	50	10
Cost reduction	1,500,000	1,000,000	500,000	100,000
Net benefit	1,476,000	976,000	476,000	76,000

*Estimation of infection reduction by the use of vicryl plus.

A clinical study compared triclosan-coated suture with standard PDS after more than 2000 mid-line laparotomies and found that the antimicrobial-coated suture significantly decreased the number of SSIs (4.9% vs 10.8%).[49] The economic implication of using triclosan-coated sutures for the reduction of sternal wound infections has been studied in 479 patients undergoing cardiac surgery. Of these, 103 patients were closed with triclosan-coated sutures and the remaining 376 were closed with non-coated sutures. Twenty-four patients, all of whom were closed with conventional suture material, had superficial or deep sternal wound infection at an estimated cost per patient of US$11,200.[50]

A recent analysis[51] of the cost of SSI in patients undergoing major surgery in a tertiary hospital found an SSI incidence of 9%. The hospital stays of patients with SSIs were 14 days longer than those without an SSI, with additional hospital costs of US$10,232 per patient (US$97,433 including indirect social costs). A simple, cost-effectiveness analysis based on this article is shown in Table 1 (column 2). A small hospital performing 20,000 surgical procedures annually with an infection rate of 5% would have 1000 SSIs. Assuming an SSI reduction using triclosan-coated sutures of only 10%, use of such a suture, based on current costs, would avoid 100 SSIs yielding a cost saving of €976,000. A sensitivity analysis can also be performed when the SSI rate using triclosan-coated sutures is reduced by only 1%; this still offers a net benefit of €76,000. After procedures which have a higher SSI rate the benefits could be even greater.

Conclusions of the panel meeting

The panel agreed that greater use should be made of antiseptics to reduce reliance on antibiotics with their associated risk of antibiotic resistance. When choosing an antiseptic for clinical use, the Biocompatibility Index, which considers both the microbiocidal activity and any cytotoxic effects of an antiseptic agent, was considered to be a useful tool.

The need for longer and more pro-active post-discharge surveillance of surgical patients was also agreed to be a priority, especially given the current growth of day-case surgery. It is clear that SSIs are currently under-reported but initiatives will only be fully funded when accurate data about the incidence, cost and causes of SSI are available.

The introduction of surgical safety checklists, such as the World Health Organization's *Safe Surgery Saves Lives* initiative, is a useful contribution to improving safety and prevention of SSIs and should be used universally. Further refinement of checklist items pertinent to SSI should be encouraged.

Considering sutures as 'implants', with a hard or non-shedding surface to which micro-organisms can form biofilm and cause SSIs, was felt to be a useful concept. Coating sutures with an antimicrobial such as triclosan provides an effective strategy for reducing SSIs. The panel commented that further randomised controlled trials in a wider range of surgery are required, with cost-benefit analyses of outcomes.

Acknowledgement

This report is based on a Hygienist Panel Meeting held at St Anne's Manor, Wokingham on 24–25 June 2009.

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