Association between elevated pre-operative glycosylated hemoglobin and post-operative infections after non-emergent surgery

Joseph M. Blankush [a, b], I. Michael Leitman [a, b, *], Aron Soleiman [a, b], Trung Tran [a, b]

[a] Department of Surgery, Mount Sinai Beth Israel, United States
[b] Department of Surgery, Icahn School of Medicine at Mount Sinai, United States

H I G H L I G H T S

- This study reviews the impact of pre-operative HbA1c across many specialties undergoing elective surgery.
- The risk factors of post-operative infection are multiple and likely synergistic.
- Elevated serum HbA1c is not independently associated with an increased risk of post-operative infection.

A R T I C L E   I N F O

A B S T R A C T

Background: A chronic state of impaired glucose metabolism affects multiple components of the immune system, possibly leading to an increased incidence of post-operative infections. Such infections increase morbidity, length of stay, and overall cost. This study evaluates the correlation between elevated pre-operative glycosylated hemoglobin (HbA1c) and post-operative infections.
Study design: Adult patients undergoing non-emergent procedures across all surgical subspecialties from January 2010 to July 2014 had a preoperative HbA1c measured as part of their routine pre-surgical assessment. 2200 patient charts (1100 < 6.5% HbA1c and 1100 ≥ 6.5% HbA1c) were reviewed for evidence of post-operative infection (superficial surgical site infection, deep wound/surgical space abscess, pneumonia, and/or urinary tract infection as defined by Centers for Disease Control criteria) within 30 days of surgery.
Results: Patients with HbA1c < 6.5% and those with HbA1c ≥ 6.5% showed no statistically significant difference in overall infection rate (3.8% in the HbA1c < 6.5% group vs. 4.5% in the HbA1c ≥ 6.5% group, p = 0.39). Both linear regression and multivariate analysis did not identify HbA1c as an individual predictor of infection. Elevated HbA1c was, however, predictive of significantly increased risk of post-operative infection when associated with increased age (≥81 years of age) or dirty wounds.
Conclusions: The risk factors of post-operative infection are multiple and likely synergistic. While pre-operative HbA1c level is not independently associated with risk of post-operative infection, there are scenarios and patient subgroups where pre-operative HbA1c is useful in predicting an increased risk of infectious complications in the post-operative period.

1. Introduction

Studies have suggested that pre-existing diabetes mellitus (DM) and hyperglycemia are predictors of post-operative complications in patients undergoing cardiac, bariatric, vascular, orthopedic and colorectal surgery [1–5]. Commonly, these complications are infectious in etiology, with superficial surgical site infections (SSIs), deep wound infections and surgical space abscesses, urinary tract infections (UTIs), and pneumonia (PNA) accounting for a large percentage of these infectious complications [6].

It has also been suggested that optimizing a patient's pre-operative glycemic control (<7% glycosylated hemoglobin) may reduce post-operative infections in non-cardiac surgery patients [7]. And while tight post-operative control of a patient's blood glucose has been shown to reduce the incidence of infectious complications in post-operative patients, a review of pre- and post-

* Corresponding author. Department of Surgery, Mount Sinai Beth Israel, 10 Union Square East, 2M, New York, NY, 10003, United States.
E-mail address: Michael.Leitman@mssm.edu (I.M. Leitman).

operative glycemic control protocols concluded that there is still insufficient evidence to determine what role strict glycemic control plays in reducing SSIs and other relevant post-operative infections [8–10]. Subsequently, there continues to be some uncertainty regarding the risk of infection associated with patients with a known history of diabetes and derangements in peri-operative blood glucose levels and what should be done in the pre- and post-operative period to mitigate these risk factors.

A challenge often cited in determining the effectiveness of any protocol to optimize blood glucose is the transient nature of hyperglycemia and the multiplicity of factors and events that may influence blood glucose levels, especially in the post-operative period [11]. Alternatively, there has been long-standing interest in the use of glycosylated hemoglobin (HbA1c) levels for screening and the identification of patients with impaired glucose metabolism and diabetes mellitus (DM). In June 2009, an International Expert Committee issued a consensus report recommending that a HbA1c level greater than or equal to 6.5% be used to diagnose diabetes mellitus, and the American Diabetes Associated affirmed this recommendation [12].

What is known is that post-operative infections across all patient subtypes and surgical specialties increase morbidity, length of stay, and overall cost [13,14]. Additionally, there is evidence demonstrating that a chronic state of impaired glucose metabolism weakens multiple components of the immune system, and it has been postulated that these impairments of the immune system may contribute to the development of post-operative infections [15–17].

The present study was designed to assess the correlation between pre-operative HbA1c and the incidence of post-operative infections in surgical patients undergoing non-emergent operations. Our hypotheses were: diabetic patients (defined as those with a HbA1c $\geq$ 6.5%) are at increased risk of post-operative infection; elevated HbA1c is an independent risk factor for post-operative infections and higher pre-operative levels are associated with increased risk; and if HbA1c is not an independent risk factor, there are specific patient groups and/or scenarios where an elevated HbA1c increases the likelihood of a patient developing a post-operative infection.

2. Methods

This study was reviewed and approved by the Human Research Committee of the Institutional Review Board at Mount Sinai Beth Israel (IRB #178-14) as a retrospective study. Beginning in January of 2010, adult patients undergoing non-emergent procedures had a pre-operative serum hemoglobin A1c (HbA1c) level included in the routine pre-operative testing performed for each patient. Patients included in the study were those undergoing general surgery including vascular, orthopedic, gynecology, otolaryngology, urology, plastic surgery, ophthalmology, and neurosurgery procedures. Patients undergoing both inpatient and outpatient procedures were included.

That national rate of surgical site infection published by the Centers for Disease Control (CDC) of 1.9% across all surgical procedures, assuming a large percentage of elective procedures with clean wounds, was used as a hypothesized rate of infection seen in non-diabetic (pre-operative HbA1c < 6.5%) individuals presenting for non-emergent surgery. From previously published studies reporting the increased rates of SSI, UTI, and PNA in patients with DM (about a two-fold increase), we hypothesized a rate of infection near 4% for patients with a pre-operative HbA1c $\geq$ 6.5% and used these hypothesized rates in our power analysis before beginning this study [18,19].

Assuming 80% power, the hypothesized rates of infection

suggested that 1100 patients in each of the <6.5% HbA1c group and the $\geq$6.5% group would be needed to appropriately compare the two groups and be able to draw valid comparative conclusions. Subsequently, the first 1100 consecutive patients in each group to undergo non-emergent surgery were recorded and included in the medical record review and analysis.

Charts were reviewed for details of the procedure, post-operative course, and evidence of post-operative infection during the 30 days following surgery. Pre-operative white blood cell count was also recorded and patient charts were reviewed for evidence of pre-existing infection. Patients believed to have had a pre-existing, pre-operative infection were excluded from the analysis. Also, if an attending physician acted on his or her own to optimize a patient's pre-operative HbA1c prior to the procedure, only the most recent pre-operative HbA1c was considered for this analysis.

Operative reports were reviewed and each procedure was assigned to a wound classification of either clean, clean/contaminated, contaminated, or dirty [20]. Recognizing the wide range of procedures within each surgical specialty, procedures were also grouped into low, medium, and high surgical risk classification according to the Modified Johns Hopkins Surgical Criteria [21,22].

Patient charts were further reviewed for evidence of post-operative infection in the 30 days following their procedure using the CDC criteria for nosocomial infections, specifically surgical site infection including both superficial and deep wound infection/surgical space abscess, urinary tract infection, and pneumonia [23,24]. Surgical site infection was considered positive with either the isolation of an organism in an aseptically collected culture or with documented purulence, pain, redness, tenderness, and/or swelling and suspicion of surgical site infection upon physical exam. Pneumonia was considered present with physical examination findings, including the onset of purulent sputum, consistent with PNA and the initiation of treatment for PNA and/or the isolation of pathogen from a sputum sample. PNA was also considered present if focal consolidation was identified on radiographic imaging. UTI required documented symptoms of UTI (either fever, urgency, frequency, dysuria, suprapubic tenderness) along with a positive urinalysis and/or positive urine cultures with 10^5 colony-forming units of no more than two different organisms. Deep wound/surgical space abscess required isolation of cultured organism upon drainage or re-operation.

Statistical analysis was performed using Stata release 14.0 (StataCorp (2015) *Stata Statistical Software: Release 14*. College Station, TX) and R Version 3.2.0 (The R Foundation for Statistical Computing (2015). Vienna, Austria). The overall impact of the effect of each of the major predictor variables was evaluated using logistic regression. The presence of any type of infection (SSI, deep wound infection/surgical space abscess, UTI, PNA) was modeled as a binary outcome against gender, wound type, surgical risk classification, age in years, and preoperative HbA1c [25].

3. Results

Medical record review and statistical analysis was completed for 2200 patients. In both groups, the vast majority of the procedures were classified as clean wounds (Table 1). Orthopedic procedures made up 69% of the procedures in the <6.5% group and 60% of the procedures in the $\geq$6.5% group. Other surgical services were generally equally represented between the two groups with the <6.5% group having a higher number of gynecologic surgery procedures and the $\geq$6.5% group having a much higher number of vascular procedures. The group with HbA1c $\geq$ 6.5% included significantly higher numbers of high-risk procedures, many of which were vascular operations. The higher number of moderate risk procedures in the <6.5% group was mostly due to the higher

Table 1
Comparison of demographics risk classification, wound classification, and procedure types between each HbA1c sub-group.

Demographic category	HbA1c < 6.5% N = 1100	HbA1c ≥ 6.5% N = 1100
Surgical risk classification		
- Low	568 (52%)	468 (43%)
- Moderate	498 (45%)	398 (36%)
- High	34 (3%)	234 (21%)
Surgical wound classification		
- Clean	1034 (94%)	1000 (91%)
- Clean/Contaminated	54 (5%)	70 (6%)
- Contaminated	0 (0%)	3 (0.3%)
- Dirty	12 (1%)	27 (2%)
Surgical service		
- Orthopedic	759 (69%)	665 (60%)*
- Gynecology	138 (13%)	43 (4%)*
- General	86 (8%)	109 (10%)
- Otolaryngology	49 (4%)	41 (4%)
- Vascular	27 (2%)	172 (16%)
- Urology	19 (2%)	49 (4%)
- Plastics	9 (1%)	12 (1%)
- Ophthalmology	9 (1%)	0 (0%)
- Neurosurgery	4 (0.4%)	9 (1%)

*$p < 0.05$.

number of gynecologic procedures in that group. These differences were statistically significant.

The overall rate of infection across the 2200 patients was 4.2%. Statistical analysis comparing the groups of patients with HbA1c < 6.5% and those with HbA1c ≥ 6.5% showed no statistically significant difference in the overall infection rates (3.8% in the HbA1c < 6.5% group vs. 4.5% in the HbA1c ≥ 6.5% group, $p = 0.39$) or significant difference in the individual types of infections (Table 2).

Linear regression analysis indicated no significant correlation between elevated pre-operative HbA1c level and post-operative infections overall or for any of the specific types of infection assessed in the study. However, among the study cohort increasing age was found to be an independent risk factor for post-operative infection with a patient's risk increasing about 2% per year above the mean age of the study cohort of 51 years of age (Table 3).

As expected, wound classification (clean, clean/contaminated, contaminated, dirty) was also found to be independently associated with a higher risk of post-operative infection. A wound classification of clean/contaminated (OR 2.04; 95% CI 1.02–4.09; $p < 0.05$) or dirty (OR 12.59; 95% CI 5.77–27.46; $p < 0.001$) was significantly more likely to result in a post-operative infection compared to a clean wound. Additionally, moderate-risk (OR 1.84; 95% IC 1.09–3.10; $p < 0.05$) and high-risk (OR 2.57; 95% CI 1.34–4.92, $p < 0.005$) procedures were statistically more likely to be associated with a post-operative, infectious complication (Table 3).

Subgroup analysis indicated that an elevated HbA1c is predictive of a significantly higher risk of post-operative infection when associated with increased age or dirty wounds (Fig. 1). More specifically, if a patient's wound is classified as either clean, clean/contaminated, or contaminated and the patient is 81 years of age or older, then there is a significantly increased risk of infection in a patient with a HbA1c of 7.5% or greater (infection rate of 27% compared to the overall infection rate of 4.2%, $p < 0.05$). Additionally, if a patient's wound is classified as dirty and the patient has a pre-operative HbA1c of 8.0% or greater, then there is a significantly increased risk of post-operative infection (56% rate of infection compared with 4%, $p < 0.05$), Table 4.

4. Discussion

Among surgical patients in the United States, approximately 9–30% of patients acquire a nosocomial infection [26]. Surgical site infections are second only to UTI across all patients and account for 37% of hospital acquired infections in post-operative patients with an incidence of 1.9% among the 16 million patients undergoing surgical procedures in the US each year [27]. The impact of SSIs alone on morbidity and mortality, not to mention UTI and PNA, is substantial. SSIs increase the post-operative length of stay by 7–10 days, and in patients with an SSI, mortality rates reach as high as 3% with 75% of these deaths directly attributable to complications that arise from the SSI itself [28]. Additionally, post-operative infections are costly. An SSI, for example, has been shown to increase cost by $20,785 on a per-case basis while a single UTI increases cost by about $896 [14].

There is clear value in determining, prior to elective surgery, which patients might be at the highest risk for an infectious, post-operative complication and if there are modifiable, pre-operative risk factors. To date, many efforts have been aimed at identifying single variables applied across all patients and procedure-types, which might guide a surgeon in determining if the post-operative risk outweighs the inherent benefit of a planned procedure, but results have been mixed. Some studies have shown, for example, that patients with elevated HbA1c, a history of DM, and/or pre-operative hyperglycemia have higher rates of infection post-operatively, and many surgeons will recount anecdotally that patients with DM simply do not fair as well in the post-operative course as non-diabetic patients [29–31].

Multiple studies of glycemic control protocols in the pre-operative phase as well as the immediate post-operative period have contributed a great deal to our understanding of the potential role that glycemic control can play in modifying post-operative outcomes, yet these studies have been unable to establish a pre- or post-operative regimen that ideally reduces post-operative infectious complications. Furthermore, tight glycemic control, initially a promising strategy to reduce post-operative morbidity and mortality, has largely been abandoned in favor of more moderate blood glucose control protocols applied across all post-operative patients, as large scale analyses have shown that moderate control limits post-op morbidity, but neither tight nor moderate control contributed to a reduction in post-operative infectious complications [9,32]. Still, some continue to assert that tight glycemic control is beneficial in certain populations [33].

The present study suggests that elevated pre-operative HbA1c is not an independent indicator of post-operative infection risk. The study data further suggests that other characteristics of the patient

Table 2
Comparison of incidence of infection between HbA1c sub-groups.

Type of post-operative infection	HbA1c < 6.5% N = 1100	HbA1c ≥ 6.5% N = 1100	p-value
Surgical Site Infection	21 (1.9%)	30 (2.7%)	0.20
Urinary Tract Infection	20 (1.8%)	18 (1.6%)	0.74
Pneumonia	4 (0.4%)	6 (0.5%)	0.53
Deep Wound Infection/Surgical Space Abscess	3 (0.2%)	2 (0.2%)	0.65
Total patients with 1 or more infection	42 (3.8%)	50 (4.5%)	0.39

Table 3
Statistical analysis of pre-operative predictors of post-operative infection.

| Potential pre-operative predictor of post- operative infection	Odds ratio	95% confidence interval	p-Value
Gender			
- Male	1.01	0.65–1.56	p = 0.98
Wound (vs. clean wound)			
- Clean/Contaminated	2.04	1.02–4.09	p < 0.05
- Dirty	12.59	5.77–27.46	p < 0.001
Surgical risk (vs. low risk)			
- Moderate	1.84	1.09–3.10	p < 0.05
- High	2.57	1.34–4.92	p < 0.005
Age (linear regression analysis)	1.02	1.01–1.04	p < 0.005
Hemoglobin A1c (linear regression analysis)	0.93	0.80–1.07	p = 0.313
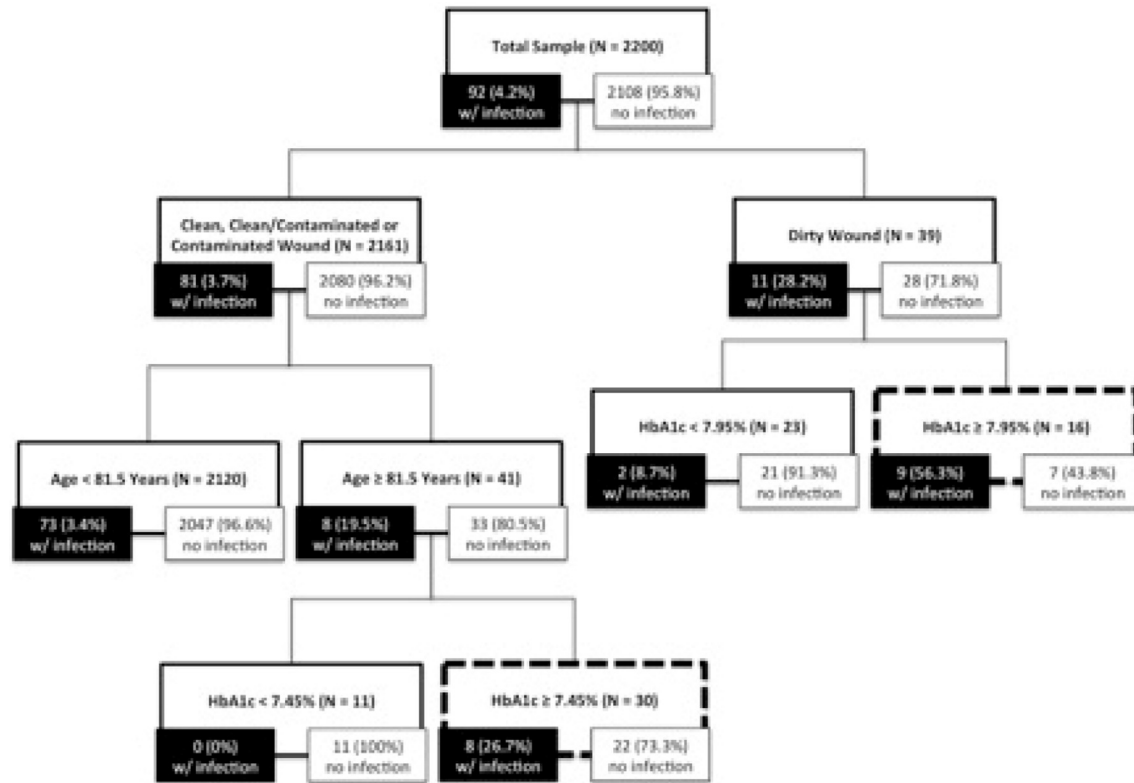
Fig. 1. Recursive partitioning decision tree. Parent node represents all 2200 patients included in the study. All cut points in the figure represent a level of a given predictor that portends a statistically significant (p < 0.05) difference in the rate of post-operative infection at that specified cut point.

and the procedure – age, surgical risk classification, and wound classification – have stronger predictive value than HbA1c alone but that elevated HbA1c does have a predictive capacity when applied to specific patient subgroups.

The multiplicity of outcomes from various studies for assessing pre-operative risk factors of infection such as blood glucose and HbA1c, including the present study, is likely due to the association of multiple risk factors that contribute to a patient's risk of post-operative infection [34].

With a rate of 4.2% in this study, a post-operative infection is a relatively infrequent event but also one that could lead to significant morbidity and increased cost. Surgeons might be reluctant to

Table 4
Patients where specific elevation of pre-operative HbA1c portends statistically significant (p < 0.05) increase in risk of post-operative infection.

Procedure risk classification	Wound type	Age	HbA1c	Rate of infection
All procedures	Dirty	All ages	≥8.0%	56%
All procedures	Clean, Clean/Contaminated, Contaminated	Age ≥81 years	≥7.5%	27%
Low Risk	Clean	Age ≥69 years	≥7.1%	24%
Low Risk	Clean	Age ≥69 years	≥8.1%	64%
Moderate Risk	Dirty	All ages	≥6.9%	60%
High Risk	Clean	Age <68 years	≥10.8%	22%
High Risk	Clean	Age ≥68 years	≥6.6%	21%
High Risk	Clean	Age ≥68 years	≥8.1%	28%

delay elective procedures when the risk of post-operative infection is relatively low, so clinically impactful research and statistical analysis should be aimed at evaluating large numbers of surgical patients and identifying specific constellations of procedure, patient characteristics, and risk factors that represent a many-fold increase in post-operative infections. Data from the present study begins to show how this type of research and analysis could influence clinical practice.

In first identifying independent risk factors, wound classification has long been shown to be a predictor of post-operative infection, so it is no surprise that clean/contaminated and dirty wounds were predictive of increased risk of infection [20,35]. Furthermore, a prior study evaluating the effect of age on surgical site infections demonstrated that increasing age between 17 and 65 years of age carried a 1.1% greater risk of SSI per year while increasing age over 65 years was actually associated with 1.2% decrease in risk per year [36]. Results from another study suggest that the risk continues to increase throughout a patient's life [37]. The present study suggests that increasing age is both an independent predictor of post-operative infection as well as a component of a constellation of predictive variables when combined with pre-operative HbA1c level, wound classification, and surgical risk classification.

While multivariate analysis demonstrated that HbA1c was not an individual predictor of post-operative infectious complication, subgroup analysis identified a cohort of patients where an elevated pre-operative HbA1c did correlate with an increased risk of post-operative infection. Patients with a dirty wound and a pre-operative HbA1c of 8.0% or greater appear to be more likely to develop a post-operative infection, and surveillance for infectious complication should be greater for these patients in the post-operative period. Similarly, older patients (81 years of age or older) with clean, clean/contaminated, or contaminated wounds and a pre-operative HbA1c of 7.5% or greater are at increased risk to suffer a post-operative infectious complication at a rate of slightly greater than 1 in 4.

It may be impractical to postpone most procedures with dirty wounds in order to optimize pre-operative risk factors, but surgeons can use the present study to plan accordingly and discuss this with patients and their families. Subgroup analysis identified other clinically relevant patient cohorts with a risk of infection well above the overall incidence of 4.2%. These represent cases in which the surgeon might elect to optimize a patient's HbA1c prior to surgery, and this study provides statistically significant levels of HbA1c where the infection risk is significantly lower.

The work done with the American College of Surgeons NSQIP surgical risk calculator provides some direction in developing assessment tools to evaluate multifactorial risk [38]. The list of single, modifiable risk factors that definitively portend a high post-operative infection risk is small, and rarely would a surgeon decide to delay a procedure based on a single risk factor. However, consideration of a combination of factors should provide helpful information and potentially more definitive direction as to whether or not to proceed with non-emergent surgery.

We recognize several limitations in the present study. The study was purposefully broad in its inclusion criteria, essentially capturing all patients undergoing non-emergent procedures. As we have highlighted in the discussion, there are likely to be differences for subsets of surgical procedures that will be the subject of future review. We recognize the limitation that there are differences between the two population groups. Our power analysis allowed us to calculate a sufficient sample size to detect a difference if one were to exist. The prediction model and outcomes were similar and therefore we have confidence in the finding that preoperative HbA1c was not predictive for the development of post-operative

infection. A review of specific procedures or patient populations may result in different conclusions when assessing pre-operative HbA1c and the risk of post-operative infections. We believe this is the first paper to examine a large enough patient cohort to be able to evaluate whether or not HbA1c specifically and independently influences post-operative infection rates in elective operations.

5. Conclusions

Risk factors of post-operative infectious complication are multifactorial, likely synergistic, and affect some patient populations differently. The present study shows that while pre-operative HbA1c level is not independently associated with the risk of post-operative infection, there are scenarios and patient subgroups where pre-operative HbA1c level is useful in predicting increased risk of infectious complications in the post-operative period. Future study should be aimed at recording, analyzing, and identifying other combinations of patient subgroups and perioperative conditions that act in concert and in doing so are predictive of post-operative infection. Assessing these risk factors accordingly will likely assist surgeons in more readily identifying the patient at highest risk of post-operative infection.

Author contribution

Study conception and design: Blankush, Leitman.
Acquisition of data: Blankush, Soleiman, Tran.
Analysis and interpretation of data: Leitman, Blankush.
Drafting of manuscript: Blankush, Leitman.
Critical revision: Leitman.

Guarantor

Michael Leitman.

References

[1] T. Alserius, R.E. Anderson, N. Hammar, T. Nordqvist, T. Ivert, Elevated glyco-sylated haemoglobin (HbA1c) is a risk marker in coronary artery bypass surgery, Scand. Cardiovasc J. 42 (2008) 392–398.

[2] R.A. Perugini, R. Mason, D.R. Czerniach, Y.W. Novitsky, S. Baker, D.E. Litwin, J.J. Kelly, Predictors of complication and suboptimal weight loss after lapa-roscopic Roux-en-Y gastric bypass: a series of 188 patients, Arch. Surg. 138 (2003) 541–545 discussion 545–546.

[3] C.J. O'Sullivan, N. Hynes, B. Mahendran, E.J. Andrews, G. Avalos, S. Tawfik, A. Lowery, S. Sultan, Haemoglobin A1c (HbA1C) in non-diabetic and diabetic vascular patients. Is HbA1C an independent risk factor and predictor of

adverse outcome? Eur. J. Vasc. Endovasc. Surg. 32 (2006) 188–197.

[4] T. Hikata, A. Iwanami, N. Hosogane, K. Watanabe, K. Ishii, M. Nakamura, M. Kamata, Y. Toyama, M. Matsumoto, High preoperative hemoglobin A1c is a risk factor for surgical site infection after posterior thoracic and lumbar spinal instrumentation surgery, J. Orthop. Sci. 19 (2014) 223–228.

[5] U.O. Gustafsson, A. Thorell, M. Soop, O. Ljungqvist, J. Nygren, Haemoglobin A1c as a predictor of postoperative hyperglycaemia and complications after major colorectal surgery, Br. J. Surg. 96 (2009) 1358–1364.

[6] W.C. Wallace, M.E. Cinat, F. Nastanski, W.B. Gornick, S.E. Wilson, New epidemiology for postoperative nosocomial infections, Am. Surg. 66 (2000) 874–878.

[7] A.S. Dronge, M.F. Perkal, S. Kancir, J. Concato, M. Aslan, R.A. Rosenthal, Long-term glycemic control and postoperative infectious complications, Arch. Surg. 141 (2006) 375–380 discussion 380.

[8] A.N. Al-Niaimi, M. Ahmed, N. Burish, S.A. Chackmakchy, S. Seo, S. Rose, E. Hartenbach, D.M. Kushner, N. Safdar, L. Rice, et al., Intensive postoperative glucose control reduces the surgical site infection rates in gynecologic oncology patients, Gynecol. Oncol. 136 (2015) 71–76.

[9] G. van den Berghe, P. Wouters, F. Weekers, C. Verwaest, F. Bruyninckx, M. Schetz, D. Vlasselaers, P. Ferdinande, P. Lauwers, R. Bouillon, Intensive insulin therapy in critically ill patients, N. Engl. J. Med. 345 (2001) 1359–1367.

[10] L.S. Kao, D. Meeks, V.A. Moyer, K.P. Lally, Peri-operative glycaemic control regimens for preventing surgical site infections in adults, Cochrane Database Syst. Rev. (2009) CD006806.

[11] R.S. Jackson, R.L. Amdur, J.C. White, R.A. Macsata, Hyperglycemia is associated with increased risk of morbidity and mortality after colectomy for cancer, J. Am. Coll. Surg. 214 (2012) 68–80.

[12] American Diabetes A: Diagnosis and classification of diabetes mellitus, Diabetes Care 33 (Suppl 1) (2010) S62–S69.

[13] L.A. Herwaldt, J.J. Cullen, D. Scholz, P. French, M.B. Zimmerman, M.A. Pfaller, R.P. Wenzel, T.M. Perl, A prospective study of outcomes, healthcare resource utilization, and costs associated with postoperative nosocomial infections, Infect. Control Hosp. Epidemiol. 27 (2006) 1291–1298.

[14] E. Zimlichman, D. Henderson, O. Tamir, C. Franz, P. Song, C.K. Yamin, C. Keohane, C.R. Denham, D.W. Bates, Health care-associated infections: a meta-analysis of costs and financial impact on the US health care system, JAMA Intern Med. 173 (2013) 2039–2046.

[15] J.D. Bagdade, R.K. Root, R.J. Bulger, Impaired leukocyte function in patients with poorly controlled diabetes, Diabetes 23 (1974) 9–15.

[16] P.J. Hennessey, C.T. Black, R.J. Andrassy, Nonenzymatic glycosylation of immunoglobulin G impairs complement fixation, JPEN J. Parenter. Enter. Nutr. 15 (1991) 60–64.

[17] M. Qadan, E.B. Weller, S.A. Gardner, C. Maldonado, D.E. Fry, H.C. Polk Jr., Glucose and surgical sepsis: a study of underlying immunologic mechanisms, J. Am. Coll. Surg. 210 (2010) 966–974.

[18] T. Benfield, J.S. Jensen, B.G. Nordestgaard, Influence of diabetes and hyperglycaemia on infectious disease hospitalisation and outcome, Diabetologia 50 (2007) 549–554.

[19] P. Njomnang Soh, F. Vidal, E. Huyghe, P. Gourdy, J.M. Halimi, B. Bouhanick, Urinary and genital infections in patients with diabetes: how to diagnose and how to treat, Diabetes Metab. 42 (1) (2016 Feb) 16–24.

[20] F. Berard, J. Gandon, Postoperative wound infections: the influence of ultraviolet irradiation of the operating room and of various other factors, Ann. Surg. 160 (1964) 1–192.

[21] D.J. Anderson, L.F. Chen, D.J. Sexton, K.S. Kaye, Complex surgical site infections and the devilish details of risk adjustment: important implications for public reporting, Infect. Control Hosp. Epidemiol. 29 (2008) 941–946.

[22] A. Donati, M. Ruzzi, E. Adrario, P. Pelaia, F. Coluzzi, V. Gabbanelli, P. Pietropaoli, A new and feasible model for predicting operative risk, Br. J. Anaesth. 93 (2004) 393–399.

[23] J.S. Garner, W.R. Jarvis, T.G. Emori, T.C. Horan, J.M. Hughes, CDC definitions for nosocomial infections, Am. J. Infect. Control 1988 (16) (1988) 128–140.

[24] T.C. Horan, R.P. Gaynes, W.J. Martone, W.R. Jarvis, T.G. Emori, CDC definitions of nosocomial surgical site infections, 1992: a modification of CDC definitions of surgical wound infections, Am. J. Infect. Control 20 (1992) 271–274.

[25] L. Breiman, Classification and Regression Trees, Wadsworth International Group, Belmont, Calif., 1984.

[26] T.C. Horan, D.H. Culver, R.P. Gaynes, W.R. Jarvis, J.R. Edwards, C.R. Reid, Nosocomial infections in surgical patients in the United States, January 1986–June 1992. National nosocomial infections surveillance (NNIS) system, Infect. Control Hosp. Epidemiol. 14 (1993) 73–80.

[27] Y. Mu, J.R. Edwards, T.C. Horan, S.I. Berrios-Torres, S.K. Fridkin, Improving risk-adjusted measures of surgical site infection for the national healthcare safety network, Infect. Control Hosp. Epidemiol. 32 (2011) 970–986.

[28] S.S. Awad, Adherence to surgical care improvement project measures and post-operative surgical site infections, Surg. Infect. (Larchmt) 13 (2012) 234–237.

[29] J.M. Humphers, N. Shibuya, B.L. Fluhman, D. Jupiter, The impact of glycosylated hemoglobin and diabetes mellitus on wound-healing complications and infection after foot and ankle surgery, J. Am. Podiatr. Med. Assoc. 104 (2014) 320–329.

[30] H.S. Han, S.B. Kang, Relations between long-term glycemic control and post-operative wound and infectious complications after total knee arthroplasty in type 2 diabetics, Clin. Orthop. Surg. 5 (2013) 118–123.

[31] R. Wang, M.T. Panizales, M.S. Hudson, S.O. Rogers, J.L. Schnipper, Preoperative glucose as a screening tool in patients without diabetes, J. Surg. Res. 186 (2014) 371–378.

[32] B. Sathya, R. Davis, T. Taveira, H. Whitlatch, W.C. Wu, Intensity of peri-operative glycemic control and postoperative outcomes in patients with diabetes: a meta-analysis, Diabetes Res. Clin. Pract. 102 (2013) 8–15.

[33] B.B. Abdelmalak, M.C. Lansang, Revisiting tight glycemic control in perioperative and critically ill patients: when one size may not fit all, J. Clin. Anesth. 25 (2013) 499–507.

[34] R.G. Martindale, C.W. Deveney, Preoperative risk reduction: strategies to optimize outcomes, Surg. Clin. North Am. 93 (2013) 1041–1055.

[35] D.M. Cardo, P.S. Falk, C.G. Mayhall, Validation of surgical wound classification in the operating room, Infect. Control Hosp. Epidemiol. 14 (1993) 255–259.

[36] K.S. Kaye, K. Schmit, C. Pieper, R. Sloane, K.F. Caughlan, D.J. Sexton, K.E. Schmader, The effect of increasing age on the risk of surgical site infection, J. Infect. Dis. 191 (2005) 1056–1062.

[37] J.N. Bakkum-Gamez, S.C. Dowdy, B.J. Borah, L.R. Haas, A. Mariani, J.R. Martin, A.L. Weaver, M.E. McGree, W.A. Cliby, K.C. Podratz, Predictors and costs of surgical site infections in patients with endometrial cancer, Gynecol. Oncol. 130 (2013) 100–106.

[38] K.Y. Bilimoria, Y. Liu, J.L. Paruch, L. Zhou, T.E. Kmiecik, C.Y. Ko, M.E. Cohen, Development and evaluation of the universal ACS NSQIP surgical risk calculator: a decision aid and informed consent tool for patients and surgeons, J. Am. Coll. Surg. 217 (2013) 833–842 e831–833.