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REVIEW

Surgical wound complications after heart transplantation

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Summary

Surgical wound complications are more frequent in patients undergoing heart transplantation than in other heart surgery patients. This is probably attributed to the presence of additional risk factors in these patients, such as immunosuppression, mechanical support through assist devices and generally poor health. Analyses of wound infections in heart transplantation are based on smaller patient population than those for general heart surgery, and the reported incidences vary largely. The identification of specific risk factors in heart transplant recipients to date is mainly based on retrospective case–control studies in small patient cohorts, the results are controversial, and the comparability of data is limited because of the lack of application of consistent definitions. The impact of immunosuppression and especially immunosuppression with mammalian target of rapamycin (mTOR) inhibitors on the development of surgical wound complications has been widely discussed following reports of increased occurrence with sirolimus. However, nonheart-transplant specific risk factors should also be considered to develop risk profiles and treatment algorithms for individual patients. Data on surgical wound complications in general heart surgery patients and in heart transplant recipients are compared, the impact of modern immunosuppression reviewed, and areas for further investigation discussed.

Introduction

The improvement of surgical techniques, close patient monitoring, and the introduction of powerful immunosuppressive regimens have continuously increased the survival rates in heart transplantation (HTx) over the last 20 years [1]. However, some complications after HTx are still of concern and may even show a higher occurrence with the use of potent immunosuppressive regimens.

Surgical wound complications (SWC) after HTx, such as sternal wound infections, continue to be an important issue because of the possible complications of mediastinitis and sternal dehiscence. These complications can cause devastating and often life-threatening conditions that require early diagnosis and intervention [2,3]. Heart transplant recipients not only exhibit such severe conditions more often than patients undergoing conventional heart surgeries [4], but they are also more difficult to diagnose because immunosuppression alters the leukocyte response. In addition, treatment of SWC needs to consider the particulars of the immunosuppressive regimens.

After the first years of broader use of mammalian target of rapamycin (mTOR) inhibitors in HTx, reports of an increased occurrence of SWC raised concerns that their efficacy came with a price [5–7]. The purpose of this review is to compare the incidence and risk factors for SWC reported in heart transplant recipients, including the impact of different immunosuppressive regimens, with those of patients undergoing other cardiac surgeries.

Classification of SWC observed after heart surgery

Heart surgery procedures involving sternotomy, such as coronary artery bypass grafting, most valve procedures, ventricular assist device (VAD) placement, and HTx, have the risk of sternal wound infection in common. According to the U.S. Centers for Disease Control and Classifications (CDC) [8], the infection of surgical wounds after

sternotomy can be classified as (i) superficial; (ii) deep, depending on whether only the skin and subcutaneous tissue or deeper tissue layers are involved; or (iii) organ/space infections if the sternum and/or retrosternal space are involved, and the infection exhibits sternal osteomyelitis or mediastinitis. Sternum dehiscence can be a consequence of massive infection spreading to the sternal bone or may occur without infection, especially in severely obese patients [9].

Incidence of SWC in general cardiac surgery and heart transplantation

The incidence of SWC in general cardiac surgery ranges from 0.5% [10] to 10% [11], with the majority of more recent reports mentioning a rate well below 5% [12–14]. Superficial wound infections are reported with incidences of up to 8% [11,14,15] and deep wound infections with incidences of up to approximately 2% [11,15–18]. Mediastinitis occurs in <2% of patients in general heart surgery; [11,12,19,20] however, mortality resulting from sternal wound infections is as high as 35% [13]. Sternal dehiscence is reported with an incidence of 3% to 8% [9,18].

In heart transplant recipients, SWC have been observed in 8% to 15% of patients, [4,21,22] but much higher incidences of up to 40% [5] have also been reported. Superficial wound infections range from 3.9% to 16% of heart transplant recipients [5,21]. Deep wound infections, including mediastinitis, are reported with incidences of 2.4% to 35% [5,21,23–25]. Sternal dehiscence occurs in 12.5% to 25% of heart transplant recipients [7,26,27].

In the majority of reports from general heart surgery and HTx, Gram-positive microorganisms, especially Staphylococcus aureus, often methicillin-resistant, were isolated from the infected sternal wounds [4,14] as well as *Enterococcus faecalis*. Furthermore, instances of Gram-negative organisms, such as *Escherichia coli* and *Acinetobacter*, were also reported [25,28]. Notably, a higher incidence of fungal wound infections was described after HTx compared with other cardiac surgeries [23,28,29].

Risk factors for SWC in general heart surgery and heart transplantation

Risk factors for SWC, namely deep surgical wound infections and mediastinitis, in general heart surgery, which were confirmed in multivariate analyses of sufficiently large datasets and identified in at least two reports, include preoperative diabetes [11,20,30–33], use of bilateral internal mammary arteries [31–34], re-exploration [10,32], increased body mass index or obesity [11,14,20,34,35] as well as duration of stay in the intensive care unit [20,30] (Table 1).

Logistic regression analyses for the identification of independent risk factors of SWC in HTx are generally performed in much smaller patient samples than the analyses of other cardiac surgeries. The samples were sometimes too small to allow multivariate analysis, and only univariate analysis results were presented. An overview of the identified risk factors is given in Table 2.

In 2001, Carrier *et al.* [21] found only recipient age to be a significant independent risk factor for surgical wound infections in an analysis of 226 heart transplant recipients, whereas diabetes and the use of mycophenolic acid versus azathioprine and antithymocyte globulin were not related. The mean duration of mechanical ventilation and the use of VADs were identified as significant predictors for mediastinitis in a retrospective case control study with 15 cases and 30 controls performed by Senechal *et al.* [24] In 2005, Zucker *et al.* [6] reported that treatment with sirolimus in combination with tacrolimus, preoperative left VAD support, and rabbit antithymocyte globulin induction therapy were associated with a higher risk of mediastinitis, although this had only been tested by univariate analysis. Kuppahally *et al.* partly confirmed this in a set of 94 patients by identifying treatment with sirolimus compared with mycophenolate mofetil (MMF) as well as cardiopulmonary bypass time to be independent risk factors for the development of any wound complication, including superficial and deep wound infections as well as pericardial effusions [5]. Confirmation of VAD as a potential risk factor for deep surgical wound infections was provided by Filsoufi *et al.* [25] who also reported preoperative inotropic support, BMI > 30 kg/m^2, and previous heart surgery as further risk factors in a univariate analysis performed in a cohort of 149 heart transplant recipients. A more recent risk factor analysis by Ramos *et al.* found only the use of antibiotic prophylactic treatment with ciprofloxacin to be a significant risk factor for surgical wound infections. None of the immunosuppressive regimens used in their series of 292 heart transplant recipients, such as mycophenolic acid with or without cyclosporine A (CsA) or basiliximab, were found to be related to an increased risk of SWC. However, several relevant factors like BMI or mechanical circulatory assistance had not been analyzed [28]. We performed a retrospective analysis of data from three clinical studies in 1007 *de novo* heart transplant recipients who received immunosuppressive regimens based on everolimus, azathioprine, or MMF. In our analysis, BMI, pretransplant diabetes mellitus, and male gender of the recipient were associated with an increased risk of SWC. However, only BMI was a highly significant independent risk factor for SWC in the multivariate analysis [36].

Table 1. Independent risk factors for surgical wound complications identified by multivariate analysis in general cardiac surgery.

Risk factor	Odds ratio	Outcome studied	Patient number	Author	Year
Increased body mass	1.5	DSWI	9303	Gummert *et al.* [20]	2002
index/obesity	2.7	DSWI/mediastinitis	3008	Ridderstolpe *et al.* [11]	2001
	3.4	DSWI	1980	Olsen *et al.* [35]	2002
	1	Mediastinitis	1700	Diez *et al.* [34]	2007
	2.4	DSWI/SSWI	493	Centofanti *et al.* [14]	2007
Diabetes	2.1	DSWI	9303	Gummert *et al.* [20]	2002
	2.4	DSWI/SSWI	11 508	Kohli *et al.* [30]	2003
	2.9	DSWI/mediastinitis	3008	Ridderstolpe *et al.* [11]	2001
	2.6	DSWI	12 267	Borger *et al.* [31]	1998
	2.9	DSWI	1980	Olsen *et al.* [35]	2002
	2.5	DSWI	30 102	Tang *et al.* [32]	2004
	3.1	DSWI/mediastinitis	809	Paul *et al.* [13]	2007
	5.5	DSWI	3760	Toumpoulis *et al.* [33]	2005
	4.3	DSWI/SSWI	493	Centofanti *et al.* [14]	2007
Use of bilateral internal	12.5	DSWI	9303	Gummert *et al.* [20]	2002
mammary arteries	4.2	DSWI/mediastinitis	3008	Ridderstolpe *et al.* [11]	2001
	3.2	Mediastinitis	1700	Diez *et al.* [34]	2007
	2.6	DSWI	3760	Toumpoulis *et al.* [33]	2005
Use of internal	2.8	DSWI	9303	Gummert *et al.* [20]	2002
mammary arteries	3.2	DSWI/SSWI	11 508	Kohli *et al.* [30]	2003
	1.8	DSWI/SSWI	1268	Lepelletier *et al.* [4]	2005
Reoperation	1.8	DSWI	9303	Gummert *et al.* [20]	2002
	5.6	DSWI/SSWI	493	Centofanti *et al.* [14]	2007
	3.1	DSWI/SSWI	1268	Lepelletier *et al.* [4]	2005
	13.4	DSWI/SSWI	9201	Salehi *et al.* [10]	2007
Chronic obstructive	3.5	DSWI/mediastinitis	809	Paul *et al.* [13]	2007
pulmonary disease	3.3	Mediastinitis	1700	Diez *et al.* [34]	2007
Intensive care unit	4.2	DSWI	9303	Gummert *et al.* [20]	2002
treatment: Longer than 5 days/longer than 3 days	5.4	DSWI/SSWI	11 508	Kohli *et al.* [30]	2003

DSWI, deep surgical wound infection; SSWI, superficial surgical wound infection.

In summary, data on independent risk factors for SWC in HTx are more limited and controversial than similar data for general cardiac surgery. It can be assumed that the commonly described risk factors for SWC in general cardiac surgery, such as diabetes, reoperation, and increased BMI, are also of relevance in HTx. In addition, the specifics of HTx add risk factors – such as immunosuppression in general, specific immunosuppressive regimens, and a generally poorer state of health of the patients who are often hospitalized for an extended time before receiving the allograft, frequently present with renal insufficiency, and often depend on mechanical circulatory support as a bridge to transplantation. VAD has been identified as a risk factor for wound infections in heart transplant recipients in three reports [6,24,25]. Infections of the VAD pocket are occasionally seen and their eradication is often difficult. Patients with VAD may bear a higher risk for subsequent surgical wound infections after HTx because of intraoperative spread of the infection [37].

The role of immunosuppression

Several reports on kidney transplant recipients associate any kind of immunosuppression with a risk for SWC. In fact, an increased incidence was observed with more potent immunosuppressive drugs. A higher incidence was seen for MMF in combination with calcineurin inhibitors and steroids rather than with azathioprine [38]. Steroids are known to impact the wound healing process at various stages [39], and thymoglobulin induction has also been related to an increased risk of wound complications [40].

Lately, mTOR inhibitors, i.e. sirolimus and its derivate everolimus, have been introduced as potent immunosuppressants for use in kidney and heart transplantation. The antiproliferative action of mTOR inhibitors affects not only T cells but also endothelial cells, fibroblasts, smooth muscle cells, and several tumor cell types. The sirolimus and everolimus target, the mTOR protein, plays an important role in angiogenesis and cell proliferation [41],

Table 2. Risk factors for surgical wound complications identified by univariate or multivariate analysis in heart transplant recipients.

Author	Patient number/study design	Outcome variable	Risk factor	Odds ratio	95% Confidence intervals	*P*-value
Carrier *et al.* [21]	226/retrospective chart review, single center	Sternal wound infection	Recipient age*	1.08	1.05–1.1	N/A
Senechal *et al.* [24]	45 (15 cases, 30 control)/ retrospective, case control, single center	Mediastinitis	Ventricular assist device			<0.04
			Duration of mechanical ventilation			<0.03
Kuppahally *et al.* [5]	94 (48 sirolimus, 46 MMF)/retrospective chart review, case control, single center	Any wound complication (including effusions)	Recipient BMI	1.1.05	1.004–1.216	0.041
			Nonwhite recipient	2.683	1.038–6.936	0.042
			Sirolimus*	3.077	1.139–8.311	0.027
			Cardiopulmonary bypass time (min)*	1.011	1.000–1.022	0.048
Ramos *et al.* [28]	292/prospective, multicenter, online database	Incisional surgical complications	Ciprofloxacin prophylaxis*	15.8	1.1–216.9	0.039
			Extracorporeal circulation time >2 h	3.3	0.8–13.5	0.102
Filsoufi *et al.* [25]	149/retrospective, cohort study, single center	Deep sternal wound infection	BMI > 30 kg/m^2			0.02
			Previous heart surgery			0.028
			Previous VAD			0.006
			VAD pocket infection			<0.001
			Hemodynamic instability			0.044
Zucker *et al.* [6]	56/retrospective, case control, single center	Mediastinitis	Inclusion in treatment group (ATG/tacrolimus/sirolimus)			0.02
			LVAD support			0.03
			Use of ATG induction			0.03
Barten *et al.* [36]	1007 (710 everolimus, 214 azathioprine, 83 MMF)/retrospective pooled analysis of safety database from three randomized multicenter studies	Incisional surgical wound complications	Male recipient	1.504	0.875–2.585	0.14
			History of diabetes	1.507	0.975–2.328	0.065
			Recipient BMI*	1.128	1.08–1.18	<0.001

MMF, mycophenolate mofetil; LVAD, left ventricular assist device.
*Confirmation as an independent risk factor in multivariate analysis.

and its inhibition is likely to have a negative effect on wound healing. T cells residing in skin play a role in early wound repair, and sirolimus inhibited proliferation, migration, and growth factor production of these cells in mice experiments [42]. In rat models, sirolimus interfered with different stages of the wound healing process by decreasing the number of inflammatory cells, affecting angiogenesis, as well as the proliferation of myofibroblasts [41,43]. Sirolimus as well as everolimus delayed the wound healing process and decreased the tensile strength of the wound [43–45].

Everolimus has an additional 2-hydroxyethyl chain substitution at position 40 of the sirolimus molecule and shows a slightly better bioavailability than sirolimus as well as a shorter half-life of approximately 24–35 h compared to 60 h for sirolimus [46]. Besides these pharmacokinetic differences, everolimus and sirolimus have been reported to show a different mitochondrial distribution in rats [47,48]. Sirolimus was reported to increase the CsA-induced inhibition of glucose metabolism, whereas everolimus seems to antagonize this process [49], thereby indicating that the two mTOR inhibitors may also have different pharmacodynamic effects.

Adverse effects on wound healing have been reported for both mTOR inhibitors. A significantly higher incidence of SWC was seen in kidney transplant recipients who received sirolimus compared with MMF-based immunosuppression [50]. The Symphony study, performed on 1645 *de novo* kidney transplant recipients, also showed a higher rate of wound healing complications in the patients receiving sirolimus in combination with low-dose CsA and MMF (17%) compared with the study arms not using sirolimus (9%–11%) [51]. A higher rate of wound healing complications with everolimus

was reported in a randomized study of 833 *de novo* kidney transplant recipients in the two everolimus groups (C0 3–8 ng/ml: 35.0% and C0 6–10 ng/ml: 38.8%) compared with the control group receiving enteric-coated mycophenolate sodium (25.6%) [52]. Logistic regression analyses identified sirolimus as an independent risk factor for wound complications in kidney transplant recipients [40,53]; however, there are also reports from analyses in which this association could not be confirmed [54,55].

Incidence of SWC in heart transplant recipients treated with mTOR inhibitors

Only a small number of randomized clinical trials in heart transplant recipients reported details on the incidence of SWC, thereby impacting the assessment of the true effect of different immunosuppressive regimens.

A randomized, open-label, 12-month study of 136 *de novo* heart transplant recipients compared sirolimus with azathioprine in combination with CsA and steroids. Patients received a sirolimus loading dose followed by a maintenance dose to reach target trough levels of 1–30 ng/ml. Later in the study, because of concerns regarding nephrotoxicity and wound healing, both the sirolimus loading dose and the maintenance dose were reduced (C0: 8–18 ng/ml). Abnormal healing was reported in 14.7% and 1.8% of patients receiving 3 mg and 5 mg sirolimus, respectively, compared to 4.7% in the azathioprine group. Delayed sternal healing was reported for five patients in the sirolimus 3 mg arm, but all events occurred at one study center and were associated with high sirolimus exposure [26].

A second study, involving 343 *de novo* heart transplant recipients, compared a regimen of tacrolimus and sirolimus to tacrolimus and MMF or CsA and MMF in addition to corticosteroids. Impaired wound healing was reported in significantly more patients receiving the tacrolimus/sirolimus combination (23.4%) compared to 10.2% and 12.3% of the patients in the tacrolimus/MMF and CsA/MMF groups [22].

Everolimus was investigated in 634 *de novo* heart transplant recipients to compare two fixed doses of everolimus to azathioprine in combination with CsA and corticosteroids in a 24-month, randomized, double-blind multicenter study. The study reported an incidence of wound infection in 6.7% and 5.2% of patients in the 1.5 mg and 3 mg everolimus groups, respectively, compared to 3.3% in azathioprine-treated patients [56].

A later study with everolimus in 176 heart transplant recipients aimed to compare trough-level-controlled everolimus (C0: 3–8 ng/ml) and a reduced regimen of CsA with MMF plus a standard dose regimen of CsA. This randomized, multicenter, open-label study reported a comparable incidence of postoperative wound infections for everolimus (6.6%) and MMF (8.6%) [57].

Several retrospective cohort studies describe SWC in heart transplant recipients treated with mTOR inhibitors. Zucker *et al.* [6] compared 31 heart transplant recipients who received sirolimus in combination with tacrolimus and low-dose rabbit antithymocyte globulin and steroids with a cohort of 25 control patients who received CsA, MMF, and steroids. Patients received a sirolimus loading dose on day 3 postsurgery followed by 2 mg and 5 mg daily for maintenance therapy. Later in the study, loading doses for sirolimus were no longer used, and the starting dose was reduced to 1 mg/day and adjusted to trough levels of 8–12 ng/ml. Superficial wound infections were reported in 32.2% of the sirolimus-treated patients compared to 10% in the control group, but the difference was not significant. Mediastinitis was reported for a significantly higher proportion of patients in the sirolimus group (23.4%) versus none of the patients in the control group.

A pilot study to investigate calcineurin-inhibitor-free immunosuppression in eight *de novo* heart transplant recipients tested the treatment combination of sirolimus and MMF with steroids. The authors reported one case of delayed sternal wound healing requiring operative sternal refixation [58].

In 2006, Kuppahally *et al.* [5] corroborated these findings by reporting a higher incidence of post-SWC in *de novo* heart transplant recipients receiving sirolimus compared with MMF. They performed a single-center, retrospective hospital chart analysis including 48 patients exposed to sirolimus at a dose of 1–3 mg/day, without a loading dose, to reach a 24-h trough level of 5–10 ng/ml in combination with reduced-exposure CsA. The control group included 36 patients treated with an average MMF dose of 500–1000 mg twice a day with standard-exposure CsA. All patients received induction therapy with interleukin-2 receptor antibodies and steroids. A significantly higher incidence of wound complications was reported for the sirolimus group (58%) compared with the MMF group (28%, $P = 0.019$). Moreover, deep wound complications were noted in a higher proportion of patients in the sirolimus group than in the MMF group (35% vs. 13%, $P = 0.012$). These complications included mediastinitis with an incidence of 27% in the sirolimus group and 13% in the MMF group. The relatively high rate of mediastinitis in the MMF group is considerable when compared with the incidence observed by Carrier *et al.* [21] of 3% in a retrospective evaluation of 226 heart transplant recipients. The authors did not compare this incidence rate with the general incidence rate of mediastinitis postsurgery at their site [5].

Zakliczynski *et al.* [7] performed a retrospective analysis to determine the influence of sirolimus on SWC in 28 *de novo* heart transplant recipients treated with sirolimus and compared them to a historical control of 28 patients receiving 3 mg/kg azathioprine and CsA. In the sirolimus group, 20 patients received a loading dose of 15 mg sirolimus prior to operation, followed by 10 mg on day 1 postsurgery, and thereafter 5 mg sirolimus to target trough levels of 12–20 ng/ml. A total of eight patients received a regimen of azathioprine with sirolimus. All patients received corticosteroids. Sternum instability was observed in 25% of patients in the sirolimus group compared with none of the patients in the control group. No cases of mediastinitis or superficial wound infection were observed, which the authors suggest may be a possible effect of not using induction therapy in contrast to the previously reported treatments by Zucker *et al.* [6] and Kuppahally *et al.* [5].

An analysis of 28 *de novo* heart transplant recipients reported a higher incidence of SWC in patients treated with the mTOR inhibitors everolimus and sirolimus compared with the control group treated with MMF and CsA. Two patients in the mTOR inhibitor group developed sternal dehiscence compared with none of the patients in the control group (22.2% vs. 0%, $P = 0.09$). One patient on everolimus required sternal reopening because of suspected mediastinitis [27].

In our retrospective pooled analysis of 1007 *de novo* heart transplant recipients, SWC occurred in 8.9% of azathioprine, 7.2% of MMF, and 11.1% of everolimus patients. Wound infection was the most frequent event, observed in 7.0% azathioprine, 7.2% MMF, and 8.2% everolimus patients. Mediastinal infection was reported for 0.6% of heart transplant recipients in the azathioprine group compared with no events in the MMF-treated patients, and 0.6% in the everolimus group [36,59].

The pharmacokinetic and possible pharmacodynamic differences between the two mTOR inhibitors might also result in different adverse event profiles, thereby perhaps explaining lower rates of SWC reported for everolimus compared with sirolimus. However, the use of higher sirolimus doses as well as loading doses in the first years of sirolimus introduction might also have initially contributed to more reports of wound complications. Only one study of 56 heart transplant recipients compared the adverse event profiles of the two mTOR inhibitors directly, concluding that significantly fewer infections were reported with everolimus than sirolimus. However, no details on the nature of infection were provided [60]. No ongoing clinical study is comparing the two mTOR inhibitors, everolimus and sirolimus, directly in a larger patient group – a comparison that would help to clarify the question of clinically different adverse event profiles.

Diagnosis of SWC in heart transplant recipients

Symptoms of mediastinitis can differ in heart transplant recipients compared with patients with other heart surgeries. Immunosuppression including corticosteroids can change the typical signs of infection, e.g. fever and leukocytosis, and local signs such as erythema and purulent wound discharge might be absent [61]. Senechal *et al.* [24] as well as Filsoufi *et al.* [25] reported that fever, defined as temperature >38 °C, was only present in approximately 30% and leukocytosis only in approximately 40% of the cases of deep SWCs and mediastinitis. Senechal *et al.* reported chest pain in disproportion to sternotomy as the most frequent symptom, with an incidence of 60%, whereas erythema and/or purulent discharge were observed in only 33% of the mediastinitis cases. In computer tomography (CT) scans, Filsoufi *et al.* observed mediastinal air or fluid collections in 60% of patients with deep SWC. A chest CT scan should therefore support the diagnosis if clinical signs are inconclusive and CT-guided needle aspiration may be helpful to confirm the diagnosis [61].

In recipients of a heart transplant, especially those who indicate additional risk factors for wound complications, a high level of caution is warranted. A multidisciplinary team should be involved proactively to apply the appropriate diagnostic tools and to enable an early diagnosis of mediastinitis.

Management of SWC after heart transplantation

There is consensus that, after the initial diagnosis of mediastinitis, immediate aggressive surgical management is essential and that surgical debridement, including radical excision of necrotic tissue, must occur [21,23–25]. Apart from this initial action, the recommended options for optimal surgical management differ. Abid *et al.* [23] report early aggressive debridement followed by substernal iodine irrigation and primary sternal closure as preferred intervention, whereas Senechal *et al.* [24] report best results with closed drainage in a series of 15 patients with mediastinitis after HTx. Filsoufi *et al.* [25] followed an open-chest management protocol involving aggressive debridement of necrotic tissue and vacuum-assisted drainage accompanied by at least 6 weeks of intravenous antibiotic treatment. Vacuum-assisted drainage was safe and effective as first-line therapy in the management of sternal wounds in a series of 103 heart surgery patients including 64% of patients with mediastinitis [62] and achieved also good results in heart transplant recipients [63].

It has been recommended not to use mTOR inhibitors for 3–7 days post-transplantation to avoid adverse effects during the initial wound healing phase [64,65]. Consequently, for patients who must undergo a later surgical procedure, the mTOR inhibitor dose has been reduced or discontinued until the operation wound has healed [66].

Evidence from clinical studies for these recommendations is, however, still lacking. The Callisto study in renal transplant recipients did not show any effect of the delayed introduction of everolimus (start at week 5 post-transplantation) on the incidence of wound healing complications [67]. The EVERHEART study (NCT01017029) will address this question in approximately 200 heart transplant recipients by comparing the effect of an early versus delayed onset of everolimus or MMF on the incidence of wound healing complications. Results are expected in late 2011. The results of an ongoing trial of everolimus versus MMF in 717 heart transplant recipients (NCT00300274) will provide further insight into the incidence of wound complications in heart transplant recipients via the collection of wound complication-specific data.

Documentation of SWC in adverse event reporting

The comparability of SWC data also suffers from differences in the definitions used or the lack of any specific definition in clinical studies. The future design of clinical studies comparing immunosuppressive regimens post-HTx should consider the introduction of specific case report forms to capture detailed information on SWC events. We propose an algorithm (Fig. 1) applying definitions from CDC/NHSN [8], which can help to develop standardized data collection tools for these events. The algorithm will allow differentiation of sternal and nonsternal wound complications and will provide sufficient details to allow the categorization of events into superficial and deep surgical wound infections and mediastinitis as well as allow the collection of information on the management of the complications.

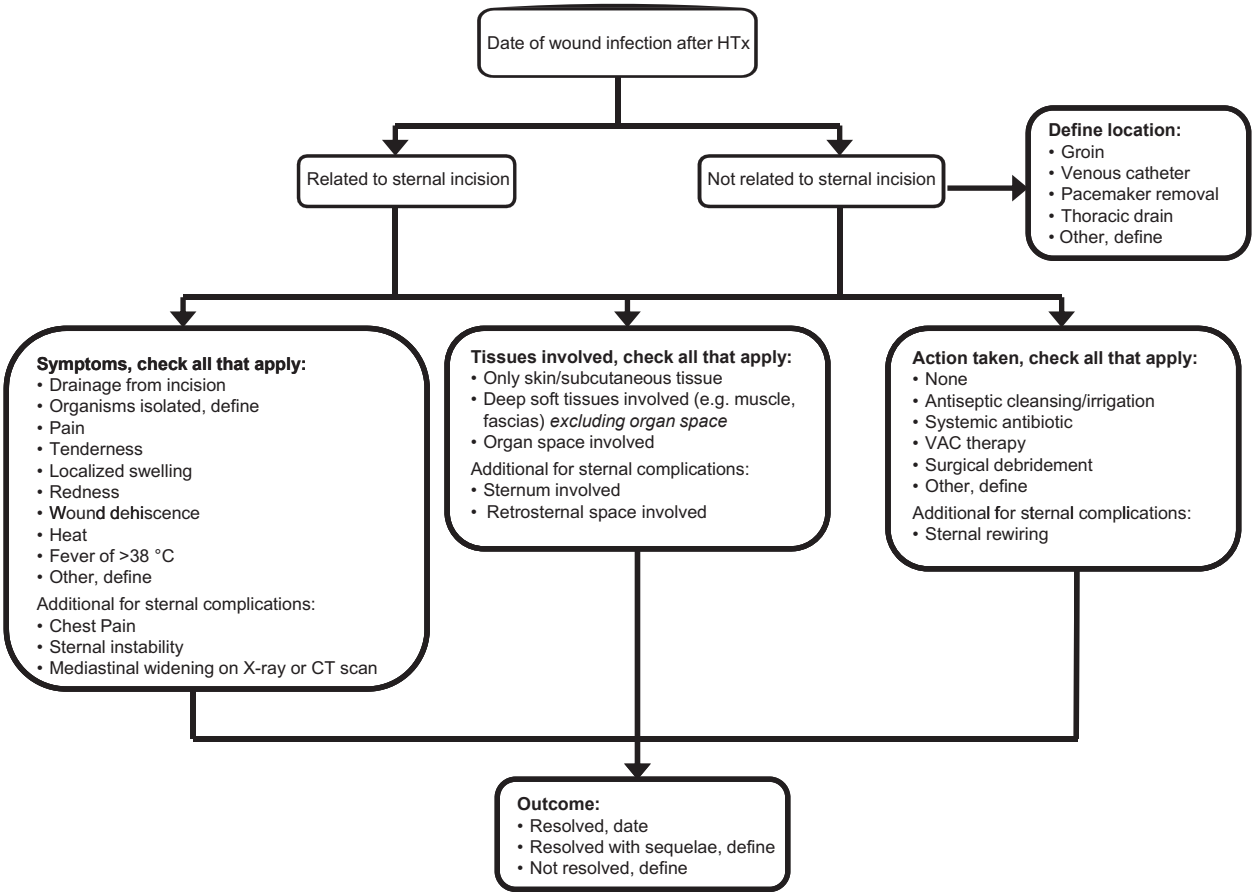

Figure 1 Algorithm for reporting surgical wound complications in heart transplant recipients in clinical studies.

Summary and conclusions

At present, there are no sufficient data available to confirm independent risk factors for SWC, including the risk of specific immunosuppressive regimens in heart transplant recipients. An adverse effect of mTOR inhibition on surgical wound healing needs to be considered in the clinical management of patients. However, current recommendations are not sufficiently evidence-based in a heart transplant setting. Confirmatory information needs to come either from studies using large databases, such as the International Society for Heart and Lung Transplantation (ISHLT) registry, or from analyses of sufficiently powered randomized clinical trials with a focus on the collection of information on wound complication adverse events.

Until such additional data are available, we recommend an approach based on the evidence from general cardiac surgery, analyses of heart transplant recipients, and current knowledge of the use of mTOR inhibitors in solid organ transplantation. If the patient has been supported by VAD, or is obese, diabetic, or in need of re-exploration, a higher risk of SWCs exists, and the introduction of an mTOR inhibitor should be delayed until wound healing has been satisfactorily completed.

All patients receiving a heart transplant should be monitored for signs of wound infection; taking into account that immunosuppression might change the presentation of signs and symptoms of severe infection. Patients should be educated about the increased risk and possible signs of wound infection. Early and sufficiently aggressive intervention is needed to detect as well as to treat severe wound infections.

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