Review Article

Initiatives to reduce Postoperative Surgical Site Infections of the Head and Neck Cancer Surgery with a special emphasis on developing countries

Short title: *Surgical Site Infections of Head and Neck Cancer Surgery*

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ABSTRACT

Introduction: Surgery in patients with head and neck cancers is frequently complicated by multiple stages of procedure that includes significant surgical removal of all or part of an organ with cancer, tissue reconstruction, and extensive neck dissection. Postoperative wound infections, termed 'surgical site infections' are a significant impediment to head and neck cancer surgery and recovery, and need to be addressed. **Areas Covered**: Up to 10-45% of patients undergoing head-and-neck cancers surgery develop SSIs. SSIs can lead to delayed wound healing, increased morbidity and mortality as well as costs. Consequently, SSIs need to be avoided where possible, as even the surgery itself impacts on patients' subsequent activities and their quality of life, which is exacerbated by SSIs. Several risk factors for SSIs

need to be considered to reduce future rates, and care is also needed in the selection and duration of antibiotic prophylaxis. **Expert commentary:** Head and neck surgeons should give personalized care, especially to patients at high risk of SSIs. Such patients include those who have had chemoradiotherapy and need reconstructive surgery, and patients from lower and middle-income countries and from poorer communities in high income countries who often have high levels of co-morbidity because of resource constraints.

KEYWORDS: Healthcare, Postoperative, Surgical Site Infections, Head, Neck, Cancer, Surgery

1. BACKGROUND

1.1. **Definition**: A surgical site infection (SSIs) is defined as an infection in a surgical wound occurring within 30 days of the procedure with no implant, or within one year if an implant is placed and the infection appears to be related to the surgery [1-3].

1.2 **History**: SSIs (previously known as 'wound infections') are one of the leading causes of healthcare-associated infections (HCAIs), increasing morbidity, mortality, and healthcare costs through increasing hospital length of stay across advanced as well as lower and middle-income countries (LMICs) [4, 5]. Before the mid-19th Century, most surgical patients developed an SSI which typically started with a pus-filled discharge from the incisional wound leading to sepsis and death [6]. In the late 1860s, Doctor Lister first introduced the principles of antisepsis which, along with other preventive measures over the last 150 years, have resulted in an appreciable reduction in postoperative infections and decreased morbidity and mortality [6-8]. However, SSIs are still a major healthcare challenge and are associated with poorer patient outcomes [9].

1.3 **Prevalence of SSIs and Sequelae**: Despite advances in infection prevention and patient safety, SSIs are still one of the most common adverse events that can occur after surgical procedures in all contexts [2, 10, 11]. Bacterial infections in surgical sites leading to SSIs are categorized as incisional or organ/space infections. This differentiates those that occur at incision sites from those associated with organs or spaces handled during operation [12]. SSIs appear particularly problematic and common in LMICs versus high-income countries [13, 14], for example, there is a pooled incidence rate of 14.8% in Africa with SSIs being a leading cause of infections in hospitals because of resource constraints [11, 15]. Even in rich nations such as the US, on study reported that SSIs account for 17% of all HCAIs among hospitalized patients [16] and another recent study found that SSIs are found in between 20-31% of

HCAIs in hospitalized patients with a death rate of 3%, prolonged hospitalization, increased readmission rates, reoperation, and costs ranging up to US$34,000 per episode [9, 17]. It is hard to determine the actual figure of SSIs in many countries around the world, and although SSIs are a leading cause of hospital acquired infections in high income countries, the poorer infrastructure (such as data record keeping) and other resource constraints in LMICs means that many SSIs go unrecorded and patients needlessly suffer. In 2012, the annual costs of SSIs in the US were estimated at US$3billion per year and rising [5, 18]. In the US, HCAIs, especially SSIs, are viewed seriously, with the government identifying the prevention of SSIs a top national priority [19]. Similar findings are seen in Europe with 19.6% of all HCAIs being SSIs in 2011-2012 [19, 20]. Overall, SSIs can lead to a doubling of the length of hospital stay and a high number of readmissions [21-23].

1.4 **SSIs related to Head-and-Neck Cancer Surgery Prevalence and Its Consequences**: Globally, the Head-and-Neck cancer prevalence rate is increasing [24-27] and HNCs continue to remain a substantial public health liability, accounting for more than 550,000 cases and 380, 000 deaths across the world every year [28]. Among such cancers, head and neck squamous cell carcinoma (HNSCC) is the fifth most common cancer worldwide, with around 600,000 newly diagnosed cases identified each year, and it is the eighth most common cause of cancer mortality [29-31]. The appreciable rise in HNCs over the last decade has been greatly influenced by a significant rise in rates in LMICs [32, 33], for example HNCs account for 30% of all cancers in India [33]. Surgery has been considered as the predominant and preferred treatment for HNCS since the introduction of the radical en bloc neck dissections in 1905 [29-31]. Over the last century more refined and safer procedures for HNCS have been introduced, decreasing morbidity and increasing survival [34-37]. However, despite improvements in aseptic surgical procedures with coverage of antimicrobial prophylaxis, SSIs remain high [38]. SSIs are particularly prevalent with patients undergoing surgery for head-and-neck cancer (HNCS), with between 10-38% developing SSIs [3]. This is a concern, as SSIs related to HNCS can cause major complications leading to increased morbidity and a poorer quality of life due to delayed wound healing and the increasing possibility of delayed postoperative chemoradiotherapy [39]. Although HNCS does not involve the pleural space or accessory respiratory muscles, an appreciable number of patients (up to 44.8%) develop lung and respiratory complications. This rate of complications is much higher than seen in the chest and abdominal surgeries and needs to be carefully monitored [40-44].

Consequently, there is a need to review key issues relating to a limiting SSIs following head and neck cancer surgery to reduce future morbidity, mortality, and costs. This is particularly important in LMICs

given rising rates of HNCs coupled with high rates of SSIs. HCAIs remain a considerable issue for health-care systems because of their complexities and complicated nature and under-reporting of infection rates by many hospitals [45-47]. Overall, SSIs are the second most frequently occurring postoperative HCAIs complication, head and neck surgery (HNS) being no exception [45]. There are also concerns with the length of prophylaxis required to prevent SSIs in LMICs due to issues such as hygiene on the wards [14, 48-50]. In many LMICs, third-generation cephalosporins (such as ceftriaxone) are widely-used as a prophylaxis to prevent SSIs, which can contribute to increasing antibiotic resistance rates [14, 48, 51-52]. These issues need to be reviewed and addressed to improve the care of patients undergoing HNS.

2. The body of the manuscript

2.1 SURGICAL SITE INFECTIONS OF THE HEAD AND NECK

A multicenter US study found that 15% of patients develop SSIs after microvascular reconstruction surgery for HNCS, with a median time to acquiring an SSI of 11.5 days [53]. In another study of head and neck free flap surgery, 13.84% of patients (67 out of 484) developed SSIs: 33.33% after 1 week, 33.33% after 2 weeks and 45% between 15-30 days post-surgery. 45% of patients developed SSIs after hospital discharge [54]. In a further study regarding squamous cell carcinoma (SCC) and HNS, there was an overall rate of SSIs of 45% (117/260) [55]. As mentioned, HNCs are an increasing concern in LMICs where often there are concerns with resources, not only in personnel but also available medicines [56]. Consequently, it is imperative in these countries to keep SSIs to a minimum.

HNC refers to malignancy in the anatomical area below the skull base and above the clavicles. A wide range of malignancies are found in the head and neck, including carcinoma, sarcoma, lymphoma and salivary gland tumors [57]. Over 90% of HNCs are SCCs that ascend from the mucosal surfaces of the oral cavity, oropharynx, and larynx [61]. HNSCC is most commonly observed in patients aged over 45 years [58], with the incidence of the oropharynx and oral cavity carcinoma increasing recently in the 18-45-year age group [59-61]. Northern America and European countries account for only 5-10% of all newly diagnosed cases of HNSCC, with higher rates now seen in LMICs [58]. Internationally, the incidence rate and anatomic distribution of HNSCC varies widely due to different socio-cultural habits such as tobacco, alcohol, and betel-nut consumption, which trigger almost 80% of all HNSCC cases [58, 62]. High-risk countries for oral squamous cell carcinoma (OSCC) are India, Sri Lanka, Bangladesh, and Pakistan [63]. The highest incidence of OSCC among the European countries is France, with high rates also observed in

Hungary, Slovakia, and Slovenia [64]. The decreasing incidence of oral and laryngeal SCC in developed countries coincides with a decline in the use of tobacco products [64]. Oncogenic human papillomavirus (HPV-16) has been idnetified as the cause of similar cancers of the tonsils and the base of the tongue [64-67]. The selection of treatment modalities for HNC can be very complicated and require a multi-disciplinary strategy, especially in elderly patients. Surgery and radiotherapy are still the cornerstone therapeutic options for the initial stages of cancers, whereas chemotherapy and targeted therapy (anti-EGFR monoclonal antibody cetuximab) are advocated for locoregionally advanced stage HNC and are used to help prolong life along with radiotherapy [68].

Three to 41.8% patients with HNC develop major impediments even with rigorous aseptic precautions and optimal antibiotic prophylaxis for the prevention of SSIs [39]. Multiple recent studies highlight the necessity of very strict aseptic surgical procedures to prevent SSIs [4, 36, 69, 70]. The development of SSIs in HNC patients often leads to spontaneous wound dehiscence, the formation of fistulae, potentially life-threatening complications of an infection, and can cause death [36]. This extends the duration of hospitalization, increases healthcare expenses, and inhibits the use of other medications, which can then increase the possibility of the reappearance of cancer [39]. Consequently, multiple studies have concluded that SSIs have a major contribution to the poor prognosis of HNC patients [71, 72]. Moreover, such post-operative infections remain as the principal reason for the non-success of reconstruction surgery after HNC excision [73]. Consequently, they should be avoided where possible, with the situation more complicated in sub-Saharan African countries with a high prevalence of HIV among hospital patients [47, 49]. Identifying pertinent risk factors for SSIs can help to reduce future rates.

2.2 RISK FACTORS FOR SURGICAL SITE INFECTIONS

A South Korean study using univariate analysis identified that pre-operative risk factors associated with SSIs were associated with the location of the tumor; the stage of the tumor; smoking; alcohol habits; diabetes; history of prior radiotherapy or chemotherapy; anemia; hypoalbuminemia; mandible cutting; flap reconstruction; tracheotomy; clean-contaminated wounds; blood transfusions, and duration of surgery [74]. Multivariate analysis revealed that the independent risk factors for developing SSIs were oral cavity cancer (odds ratio [OR]: 6.06, 95% confidence interval [CI]: 1.209-30.378), a history of prior radiotherapy (OR: 2.85, 95% CI: 1.172-6.931), tracheotomy (OR: 9.757, 95% CI: 2.609-36.491), and clean-contaminated wounds (OR: 13.953, 95% CI: 2.231-87.275)" [74]. In contrast, thyroid malignancy was an independent predictor of not developing SSIs (OR: 0.152, 95% CI: 0.035-0.658) [74]. Surgical procedures

involved in this study included neck dissection, partial or total laryngectomy, resection of the pharynx or trachea, mandibulectomy or mandibulotomy, and flap reconstruction surgery [74]. Another univariate analysis revealed that perioperative risk factors were hemorrhage; earlier instigation of cancer medicines; clean-contaminated surgery; tracheotomy; malignant tumor; advanced T-stage; flap reconstruction, and prolonged time for surgery were also statistically significantly related to SSIs [75]. Multivariate analysis ascertained that blood loss, previous chemotherapy, and the type of surgery contributed to SSIs [75]. Another recent study using multivariate analysis conducted among 173 patients with oral cancer found that operative time [odds ratio 9OR) = 1.199, 95% confidence interval (CI) =1.036-1.389], mandibulectomy (OR=2.759; 95% CI=1.245–6.111) and oro-neck communication (OR=5.358; 95% CI=2.150–13.355) were self-determining prognosticators for SSIs [76]. A recent review of SSIs in HNC found similar risk factors for SSIs including surgery with the involvement of the upper aerodigestive tract, clean-contaminated surgery as well as surgery involving simultaneous tracheostomy and reconstruction of vascularized bone [36]. The presence of co-morbidities; poor nutritional status; low preoperative albumin levels; advanced age; increased body-mass-index; previous radiotherapy; significant blood loss during surgery and smoking also increased SSI rates [36]. A recent Japanese study using univariate analysis found a statistically significant correlation between postoperative SSIs and diabetes (p=0.033), preoperative serum albumin level (p=0.009), and duration of operation (p=0.0093) [72]. Furthermore, preoperative serum albumin level (<4.0 g/dL) and operation time (≥120 minutes) were found to be independent factors affecting postoperative complications (OR 3.82, p=0.0074; OR 2.83, p=0.0086, respectively) [72].

In another study, discriminant analysis and multiple logistic regression methods identified pre-surgical tracheostomy (p<0.001), previous surgery (p=0.001) and length of pre-operative hospital stay (p<0.001) as the most significant risk factors for SSIs [77]. Surgery included partial mandible resection, the floor of the mouth resection, total larynx resection, and partial tongue resection [77]. A second South Korean retrospective study revealed that male sex (OR 4.281; p=0.004), cardiovascular diseases (OR, 1.941; p=0.020), massive hemorrhage during surgery (OR, 4.213; p=0.001), and surgery lasting longer than 6 hours (OR, 4.213; p=0.002) were statistically significantly linked with SSIs [78].

2.3 BACTERIOLOGICAL PROFILE OF SURGICAL SITE INFECTIONS

As mentioned, HNCS can involve difficult procedures involving several stages of major surgical tasks, vascularized tissue rebuilding, and restoration. These operations frequently damage the mucosal lining

of the upper respiratory and digestive tract, which necessitates a clean surgical field and reconstruction of the mucosal lining. Because of the disruption to the patency of mucous membranes, SSIs are a serious complication of HNCS, and can lead to delayed wound healing; wound dehiscence; fistula formation, and compromised tissue reconstruction [36]. One study conducted in a rural hospital in a LMIC reported that 17.8% (137 of 768) of patients undergoing HNS had SSIs, and among these patients, 96.4% yielded bacterial growth. *Staphylococcus aureus* (50.4%) was the commonest pathogen followed by *Escherichia coli* (23.02%), *Pseudomonas aeruginosa* (7.9%) and *Citrobacter* species (7.9%) [79] [~~65~~]. Identified pathogens were in 59% of SSIs in a recent multicenter US study with MRSA (6%) and *Pseudomonas aeruginosa* (9%) not that common [53]. 77% of patients had postoperative antibiotic prophylaxis (POABP), mirroring some of the findings among African countries [13, 47, 48]. Bacteria found were 17% gram-negative (GN), 52% enteric GN and 31% antipseudomonal GN; consequently, the authors concluded that POABP without GN antibiotic coverage was statistically significantly associated with SSIs [53]. Antipseudomonal POABP antimicrobial coverage for ≥6 days was found to be useful to protect against SSIs [53]. SSIs also occurred among the flap donor in 4.4% of patients with 95% of them developing SSIs after one week of surgery. MRSA or MSSA were the principal invading microorganisms in 89% of patients [54]. Another study revealed the commonest causative agents were *Staphylococcus aureus* (32.6%), and 93.2% of them were methicillin-resistant *Staphylococcus aureus* (MRSA). *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Enterococcus* species were also regularly found [78].

In another study, cultures grew multiple pathogenic microbes, with 25% being like the normal microorganisms found in the oral cavity, and 44% of GN bacilli, 20% growing MRSA and 16% growing *methicillin-sensitive Staphylococcus aureus* (MSSA) microorganisms [54]. The authors found no significant association between the onset of SSIs and the microorganism identified [54]. The majority (67%) of the antimicrobial resistant pathogens were identified after prophylactically administered antibiotic. Among the GN bacilli, 85% were resistant to an ampicillin + sulbactam combination, and resistant to clindamycin in 40% of MSSA and 67% of MRSA identified pathogens [54]. Additionally, clindamycin failed to prevent SSIs and resulted in partial or complete flap loss by two weeks [54]. Consequently, prescribing clindamycin alone is considered a significant risk factor for developing SSIs. This is perhaps not surprising in view of clindamycin's bacteriostatic mechanism and limited coverage against GN organisms [36]. Another study researching clindamycin use identified that it was associated with a four times higher chance of SSIs [OR 3.784; 95% CL: 1.367-10.470 (p=0.0100)] after regulating for possibly confounding aspects relating to head and neck free-tissue transfer surgery [80].

An Indian study also found that out of 46% (488 out of1058) of samples of SSIs, the major pathogens were GN bacilli followed by GP cocci [81]. The principal invading microorganisms were *Escherichia coli* (59.73%); *Klebsiella* species (13.98%); *Pseudomonas* species (10.39%); non-fermenting GN bacilli (8.12%); *Proteus* species and *Morganella morgani* (5.86%); *Citrobacter* species (1.89%) and *Enterococci* species (53.68%); *Staphylococcus aureus* (41.3%); MRSA (2.86%); Coagulase Negative *Staphylococcus* (1.6%); and *Streptococci* (0.2%). Extended-spectrum beta-lactamases production out of the total 1058 samples were *Escherichia Coli* (31%); *Klebsiella* species (3.02%); non-fermenting GN bacilli (1.51%); *Proteus* species (1.13%); *Pseudomonas* species (0.56%) *Citrobacter* species (0.56%) [81]. Amongst the total GN bacilli (1058), SSIs were found in 48.39% of surgical oncology; 20.79% of gynecological oncology; 6.61% of head neck oncology, and 1.70% oral oncology. Among the GP cocci, 40.98%, 31.14%, 4.91%, and 1.63% were from surgical, gynecological, head neck, and oral oncology respectively [81]. Polymicrobial and monomicrobial infections were seen in 33.37% and 24.96% of cases respectively [81]. Postoperative wound cultures in a study involving SCC and HNS revealed polymicrobial infections, with the leading contributing pathogens being *Escherichia coli*, coagulase-negative *Staphylococcus*, non-hemolytic *Streptococcus,* and *Staphylococcus aureus*. 45% were aerobes GN rods, 40% were aerobes GP cocci and 15% were anaerobes [55]. It is important therefore to understand the bacteriological profile of SSIs to improve future preventative strategies.

2.4 ROLE OF PROPHYLAXIS OF ANTIMICROBIALS

As noted earlier, many surgical procedures in the head and neck breaches of mucosa lining causing exposure to the mucosal flora of the upper aerodigestive tract and microbial contamination of surgical wounds may lead to poor outcomes [75, 82, 83]. Without the use of prophylactic antibiotics, such head and neck surgical maneuvers are often associated with a high rate of SSIs [64, 84-86]. In clean-contaminated HNC surgery, the frequency of SSIs can approach near 100% without prophylactic antibiotics [36]. Consequently, studies frequently advocate antimicrobial prophylaxis in patients about to undergo major head and neck surgical procedures, especially when they are clean-contaminated [36]. Prophylactic use of antimicrobials in the perioperative period in HNCS (especially for patients undergoing microvascular reconstruction) has now become standard practice as SSIs are the most common complication [87]. HNCS patients who have already had cancer chemotherapy and radiation have an increased rate of infection after surgery [88].

Consequently, antimicrobial prophylaxis is targeted to prevent SSIs before the invasion of pathogenic microorganisms. However, an extended period of antimicrobial prophylaxis does not ensure avoidance of an SSI [36, 89] and is often responsible for the development of resistant microorganisms. It should, therefore, be avoided where possible [83]. Several recent studies reports that the SSI rate was high regardless of preventive antimicrobials in perioperative and postoperative of HNCS patients undergoing microvascular free-tissue transfer [90-92]. However, prescribing perioperative and postoperative preventive antibiotics (POPAB) is now standard practice [85]. Another prospective randomized, double-blind study of patients undergoing major surgical procedures for malignant tumors of the head and neck in the US demonstrated that ensuring effective clindamycin further than the DOS antimicrobial prophylaxis in HNS is a high priority [93]. Patients were categorized into four treatment groups namely: Group **I**: cefazolin 1 day, placebo day 2 to 5. Group **II**: cefazolin days 1 to 5. Group **III**: gentamicin and clindamycin 1 day, placebo days 2 to 5, Group **IV**: gentamicin and clindamycin days 1 to 5 [93]. Irrespective of categorization, 15% of all patients developed significant SSIs; these included: in group **I**, 33%; Group **II**, 20%; Group **Ill**, 7%; Group **IV**, 4%. In Group **III** and Group **IV,** there was a statistically significant ($p<0.05$) reduction in the rate of postoperative SSIs [74]. The multifactorial analysis confirmed that patients needing a regional pectoral flap repair had a statistically significant ($p<0.05$) increased possibility of SSIs; however, patients needing laryngectomy (with or without neck dissection) had a statistically significantly ($p<0.05$) less probability of developing SSI than patients undergoing oropharyngeal resection [93].

A recent systematic review and meta-analysis into microvascular free flap reconstruction found that SSIs were statistically significantly higher in patients receiving prophylactic antibiotics for ≤24 hours compared to >24 hours [Relative Risk (RR) 1.56; 95% CI 1.13-2.140], with post-hoc multivariate analysis showing the risks of SSIs for ≤24 hours versus >24 hours were not statistically significant after adjusting for antibiotic type (RR 1.09; 95% CI 0.78-1.55) [94]. Additionally, patients who received ampicillin-sulbactam had less possibility (RR 2.85; 95% CI 1.95-4.17) of developing SSIs in head and neck clean-contaminated free-flap cases than with clindamycin prophylaxis [94]. Overall, as mentioned, clindamycin given alone for prevention of SSIs is associated with a statistically significantly higher risk of SSIs [39]. This compares for instance with cefazolin and metronidazole [OR, 3.78; 95% CI, 1.37-10.47] in patients needing free tissue transfer for head and neck cancer resection [80]. A retrospective database study of over 8,800 patients found that ampicillin/sulbactam, clindamycin, cefazolin + metronidazole, and cefazolin alone were regularly prescribed for perioperative prophylaxis of SSIs in HNS, with no

statistically significant difference in the odds of developing an SSI based on a selected antimicrobial only on the day of surgery (DOS). DOS and DOS+1 patients getting ampicillin/sulbactam had a reduction in the odds of developing SSI by over two-thirds [OR 0.28, 95% CI, 0.13-0.61, p=0.001] associated with ampicillin/sulbactam on DOS only [95]. However, this was not seen with clindamycin [1.82 (0.93-3.56), p=0.078] compared with clindamycin on DOS only. Extending clindamycin further than the DOS was associated with higher odds of SSIs related with DOS-only ampicillin/sulbactam [OR, 2.66; 95% CI, 1.33-5.30; p=0.006]. These associations were also detected in a different group of otolaryngologists and hospitals that utilized multiple diverse antimicrobial schedules [96]. Extending the ampicillin/sulbactam schedule for 1 or more days beyond the DOS had better protective effect against SSIs than multiple days of clindamycin [95]. Furthermore, the researchers found that vancomycin, teicoplanin, and linezolid remained highly effective against gram-positive (GP) isolated pathogens; with meropenem, piperacillin + tazobactam, and amikacin found to be highly effective against gram-negative (GN) microorganisms [79].

A retrospective cohort study of 427 patients who had undergone head and neck free flap reconstruction also showed that the use of clindamycin prophylaxis was significantly associated with a greater risk of postoperative SSIs [96]. Patients receiving clindamycin [OR, 2.54; 95% CI, 1.25-5.14 (p=0.01)] had a higher possibility of SSIs; but the risk of SSIs was not diminished with prolonged period of antimicrobials [OR, 0.63; 95% CI, 0.34-1.19 (p=0.18) [96]. Furthermore, multivariate analysis revealed that patients having clindamycin [OR, 6.71; 95% CI, 1.83-24.60 (p=0.004)] and oral tobacco consumption [OR, 1.20; 95% CI, 1.04-1.39 (p=0.02)], but not a prolonged period of preventive antimicrobials [OR, 0.75; 95% CI, 0.30-1.86 (p=0.53)] had an increased possibility of SSIs flap or neck infections [96]. An Indian study reported that single dose of antimicrobial prophylaxis with amoxicillin + clavulanic acid for clean head and neck surgeries and amoxicillin + clavulanic acid + metronidazole 3 times a day for 3 days for clean-contaminated surgeries demonstrated a lower incidence of SSI in HNCS [44]. This study concluded that short-term antimicrobial prophylaxis is feasible, realistic, and has the advantage of decreasing hospital budgets and lowering microbial resistance [44].

Overall, most studies have used intravenous cephalosporins, intravenous ampicillin-sulbactam, or oral amoxicillin-clavulanate as well as potentially metronidazole as antibiotic prophylaxis to cover GP, GN, and anaerobic invading pathogens and reduce SSIs by 3-25% [36]. However, the chosen antibiotic for prophylaxis will depend on local resistance patterns as well as cost issues where pertinent [13, 51]. A key consideration is also the length of prophylaxis with studies undertaken in Africa suggesting extended use postoperatively, which is not recommended [13, 47, 48, 50]. The instigation of antimicrobial

stewardship programs and monitoring of antibiotic usage against agreed guidance can help to address such issues including the nature and extent of prophylaxis to prevent SSIs [97-101].

2.5 METHODS TO REDUCE SURGICAL SITE INFECTIONS

Multiple prevention strategies need to be deployed to prevent SSIs. These include careful meticulous operative procedures, the prudent selection of prophylactic antimicrobials and timely administration [2, 4], and a variety of procedures aimed to offset the threat of bacterial, viral, and fungal contamination posed by operative staff, the operating room environment, and the patient's endogenous skin flora [83]. Microorganisms normally colonize on the skin surface and exposed tissues, and when the skin is incised, they can multiply and lead to SSIs. Consequently, any procedures that reduce the number of microbes on the skin near the surgical wound will lower the threat of SSIs. The bacterial flora on the skin includes fleeting microbes that are acquired through contact and resident flora that can be removed by washing with soap [102]. A thorough soap and water shower on the day of surgery effectively removes transient microorganisms [102]. Alcohol or chlorhexidine and povidone-iodine preoperative painting around the surgical area also eradicates inhabitant microbes located in deep crevices and hair follicles. Chlorhexidine has a persistent suppressive effect against microbial regrowth on the skin, and whilst alcohol kills microorganisms quickly, it does not physically remove organic material. Consequently, alcohol use alone is not recommended when the surgeon's hands or the surgical area are visibly soiled [102].

Several randomized control trials have scrutinized the practice of preoperative hair removal and its relation to SSIs. A Cochrane review established no significant variance in SSIs between patients who have had hair removed prior to surgery and those who have not [103]. Three research studies comprising 625 patients evaluating hair removal using either hair removal cream, or razors, with no hair removal, found no statistically significant difference between the groups in terms of SSIs, like the Cochrane review [104]. Interestingly, studies comparing clipping with shaving, involving 3193 patients, found that there were statistically significantly more SSIs when people were shaved rather than clipped [RR 2.02, 95%CI 1.21 to 3.36] [104-106]. However, seven studies involving 1420 patients comparing shaving with hair removing cream also found no statistically significant difference between the two groups in SSIs rates [107-113]. Several studies revealed no scientific basis for shaving and no statistically significant benefit achieved in shaving patients in terms of reducing the number of SSIs [114, 115]. A further systematic review regarding neurosurgery and shaving comprising 21 studies involving 11,071

patients also concluded that preoperative shaving does not reduce the occurrence of SSIs [116] [~~97~~]. In addition, not only does shaving not reduce the risk of SSIs but shaving (as opposed to clipping) has been shown to increase SSI rates [103-108]. This has led to surgical teams removing hair with clippers and not razors and just before surgery and not the previous evening [6, 117, 118]. It is thought that the microscopic cuts and abrasions resulting from shaving disrupt the skin's natural protective mechanism against microorganism colonization and that the appropriate use of clippers does not damage the patient's skin, which retains its natural protective defense mechanism and help prevent SSIs [82].

SSIs can develop not only from the patient's own natural flora but also from the unintentional transmission of pathogens from surgeons and surgical staff to patients [82]. Preoperative hand sterilization by the whole surgical team is consequently a vital line of attack to prevent SSIs. Multiple types of hand sterilizers and processes are used including hand washing with non-medicated or antimicrobial soap and hand rubbing with alcohol-based hand sanitizers. These approaches are accepted as appropriate to maintain hand hygiene in different countries to reduce SSIs [119]. However, any agents used in preoperative hand sterilizers' must meet specific standards to reduce antimicrobial activity [120-122].

Wearing sterile gloves is internationally considered as a primary barrier to the transfer of pathogens from doctors to patients, especially in the operating theatre. Nevertheless, sterile gloves alone cannot reduce transmission 100% [82]. Moreover, gloves can have microscopic or macroscopic perforations which can go unnoticed during surgery and lead to the transmission of pathogens [88, 123, 124]. One study regarding glove perforation revealed that the overall SSI rate was 4.5% [125]. Univariate logistic regression analyses presented a higher possibility of SSIs where the surgical team had perforated gloves when compared with interventions with maintained total asepsis [OR, 2.0; 95% CL, 1.4-2.8; $p<0.001$] [125]. Conversely, multivariate logistic regression analyses specified that a higher rate of SSIs risk with punctured gloves was different for procedures with vs. those without surgical antimicrobial prophylaxis ($p=0.005$) [125]. A perforated glove combined with no antimicrobial prophylaxis causes significantly higher odds of SSIs compared with the reference group with complete asepsis [adjusted OR, 4.2; 95% CI, 1.7-10.8; $p=0.003$] [125]. When preventive antibiotics were utilized, the probability of SSIs was not significantly higher for surgeries conducted with punctured gloves [adjusted OR, 1.3; 95% CI, 0.9-1.9; $p=0.26$] or not [125]. Multiple studies have suggested double sterile gloving as the most effective strategy to decrease the incidence of glove perforation and transmission of pathogens from the surgical team to patients and vice versa [103, 126-128].

Overall SSIs are the most frequently occurring HCAIs, increasing both morbidity, mortality, and increasing healthcare cost especially in LMICs as well as significant liability in high income countries. It has been reported that SSIs are often preventable, but the nature of these infections is highly multifarious and requires the incorporation of multiple efforts throughout the perioperative period. In this regard, the World Health Organization (WHO) has developed wide-ranging guidelines that can be utilized internationally [129, 130]. The Center for Disease Control and Prevention (CDC) has also developed very comprehensive guidelines to increase patient benefit and safeguard human life [131] to guide future care.

2.6 ANTIMICROBIAL RESISTANCE in SURGICAL SITE INFECTIONS

Evaluation of resistance patterns is key to selecting the most appropriate antibiotic in the hospital to prevent SSIs [36]. In addition to earlier findings (Section 2.2), one recent study conducted in Romania revealed that the most predominant microbial species identified were *Staphylococcus aureus* (50.72%), followed by *Escherichia coli* (17.22%) and *Pseudomonas aeruginosa* (10.05%), with glucose-non-fermenting, GN bacteria, and other *Enterobacteriaceae* identified at lower fractions [132]. The topmost resistant microbes were the non-fermenting GN rods. *Escherichia coli* showed lower resistance to the 3rd generation cephalosporins, quinolones, and carbapenems [132]. On the other hand, as *Klebsiella* produces carbapenemase enzyme, it was resistant to cephalosporins, penicillins, and carbapenems [129]. Usually, non-fermenters are extremely resistant to several antimicrobials, but polymyxin E was found effective against these pathogens [132]. *Staphylococcus aureus* was resistant to ceftriaxone (100%), penicillin (91.36%), amoxicillin plus clavulanic acid (87.50%), amikacin (80.00%) and was sensitive to levofloxacin, doxycycline, gentamycin, tigecycline and teicoplanin [132]. *Enterobacteriaceae*, especially in the Intensive Care Unit (ICU), showed higher resistance particularly to the carbapenems (imipenem, 31.20% in the ICU vs. 14.30% in the surgical wards; risk ratio=2.182) [132]. Another recent study conducted in Nepal reported that *Staphylococcus aureus* (47.4%) was most frequent invading pathogen followed by *Escherichia coli* (20.60 %), *Coagulase-negative staphylococci* (5.7%), *Acinetobacter spp*. (5.2%), *Klebsiella spp.* (5.15%), *Proteus mirabilis* (3.1%), *Pseudomonas spp.* (2.1%), *Aeromonas hydrophilia* (1.5%), *Enterococcus spp.* (2.6%), *Streptococcus spp.* (1.5%) and *Morganella morgani* (1%) [122] [~~103~~]. Other organisms identified were *Burkholderia spp*., *Erwinia spp*., *Aerococcus spp.*, *Corynebacterium spp*., and *Enterobacter spp*., and were >1% each of total pathogens [133]. The most effective antimicrobials for the GP isolates were amikacin (93.1%) followed by chloramphenicol (92.6%), piperacillin/tazobactam (86.2%), clindamycin (81.7%) and gentamicin (79.6% and amikacin (81.8%)

[130]. Imipenem (81.8%) was identified to be the antibiotic of choice for GN bacterial wound isolates followed by gentamicin (73.0%), piperacillin/tazobactam (72.2%) and meropenem (60.7%) [131]. The most effective antibiotics against *Staphylococcus aureus* were chloramphenicol (97.6%), followed by amikacin (97.3%), piperacillin/tazobactam (88.2%), clindamycin (87.0%) and gentamicin (82.0%) [133]. The Multidrug-resistant (MDR) microorganisms were *Staphylococcus aureus* (38.0%), *Escherichia coli* (40.0%), *Pseudomonas aeruginosa* (25.0%), *Klebsiella spp.* (20.0%), *Acinetobacter complex* (70%), *Proteus mirabilis* (16.7%), *Coagulase-negative staphylococci* (27.3%), *Enterococcus spp.* (80%), *Streptococcus spp*. (33.3%) and others (66.7%) [133].

Another study conducted in the US found that *Staphylococcus aureus* and *Pseudomonas aeruginosa* were the most frequently identified pathogens [134]. Other invading microorganisms were *Streptococcus, Escherichia coli, Klebsiella pneumoniae, Enterococcus, MRSA, Enterobacter aerogenes, Corynebacterium, Peptostreptococcus, and Prevotella melaningenica*. The study also revealed that gentamicin, tobramycin, meropenem, and sulfamethoxazole plus trimethoprim were the most sensitive against the laboratory identified pathogens [88]. Additionally, most postoperative SSIs were resistant to clindamycin and ampicillin-sulbactam which were frequently prescribed for prevention of infection [134] [~~115~~]. Consequently, it is imperative that the chosen antibiotic(s) for prophylaxis is selected based on local resistance patterns as well as cost issues [13, 51].

3 CONCLUSIONS

In general, whilst no statistically significant difference exists between the five-year survival rate of patients with SSIs and without SSIs after HNCS, several other factors need to be considered to help reduce SSIs as they cause stress and discomfort to patients and prolong hospital stay. These factors include the patients' previous history of chemoradiotherapy; advanced stages of carcinoma; smokers; patients with other comorbidities, and those requiring reconstructive surgery [135, 136]. Additionally, clipping is preferable to shaving, and otolaryngology surgeons need to select appropriate antimicrobials for perioperative prophylaxis [36]. Finally, more research is needed to reduce SSIs in patients with HNCS to identify invading pathogens, select appropriate antimicrobials and develop safer surgical procedures to reduce morbidity and increase survival rate. In addition, the extent of the use of excessive post-operative antibiotics should be decreased (especially in LMICs) to reduce future resistance development.

EXPERT COMMENTARY

Globally the HNCS prevalence rate is increasing, and still surgery is the treatment of choice [24-27]. HNSCC is the fifth most common cancer worldwide, with around 600,000 newly diagnosed cases added per year, and has the eighth common cause cancer-related mortality [29-31]. Consumption of alcohol, tobacco, betel-nut, and HPV-16 are considered as the principal risk factors for cancers of the oral cavity, larynx, oropharynx, tonsils, the base of tongue and hypopharynx and accounts for 75-80% of HNSCC [58, 62, 65-67]. SSIs are particularly prevalent in patients undergoing surgery for HNCS, with between 10-38% developing SSIs [3]. The preoperative risk factors associated with SSIs were associated with the location of the tumor; the stage of the tumor; smoking; alcohol habits; diabetes; history of prior radiotherapy or chemotherapy; anemia; hypoalbuminemia; mandible cutting; flap reconstruction; tracheotomy; clean-contaminated wounds; blood transfusions, and duration of surgery [74]. Multiple multivariate analyses found that the independent risk factors for developing SSIs were oral cavity cancer, a history of prior radiotherapy, tracheotomy, clean-contaminated wounds, blood loss, previous chemotherapy, the type of surgery, operative time, mandibulectomy, low preoperative albumin levels, and oro-neck communication [72, 74-76]. Similarly, multiple univariate analysis identified that the perioperative risk factors of hemorrhage; earlier instigation of cancer medicines; clean-contaminated surgery; tracheotomy; malignant tumor; advanced T-stage; flap reconstruction, diabetes, preoperative serum albumin level, and duration of operation prolonged time for surgery were also statistically significantly related to SSIs [72,75]. The presence of co-morbidities; poor nutritional status; low preoperative albumin levels; advanced age; increased body-mass-index; previous radiotherapy; significant blood loss during surgery and smoking also increases SSI rates [39]. Additionally, discriminant analysis and multiple logistic regression methods identified pre-surgical tracheostomy, previous surgery and length of pre-operative hospital stay as the most significant risk factors for SSIs [77]. *Staphylococcus aureus* was the commonest pathogen followed by *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Enterococcus, Proteus, Morganella morgani* and *Citrobacter* species [54, 78, 79, 81]. Most of these were *Staphylococcus aureus* MRSA [78].

Many surgical interventions of HNCS breach the mucosal lining, causing exposure to the mucosal flora of the upper aerodigestive tract and the consequent microbial contamination of surgical wounds may lead to poor prognosis [75, 82, 83]. Multiple earlier research studies found that the precautionary use of antimicrobials decreased the rate of SSIs and improved the prognosis by reducing postoperative morbidity, hospital stay, and healthcare costs [62, 84-86]. However, antimicrobial prophylaxis does not

always prevent an SSI and is often responsible for the development of resistant microorganisms. Antimicrobial prophylaxis should, therefore, be avoided where possible [39, 83, 89]. Multiple studies report that the SSI rate was high despite routine POPAB for inpatients having surgery for HNCS [90-92], however POPAB has now become standard practice [85]. Multiple regimens of POPAB have been developed against SSIs of HNCS [92]. A more recent study using multifactorial analysis found a statistically significantly less probability of developing SSI in patients with HNCS and surgery [93]. A systematic review and meta-analysis found that that patients receiving free flap reconstruction who had antimicrobials for more than 24 hours had more SSI than those receiving them for less 24 hours [94]. Another study failed to find any statistically significant differences between four different antimicrobial regimes [93]. Overall, most studies have used intravenous cephalosporins, intravenous ampicillin-sulbactam, or oral amoxicillin-clavulanate or metronidazole as antibiotic prophylaxis to cover GP, GN, and anaerobic invading pathogens and reduce SSIs by 3-25% [39].

The chosen antibiotic for prophylaxis will depend on local resistance patterns as well as cost issues where pertinent [14, 28]. Evaluation of resistance patterns is key to selecting the most appropriate antibiotic in the hospital setting to prevent SSIs [39]. Multiple prevention strategies need to be deployed to prevent SSIs. These include careful meticulous operative procedures, the prudent selection of prophylactic antimicrobials and timely administration [2, 4], and a variety of procedures aimed to offset the threat of bacterial, viral, and fungal contamination posed by operative staff, the operating room environment, and the patient's endogenous skin flora [83]. In this regard, the World Health Organization (WHO) has developed wide-ranging guidelines that can be utilized internationally [129, 130]. The Center for Disease Control and Prevention (CDC) has also developed comprehensive care guidelines to help reduce morbidity and mortality [131]. In general, whilst no statistically significant differences exist between the five-year survival rate of patients with SSIs and without SSIs after HNCS, several other factors need to be considered to help reduce SSIs as they cause stress and discomfort to patients and prolong hospital stay. These factors include the patients' previous history of chemoradiotherapy; advanced stages of carcinoma; smokers; patients with other comorbidities, and those requiring reconstructive surgery [135, 136]. Finally, more research is needed to reduce SSIs in patients with HNCS to identify invading pathogens, select appropriate antimicrobials and develop safer surgical procedures to reduce morbidity and increase survival rate. In addition, the extent of the use of excessive post-operative antibiotics should be decreased (especially in LMICs) to reduce future resistance development. The application of appropriate infection prevention and control strategies can reduce the risk of SSIs, as

most of them are preventable. High rates of inappropriate Infection prevention and control measures including incorrect use of prophylactic antibiotics continue to be reported in the literature. It is obviously important to improve patient safety by reducing the occurrence of SSIs especially in LMICS where less resources to treat them are available. This review aims to focus on the need for proper prevention of SSIs of the head and neck cancer surgery especially in high risk patients and summarize the best practices to reduce them.

FIVE-YEAR VIEW

SSIs remain a major clinical problem in terms of morbidity, mortality, length of hospital stay and overall direct and not-direct costs in all regions of the world. Both the WHO and the CDC have recently published guidelines for the prevention of SSIs. However, despite clear evidence and guidelines to direct SSIs, knowledge, attitude, and awareness of infection prevention and control (IPC) measures among surgeons are often inadequate. Raising the awareness of IPC measures to stakeholders is a crucial factor in changing behaviors. We hope that in the next few years there will be a greater awareness of this problem.

KEY ISSUES

- Head and Neck cancers are increasing in lower and middle-income countries, largely due to increased tobacco and alcohol consumption
- Surgical site infections (SSIs) are a common postoperative complication of head and neck surgery
- SSIs cause distress to patients, longer hospital stays and higher healthcare costs, delayed recovery and increased morbidity
- A number of risk factors need to be addressed which contribute towards increased SSIs, including co-morbidities, increased age, and previous chemoradiotherapy
- Pre-operative and postoperative antimicrobials can help reduce infection but must be selected and used appropriately in line with current research evidence on their effectiveness and duration to help reduce resistance

DECLARATION

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COMPETING INTERESTS

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