

Clinical practice guideline: evidence, recommendations and algorithm for the preoperative optimization of anemia, hyperglycemia and smoking

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Preoperative optimization has not been explored comprehensively in the surgical literature, as this responsibility has often been divided among surgery, anesthesia and medicine. We developed an evidence-based clinical practice guideline to summarize existing evidence and present diagnostic and treatment algorithms for use by surgeons caring for patients scheduled to undergo major elective surgery. We focus on 3 common comorbid conditions seen across surgical specialties — anemia, hyperglycemia and smoking — as these conditions increase complication rates in patients undergoing major surgery and can be optimized successfully as soon as 6–8 weeks before surgery. With the ability to address these conditions earlier in the patient journey, surgeons can positively affect patient outcomes. The aim of this guideline is to bring optimization in the preoperative period under the existing umbrella of evidence-based surgical care.

L'optimisation préopératoire n'a pas été explorée de manière exhaustive dans la littérature chirurgicale, car cette responsabilité a souvent été divisée entre la chirurgie, l'anesthésie et la médecine. Cette ligne directrice de pratique clinique fondée sur des données probantes a été conçue pour résumer les données existantes et présenter des algorithmes diagnostics et thérapeutiques relatifs à des comorbidités fréquentes chez les patients vus dans toutes les spécialités chirurgicales. L'accent a été placé sur l'optimisation préopératoire de l'anémie, de l'hyperglycémie et du tabagisme, étant donné que ces problèmes de santé accroissent le risque de complications chez les patients qui doivent subir une chirurgie majeure et qu'il est possible de les corriger en bonne partie dans les 6–8 semaines précédant la chirurgie. Or, si les chirurgiens arrivent à corriger ces problèmes de santé plus tôt dans le parcours des patients, ils pourraient améliorer leurs résultats. Le but de cette ligne directrice est que l'optimisation préopératoire soit intégrée à l'ensemble actuel des soins chirurgicaux fondés sur des données probantes.

For most of the 20th century, the focus of research in surgery was improvements in intraoperative technique, which led to major technical paradigm shifts exemplified by the evolution of transurethral resection of the prostate,¹ laparoscopic cholecystectomy,² endovascular aneurysm repair³ and total mesorectal excision for rectal cancer,⁴ among many others. The late 1990s and early 2000s marked a shift in surgical research toward the evidence-based management of patients in the perioperative period, beginning with the Enhanced Recovery After Surgery Group's systematic review of patients undergoing colorectal surgery.⁵ That publication introduced a new paradigm focused on the impact that standardized perioperative care could have on patient outcomes such as length of stay, postoperative pain and overall complication rates.^{6,7}

Although a large body of literature now exists to help guide the intraoperative and perioperative management of surgical patients, our working group believes that the preoperative period, which we define as the 8 weeks

preceding elective surgical procedures, is an area of inquiry that remains underexplored in surgical literature. This “orphan” period in the care of a surgical patient exists for many reasons. The preoperative period has not traditionally been the responsibility of any single clinical specialty, with care often divided among surgeons, anesthesiologists and internists. As a result, there is little in the way of a standardized, evidence-based approach to the identification and treatment of comorbid conditions that could be effectively optimized in the preoperative period to improve patient outcomes.

In this evidence-based clinical practice guideline, we summarize existing evidence and present diagnostic and treatment algorithms for use by surgeons caring for patients undergoing major elective surgery. We focus on 3 common comorbid conditions seen across surgical specialties — anemia, hyperglycemia and smoking — and present evidence of improved patient outcomes with optimization strategies started as soon as 6–8 weeks before surgery.

The evidence presented here points to a new paradigm shift in the way multidisciplinary teams care for patients undergoing elective surgery, bringing the preoperative period under the existing umbrella of evidence-based surgical care.

LITERATURE SEARCH

Our search strategy for anemia is presented in Appendix 1 (available at canjsurg.ca). A similar search strategy was used for hyperglycemia and for smoking, with lines 1 and 3 changed to reflect the different components. We determined the strength of recommendations and the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.⁸ Recommendations were developed by 2 reviewers for each subject area (anemia and diabetes: J.A.G. and T.M.Z., smoking: J.S. and J.A.G.). Disagreements were resolved by a third reviewer (H.M.).

ANEMIA

The prevalence of preoperative anemia is high. In 2 large studies of patients undergoing noncardiac surgery ($n = 319\,703$), preoperative anemia was identified in 28%–30% of patients across multiple specialties.^{9,10} In certain surgical specialties, the prevalence approaches half of all patients, as seen in colorectal surgery (40.4%–47.4%),^{11,12} orthopedic surgery (25%–44%)^{13–15} and urology (8%–45%).¹⁶ According to the World Health Organization (WHO), a prevalence of anemia greater than 40% in a population has severe health consequences, and, therefore, anemia should be an essential consideration in most surgical patients.¹⁷

The WHO defines anemia as a hemoglobin level less than 120 g/L in women and less than 130 g/L in men.^{18,19} These definitions have been validated by large population

studies examining mean hemoglobin values by age, race and sex.²⁰ A second definition of anemia is a hematocrit value less than 0.39 for both sexes, which has also been validated in large database studies.^{9,11} The WHO estimates a prevalence of anemia of 29.4% among all women of reproductive age,¹⁸ which makes anemia an underrecognized condition warranting consideration even in young, healthy populations.

Anemia may be caused by chronic inflammatory conditions, kidney disease, malnutrition, ongoing small-volume blood loss and iron deficiency. Iron-deficiency anemia (IDA) is widely accepted to be the most common cause, and, in a recent study of 3342 patients undergoing gynecologic, urologic, colorectal, cardiac or orthopedic surgery, almost two-thirds (62%) of patients with preoperative anemia had some component of IDA.²¹ In patients with cancer, chronic bleeding from gastrointestinal tumours can also contribute to preoperative anemia.^{22–24} Given the increased incidence of most surgical conditions with increasing age, the mean age of surgical patients is older than that of other cohorts and is associated with an increased prevalence of anemia.^{20,22} Unlike in the general population, the cause of anemia in older patients is multifactorial in almost two-thirds of cases.²⁵

Several centres have reported improved postsurgical outcomes through preoperative diagnosis of anemia and treatment plans. These outcomes include shorter length of hospital stay,^{15,26} decreased rates of postoperative nosocomial infections,²⁶ decreased 90-day readmission rates¹⁵ and lower rates of blood transfusion.^{15,26–28} The following clinical practice guideline summarizes the current evidence informing the recommendations within the proposed diagnostic and treatment algorithm for preoperative anemia (Figure 1).

Recommendations

1. Preoperative anemia is associated with adverse surgical outcomes, and all patients undergoing major surgery should be screened for anemia at their first surgical clinic visit and investigated further, as appropriate (Table 1).

Preoperative anemia was shown to be an independent risk factor associated with increased 1-year and overall mortality in 319 703 patients undergoing noncardiac surgery (adjusted hazard ratio [HR] 2.86, 95% confidence interval [CI] 2.56–3.20, and odds ratio [OR] 1.42, 95% CI 1.31–1.54, respectively).^{9,10} In a propensity-matched cohort of 7759 patients undergoing noncardiac surgery, an independent association between preoperative anemia and increased 90-day mortality was shown (OR 2.29, 95% CI 1.45–3.63).²⁹ A National Surgical Quality Improvement Program (NSQIP) study of 5081 patients undergoing vascular surgery showed increased mortality for both moderate (OR 2.6, 95% CI 1.2–5.5) and severe (OR 2.8, 95% CI 1.3–6.3) anemia.³⁰

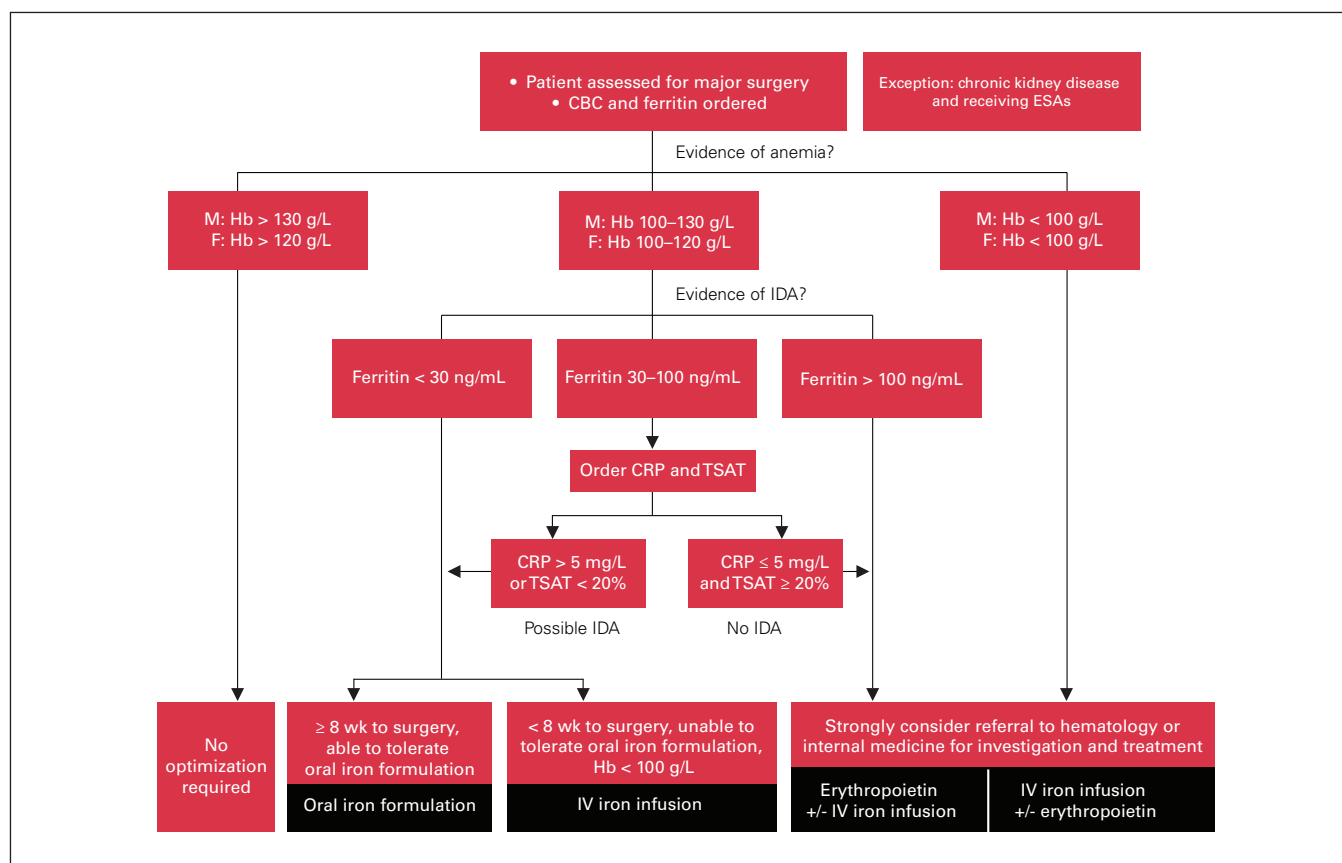


Fig. 1. Algorithm for diagnosis and treatment of preoperative anemia in patients undergoing major elective surgery. CBC = complete blood count; CRP = C-reactive protein; ESA = erythropoietin-stimulating agent; F = female; Hb = hemoglobin; IDA = iron-deficiency anemia; IV = intravenous; M = male; TSAT = transferrin saturation index.

Preoperative anemia is independently associated with early postoperative complications such as increased overall 30-day postoperative morbidity in patients undergoing noncardiac surgery (OR 1.35, 95% CI 1.30–1.40),⁹ increased rates of major cardiac events (5.1%–6.8% v. 2.6%; $p = 0.001$) and acute kidney injury (52.0%–63.2% v. 31.0%; $p = 0.01$) in patients undergoing vascular surgery,^{30,31} and increased infectious complication rates in patients undergoing orthopedic surgery (57.1% v. 6.3%; $p = 0.006$)³² and those with gastric cancer (OR 3.70, 95% CI 1.43–9.58).³³ In a large NSQIP database study, preoperative anemia in patients undergoing colorectal surgery was independently associated with a significantly increased frequency of composite outcome events (myocardial infarction, acute renal injury, stroke and death) that was proportional to anemia severity (mild: OR 1.49, 95% CI 1.20–1.86; moderate: OR 2.19, 95% CI 1.63–2.94; severe: OR 1.83, 95% CI 1.05–3.19).¹¹

Preoperative anemia was independently associated with significant increases in length of postoperative hospital stay in a systematic review of orthopedic literature,¹³ a retrospective analysis of 2394 patients who underwent total knee arthroplasty (OR 1.71–2.29; $p < 0.001$)¹⁴ and

an NSQIP study of 23 348 patients who underwent colorectal surgery (0.5–2.2 d longer; $p < 0.01$).¹¹

Unsurprisingly, preoperative anemia is independently associated with significantly increased rates of postoperative blood transfusion. This association has been shown after urologic (OR 6.28, 95% CI 3.43–11.51),³⁴ colorectal (24% v. 3%)³⁵ and orthopedic (OR 4.13–9.13; $p < 0.001$)¹⁴ procedures. Compared to anemic values, a normal preoperative hemoglobin value was shown to significantly reduce the likelihood of transfusion after laparoscopic colorectal resection (HR 0.547, 95% CI 0.468–0.637).³⁶

Finally, preoperative anemia is independently associated with worse oncologic outcomes in patients with urologic, gastric, colorectal or mesenchymal cancer, with decreased disease-free survival,^{37,38} cancer-specific survival^{39,40} and overall survival,^{39,41–43} and increased rates of cancer recurrence.^{40,44}

2. Complete blood count and ferritin are the most appropriate screening blood tests.

Hemoglobin levels, as determined by a complete blood count, represent the gold standard diagnostic test for anemia. This was established through a series of reports published by the WHO between 1968 and 2015 in which

Table 1. Grading of Recommendations Assessment, Development and Evaluation (GRADE) analysis of clinical practice guideline evidence for the preoperative optimization of anemia, hyperglycemia and smoking

Recommendation no.	Recommendation	Strength of recommendation*	Quality of evidence†
Anemia			
1	Preoperative anemia is associated with adverse surgical outcomes, and all patients undergoing major surgery should be screened for anemia at their first surgical clinic visit and investigated further, as appropriate.	Strong	High
2	Complete blood count and ferritin are the most appropriate screening blood tests.	Strong	Moderate
3	Patients without evidence of anemia should not be treated with iron supplementation.	Weak	Low
4	For patients with anemia and a serum ferritin level of 30–100 ng/mL, transferrin saturation index and C-reactive protein tests should be ordered to better determine the presence of iron deficiency.	Strong	Low
5	Oral iron supplementation is the preferred treatment for patients with iron-deficiency anemia (IDA) and no contraindications (i.e., ≥ 8 wk until surgery, able to tolerate/absorb oral iron formulation, hemoglobin level ≥ 100 g/L).	Strong	High
6	Intravenous iron infusions may be appropriate for patients with IDA in certain circumstances (i.e., < 8 wk until surgery, unable to tolerate/absorb oral iron formulation, hemoglobin level < 100 g/L).	Strong	High
7	For patients with anemia who have no evidence of IDA or IDA refractory to iron supplementation, referral to a hematologist should be considered for treatment with erythropoietin and intravenous iron infusions.	Strong	High
Hyperglycemia			
1	Perioperative hyperglycemia increases the risk of postoperative complications, and all patients undergoing major surgery should be screened for diabetes.	Strong	Moderate
2	Measurement of the glycated hemoglobin (HbA _{1c}) level is the most appropriate screening test for hyperglycemia.	Weak	Low
3	A preoperative HbA _{1c} less than 6.0% does not require any further action or preoperative optimization.	Strong	High
4	A preoperative HbA _{1c} level of 6.0%–6.9% in a patient with no history of diabetes does not require preoperative optimization. However, it may represent prediabetes or a new diagnosis of diabetes, and the patient should be referred to a family physician, internist or endocrinologist for follow-up and confirmation.	Strong	Low
5	A preoperative HbA _{1c} level of 7.0%–8.4% requires preoperative optimization, and these patients should be referred to their family physician, an internist or an endocrinologist for optimization to a target blood glucose level of 5–10 mmol/L.	Strong	High
6	A preoperative HbA _{1c} level of 8.5% or greater indicates poor glycemic control and requires preoperative optimization, and these patients should be referred to an internist or endocrinologist for preoperative optimization.	Strong	High
7	Patients with known diabetes with a preoperative HbA _{1c} level less than 7.0% do not require preoperative optimization.	Strong	Low
8	All patients (both with and without diabetes) with a preoperative HbA _{1c} level greater than 6.0% should undergo intra- and postoperative blood glucose monitoring, with a target blood glucose level of 6–10 mmol/L, to reduce the risk of postoperative complications.	Strong	Moderate
Smoking			
1	Tobacco smoking is associated with increased adverse postoperative outcomes, and all patients undergoing major surgery should have their smoking status identified and documented at every preoperative clinic visit.	Strong	High
2	All surgical patients who smoke should be advised to quit smoking preoperatively and have their willingness to quit assessed to guide next steps. Because of the high risk of relapse, those who have quit within the previous 6 months should be treated as active smokers.	Strong	Moderate
3	A quit date should be set more than 8 weeks preoperatively to achieve the most substantial improvements in postoperative outcomes; however, outcome benefits may still be seen with cessation as late as the day of surgery.	Strong	Moderate
4	In patients who are unwilling to quit smoking, motivational interviewing techniques can be used to increase motivation to quit, thereby increasing quit rates.	Strong	Moderate
5	In patients who are unwilling to quit smoking but willing to reduce, clinicians should offer full cessation treatment to support reduction goals.	Strong	Moderate
6	All surgical patients who smoke should be offered the combination of counselling and pharmacotherapy preoperatively. When this is not possible, they should still be offered either intervention individually.	Strong	High
7	All surgical patients who smoke should be offered combination nicotine replacement therapy (NRT) preoperatively. Prescribers capable of follow-up may consider varenicline as a first-line agent. Second-line options include single-agent NRT and bupropion.	Strong	High
8	All surgical patients who smoke should be given brief counselling on the consequences of smoking and the benefits of smoking cessation preoperatively. When possible, counselling should be face to face, frequent and of sufficient duration, all of which increase cessation rates.	Strong	High
9	All surgical patients who smoke should be offered clinical follow-up.	Strong	Moderate
*Represents a combination of quality of supporting evidence, balance between desired and undesired effects, how wise the proposed use of resources is, and variability of individual preferences and values. Can be “strong” or “weak.”			
†Based on how likely further research is to change confidence in the estimate of effect. Classified in 1 of 4 levels: “high,” “moderate,” “low” or “very low.”			

the normal hemoglobin ranges for adult and pediatric populations (by sex) were determined and the definitions of anemia refined.^{17–19,45–48} Large population-based studies examining mean hemoglobin values by age, race and sex further validated the accepted normal ranges and the use of hemoglobin level to diagnose anemia.²⁰ The hematocrit, as determined by a complete blood count, has also been validated as an indicator of anemia in more recent large database studies, such as those using NSQIP data.^{9,11,49}

Iron-deficiency anemia is the most common cause of anemia in surgical patients and should be assessed as part of the initial investigation.^{21,50–52} In a meta-analysis of 55 studies, Guyatt and colleagues⁵³ compared several blood tests to the gold standard for the diagnosis of IDA (absence of stainable iron in a bone marrow aspirate). They found the serum ferritin radioimmunoassay to be the most reliable test for the diagnosis of IDA, with an area under the ROC curve of 0.95. Although the radioimmunoassay is no longer commonplace, equivalence has been shown between this assay and the enzyme-linked immunoassays that are more common today, with an intraclass correlation coefficient of at least 0.98, which implies that the tests are interchangeable.⁵⁴ A serum ferritin level less than 30 µg/L has been shown to be both sensitive (92%) and specific (98%) for the diagnosis of IDA.^{55–57} The diagnostic utility of serum ferritin level as an effective first-line test for IDA was reaffirmed in more recent reviews on the topic.^{47,55,58}

3. Patients without evidence of anemia should not be treated with iron supplementation.

Pratt and Khan⁵⁹ advocated consideration of iron supplementation for patients with nonanemic iron deficiency. However, currently there is insufficient evidence of clinical benefit to recommend treatment for patients with a preoperative hemoglobin level greater than 130 g/L for men or greater than 120 g/L for women. Although the rate of serious toxic effects related to oral iron supplementation is low, gastrointestinal adverse effects are common.⁶⁰ Therefore, given the low potential for benefit and high probability of adverse effects, this therapy should not be recommended for patients without evidence of anemia.

4. For patients with anemia and a serum ferritin level of 30–100 ng/mL, transferrin saturation index and C-reactive protein tests should be ordered to better determine the presence of iron deficiency.

In cases in which anemia is diagnosed but the serum ferritin level is nondiagnostic (30–100 ng/mL), 2 tests should be added to confirm IDA: measurement of the transferrin saturation index and the C-reactive protein level.^{56,58} In the context of anemia with a serum ferritin level of 30–100 ng/mL, a transferrin saturation index less than 20% implies inadequate iron for normal erythropoiesis and is therefore strongly suggestive of IDA.^{51,56,58}

Serum ferritin is known to be an acute-phase reactant,^{61,62} and the level can rise with increasing age.^{20,62}

Therefore, in the context of anemia with a serum ferritin level of 30–100 ng/mL, a C-reactive protein level greater than 5 mg/L is consistent with an inflammatory state and falsely elevated serum ferritin levels, and is therefore strongly suggestive of IDA.^{51,56,58}

5. Oral iron supplementation is the preferred treatment for patients with IDA and no contraindications (i.e., ≥ 8 wk until surgery, able to tolerate/absorb oral iron formulation, hemoglobin level ≥ 100 g/L).

A randomized controlled trial (RCT) involving 90 older inpatients with IDA showed significant increases in mean hemoglobin level after 60 days of treatment with low-, medium- or high-dose oral iron supplementation (increases of 13 g/L, 14 g/L and 14 g/L, respectively; $p < 0.001$ for all dosages).⁶³ In a multicentre RCT involving 46 patients with inflammatory bowel disease and IDA, an oral iron regimen administered for 6 weeks resulted in a mean increase in hemoglobin level of 21 g/L, which was not significantly different from that in patients receiving intravenous iron infusions.⁶⁴ In an RCT involving 45 patients awaiting resection for colon or rectal cancer, 2 weeks of oral iron treatment resulted in significantly higher hemoglobin levels at the time of surgery (mean 131 g/L v. 118 g/L; $p = 0.04$),⁶⁵ and a second prospective study in 58 similar patients showed a significant increase in preoperative hemoglobin level (+17.3 g/L; $p < 0.001$) after an average of 39 days of oral iron treatment.⁶⁶

Owing to the demonstrated effectiveness of oral iron therapy, and the lower cost and ease of administration for both the patient and the health care system, most blood management strategies recommend oral iron supplementation as first-line treatment for patients with IDA with no contraindications.^{15,51,53,67} Although many dosages have been found to be effective, there is evidence to suggest that lower dosages (e.g., elemental iron equivalent of 40–60 mg orally daily or 80–100 mg orally every 2 d) are associated with fewer adverse effects such as abdominal discomfort, nausea, vomiting and changes in bowel habits.^{51,63,68}

A recent summary of evidence regarding the safety of oral iron supplementation did not identify any major safety concerns, although adverse effects such as nausea, heartburn, pain, and constipation or diarrhea are more common with oral formulations than with intravenous iron infusions.⁶⁹

6. Intravenous iron infusions may be appropriate for patients with IDA in certain circumstances (i.e., < 8 wk until surgery, unable to tolerate/absorb oral iron formulation, hemoglobin level < 100 g/L).

In an RCT involving 76 patients with menorrhagia and severe IDA comparing 3 weeks of intravenous versus oral iron supplementation, intravenous iron supplementation

was associated with a larger increase in posttreatment hemoglobin levels (mean +30 g/L v. +8 g/L; $p < 0.001$) and ferritin levels (mean +170.1 $\mu\text{g/L}$ v. +4.1 $\mu\text{g/L}$; $p < 0.001$), and a higher frequency of reaching a target hemoglobin level of 100 g/L or greater (76.7% v. 11.5%; $p < 0.001$).⁷⁰ A prospective trial involving 266 patients with colon cancer receiving intravenous versus oral iron supplementation showed that intravenous iron supplementation was associated with a significantly shorter mean length of stay (8.4 d [standard deviation (SD) 6.8 d] v. 10.9 d [SD 12.4 d]; $p < 0.001$), lower frequency of transfusion (9.9% v. 38.7%, $p < 0.001$), and larger increases in preoperative (+15 g/L v. +5 g/L; $p < 0.001$) and 30-day postoperative (+31 g/L v. +15 g/L; $p < 0.001$) hemoglobin levels.⁷¹ In addition, patients receiving iron intravenously had a higher rate of normalized hemoglobin 30 days postoperatively (40% v. 26.7%; $p < 0.05$). In a multicentre RCT involving 116 patients undergoing elective surgery for colorectal cancer, the mean increase in total hemoglobin level was significantly greater with intravenous than oral iron therapy (+15.5 g/L v. +5.0 g/L; $p < 0.001$), and a smaller proportion of patients in the intravenous iron group were anemic at the time of surgery (75% v. 90%; $p = 0.048$).⁷² These findings are consistent with those of a systematic review of 8 low-bias RCTs showing that patients with IDA preoperatively may have earlier and more robust recovery of the hemoglobin level with intravenous iron therapy than with oral supplementation.⁷³ In a prospective RCT, 72 patients with IDA were randomly allocated to receive intravenous iron supplementation versus usual care within 3 weeks before elective abdominal surgery.⁷⁴ Increases in hemoglobin level were significantly higher in the intravenous iron group preoperatively and 4 weeks after discharge (+8 g/L v. +1 g/L, $p = 0.01$; and 19 g/L v. 9 g/L, $p = 0.01$, respectively), with a significant associated reduction in postoperative allogenic blood transfusion (12.5% v. 53%; $p < 0.001$). Finally, a retrospective review of 318 patients with colorectal cancer and anemia who received intravenous iron treatment less than 6 weeks before surgery showed a significantly greater increase in hemoglobin level compared to no treatment (+10.5 g/L v. +1.6 g/L; $p < 0.001$).⁷⁵

Two studies have shown the utility of intravenous iron infusion for patients with anemia with minimal time until surgery. An RCT in 108 patients undergoing bilateral total knee replacement showed that, compared to no infusions, intraoperative intravenous infusions of iron and erythropoietin resulted in significantly higher hemoglobin levels in the first, second and sixth weeks postoperatively, and a significantly lower rate of blood transfusion (20.4% v. 53.7%; $p = 0.01$).⁷⁶ In a retrospective analysis of 2547 patients at risk for severe postoperative anemia who underwent major orthopedic surgery, compared to standard treatment, intravenous iron treatment at any time from 5 days preoperatively to 3 days postoperatively was associated with a sig-

nificantly lower rate of postoperative nosocomial infections (10.7% v. 26.9%; $p = 0.001$) and shorter length of stay (11.9 d v. 13.4 d; $p = 0.001$), independent of transfusion status; the proportion who received transfusions was also lower (32.4% v. 48.8%; $p = 0.001$).²⁶

The safety of intravenous iron therapy is comparable to that of oral iron therapy, as shown in a systematic review of 8 low-bias RCTs and a prospective study of 266 patients that showed no deaths, hypersensitivity reactions or other serious drug reactions.^{71,73} In addition to being safe, intravenous iron treatment is rarely associated with the adverse gastrointestinal effects seen with oral iron supplementation, which results in increased compliance with intravenous treatment.^{28,70}

7. For patients with anemia who have no evidence of IDA or IDA refractory to iron supplementation, referral to a hematologist should be considered for treatment with erythropoietin and intravenous iron infusions.

In a systematic review of 8 low-bias RCTs, Lin and colleagues⁷³ concluded that a short preoperative course of erythropoietin or a single dose of erythropoietin plus intravenous iron infusion pre- or intraoperatively may reduce transfusion requirements significantly, with a number needed to treat to avoid allogenic blood transfusion of 3–6. In an RCT involving 201 patients with undifferentiated anemia scheduled to undergo hip arthroplasty, participants were randomly allocated to receive 4 weeks of high-dose erythropoietin with oral iron therapy, low-dose erythropoietin with oral iron therapy, or placebo; there was a significant dose-proportional reduction in the blood transfusion rate (11.4%, 22.8% and 44.9%, respectively; $p < 0.003$) and increase in the preoperative hemoglobin level (+19.5 g/L, +17.2 g/L and +1.2 g/L, respectively; $p < 0.001$).⁷⁷ In an RCT in which 74 patients with anemia undergoing valvular heart surgery were randomly allocated to receive erythropoietin and intravenous iron infusion or placebo 1 day before surgery, the intervention was associated with a significant reduction in the rate of blood transfusion (59% v. 86%; $p = 0.009$), with a number needed to treat to avoid allogenic blood transfusion of 4, as well as a reduction in the mean number of units of packed red blood cells transfused per patient (3.3 [SD 2.2] v. 1.0 [SD 1.1]; $p = 0.001$).⁷⁸ In an RCT involving 108 iron-deficient patients undergoing bilateral total knee replacement, compared to standard care, administration of erythropoietin and intravenous iron infusion intraoperatively resulted in a significantly lower perioperative transfusion rate (20.4% v. 53.7%; $p = 0.01$), significantly fewer units of packed red blood cells transfused per patient (mean 0.2 [SD 0.5] v. 0.8 [SD 0.8]; $p = 0.005$), and significantly higher hemoglobin levels 1, 2 and 3 days, and 2 and 6 weeks postoperatively.⁷⁶ Finally, in a retrospective study involving 412 patients with IDA who underwent elective orthopedic surgery, Basora and colleagues⁷⁹

compared those who received intravenous iron treatment alone to those who received intravenous iron treatment and erythropoietin preoperatively and found a significantly greater increase in the preoperative hemoglobin level with the latter treatment (+15 g/L v. +8 g/L; $p < 0.01$).

A safety/noninferiority RCT involving 680 patients undergoing spinal surgery showed a significantly increased risk of deep vein thrombosis (DVT) in those who received erythropoietin compared with standard care (4.7% v. 2.1%, 97.5% CI exceeding the boundary for noninferiority); however, only mechanical (no pharmacologic) venous thromboembolism prophylaxis was used.⁸⁰ Importantly, neither the DVT rate, confirmed on Doppler imaging (4.1% v. 2.1%), nor the rate of all adverse events (76.5% v. 73.2%) was statistically significant.

The safety of treatment with erythropoietin-stimulating agents (ESAs) in patients undergoing active treatment for malignant disorders has been questioned owing to concerns regarding tumour progression.⁸¹ Thus, the use of ESAs in this patient population should be considered with caution.

Special considerations

Inflammatory bowel disease

In a 2015 systematic review on the management of IDA in patients with inflammatory bowel disease that included 13 studies (2906 patients), Nielsen and colleagues⁸² recommended oral iron therapy for patients with quiescent disease or mild anemia, and intravenous iron infusions for patients with moderate to severe anemia, active inflammatory bowel disease flare-ups or intolerance to oral supplementation.

Severely impaired renal function

Owing to decreased or absent production of erythropoietin, anemia is a nearly universal complication in patients with severely impaired renal function. The mainstay of treatment for anemia in these patients is ESAs, often with the adjunct use of iron supplementation. The Canadian Society of Nephrology does not recommend targeting a hemoglobin level within the standard normal range for these patients but, rather, maintaining a level around 100 g/L.⁸³ Thus, patients with renal impairment who are already taking an ESA or who may have anemia requiring ESA therapy may not be candidates for treatment according to the algorithm (Figure 1). For this reason, management of perioperative anemia in patients with renal disease should be undertaken in collaboration with the patient's nephrologist.

Conclusion

Preoperative anemia is a risk factor independently associated with a variety of postoperative complications. There is sufficient evidence from high-quality trials to inform recommendations for the diagnosis and management of pre-

operative anemia. Routine screening, investigation and treatment for preoperative anemia in keeping with the evidence presented in this guideline is a cost-effective, high-yield approach to optimizing anemia in any patient being assessed for major surgery. Coordinated preoperative assessment and treatment programs have proven effective in reducing rates of preoperative anemia and its associated complications, but they require collaboration among perioperative specialties including surgeons, anesthesiologists, internists, hematologists and perioperative nurses.^{15,26–28,84} Given the potential for substantial benefit to patient outcomes, as well as the efficiencies to be gained by health care systems, development of such preoperative optimization programs is recommended for all centres with moderate- to high-volume surgical services, whether academic or community-based. To ensure the effectiveness of these programs, continuous quality-assurance projects should be carried out.

HYPERGLYCEMIA

Diabetes has been defined as a fasting blood glucose level of 7.0 mmol/L or greater, a glycated hemoglobin (HbA_{1c}) value of 6.5% or greater, a 2-hour plasma glucose level in a 75-g oral glucose tolerance test of 11.1 mmol/L or greater, or a random plasma glucose level of 11.1 mmol/L or greater.^{85,86} Prediabetes (fasting plasma glucose level of 6.1–6.9 mmol/L, a 2-hour plasma glucose level in an oral glucose tolerance test of 7.8–11.0 mmol/L, and an HbA_{1c} level of 6.0%–6.4%) places patients at very high risk for diabetes. The American Diabetes Association (ADA) expands the HbA_{1c} range for prediabetes to 5.7%–6.4%.⁸⁶ Screening guidelines for the general population vary by organization.^{85,87,88}

The prevalence of diabetes continues to rise, with the disease affecting an estimated 371 million people worldwide in 2012; this number is expected to increase to 552 million by 2030.⁸⁵ In the United States, the prevalence was 9.4% in 2015, and in Canada, the estimated prevalence was 6.8% in 2009.^{85,89} Diabetes is even more common in surgical patients than in the general population: patients with diabetes account for an estimated 10%–20% of all surgical patients; a further 23%–60% of surgical patients have undiagnosed diabetes.^{90–93}

Major surgical procedures produce a catabolic state and lead to transient hyperglycemia in patients without diabetes. This physiologic response is more pronounced in patients who have insulin resistance or no insulin production.⁹³ Diabetes-related complications include those from macrovascular and microvascular disease, such as myocardial infarction, stroke, retinopathy, nephropathy and neuropathy.⁹⁴

The appropriate management of hyperglycemia intra- and postoperatively has been shown to improve outcomes.⁹⁵ The preoperative management of hyperglycemia is an area that can be improved. The following clinical practice

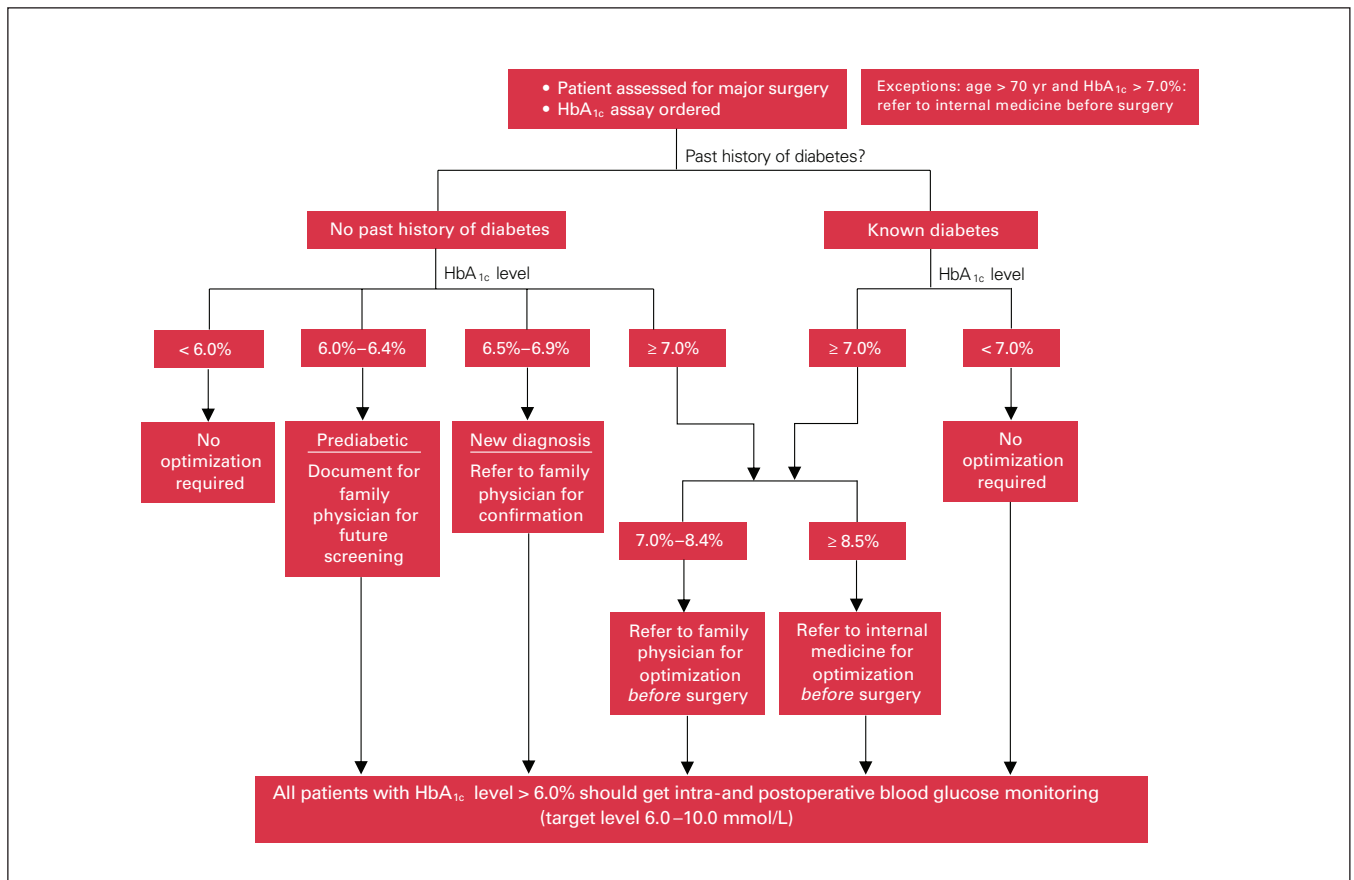


Fig. 2. Algorithm for diagnosis and treatment of preoperative hyperglycemia in patients with and without diabetes. HbA_{1c} = glycated hemoglobin.

guidelines summarize the evidence that we used to develop the recommendations in the proposed diagnostic and treatment algorithm for preoperative hyperglycemia (Figure 2).

Recommendations

1. Perioperative hyperglycemia increases the risk of postoperative complications, and all patients undergoing major surgery should be screened for diabetes.

In its clinical practice guidelines, Diabetes Canada recommends admission screening with a random blood glucose test for all hospitalized patients owing to a high prevalence of undiagnosed and poorly controlled diabetes.⁸⁵ Diabetes Canada and the ADA also recommend measuring the HbA_{1c} level in all patients with diabetes or hyperglycemia if this has not been done in the previous 3 months.⁹⁶ In addition, an increased risk of postoperative complications has been well documented in the literature for patients with preoperative hyperglycemia in many different surgical specialties.^{97–104}

An elevated HbA_{1c} level ($\geq 6.5\%$) and perioperative hyperglycemia were associated with an increased risk of major complications (Clavien–Dindo grade III–V) in a prospective cohort of 478 patients undergoing abdominal sur-

gery (OR 1.95, 95% CI 1.17–3.24).⁹⁷ Analysis of prospectively collected colorectal cancer data showed that diabetes was a risk factor for increased postoperative surgical complications such as surgical site infection (SSI), wound dehiscence, anastomotic leak, enterocutaneous fistula, ileus, hemorrhage, obstruction, urinary retention and ureteric injury (OR 1.44, 95% CI 1.02–2.04) but not mortality.⁹⁸ Patients with diabetes who had diabetic complications also had increased 30-day mortality (OR 13.7, 95% CI 3.4–54.7) and length of stay (3.8 d, 95% CI 0.7–7.1) compared to patients without complications. A systematic review showed that patients with diabetes who underwent carotid artery revascularization were at higher risk for perioperative stroke (OR 1.38, 95% CI 1.02–1.88), death (OR 1.94, 95% CI 1.36–2.75) and long-term mortality (OR 1.57, 95% CI 1.22–2.03).⁹⁹ In a large retrospective study, elevated HbA_{1c} levels in patients with peripheral vascular disease were associated with an increased risk of amputation and other complications.¹⁰⁰ Amputation was increasingly likely with HbA_{1c} levels of 6.1%–7.0% (HR 1.26, 95% CI 1.15–1.39), 7.1%–8.0% (HR 1.53, 95% CI 1.37–1.7) and greater than 8% (HR 2.05, 95% CI 1.87–2.26). The study also highlighted the increased risk of preoperative hyperglycemia in patients without diabetes compared to patients with diabetes with good control (HbA_{1c} level < 7.0%).

Preoperative hyperglycemia has also been shown to increase the rate of postoperative complications in patients undergoing cardiac surgery. A large retrospective study showed an increased risk of death or major cardiac event with an HbA_{1c} level of 8.1% or higher (8.1%–9.0%: HR 1.17, 95% CI 1.04–1.33; 9.1%–10.0%: HR 1.44, 95% CI 1.22–1.70; > 10.0%: HR 1.50, 95% CI 1.22–1.84).¹⁰¹ Subramaniam and colleagues¹⁰² conducted a prospective cohort study of patients undergoing coronary artery bypass grafting and found an increase in major adverse events including in-hospital death, myocardial infarction, tamponade, reoperation, SSI, renal failure, pneumonia and stroke in those with an HbA_{1c} level of 6.5% or higher (OR 1.6, 95% CI 1.1–2.3).

There is conflicting evidence in the orthopedic literature with regard to preoperative diabetes and HbA_{1c} levels. In a large NSQIP study, diabetes was found to be an independent predictor of postoperative complications (OR 1.67, 95% CI 2.217–1.253) and longer length of stay (OR 1.878, 95% CI 2.262–1.559).¹⁰³ Miller and colleagues¹⁰⁴ reported that an HbA_{1c} level greater than 6.4% was an independent risk factor for reoperation (HR 1.13, 95% CI 1.02–1.29) among patients who underwent spinal operations. However, 2 previous studies showed no difference in rates of postoperative joint infection, revision or DVT in patients with elevated HbA_{1c} levels.^{105,106}

Patients with previously undiagnosed diabetes (elevated HbA_{1c} level without a documented history of diabetes) have been shown to be at higher risk for postoperative complications than patients with known diabetes or patients with normal preoperative blood glucose levels.^{92,107–109} A recent systematic review showed that patients with undiagnosed diabetes have an increased risk for overall postoperative complications after bariatric (OR 1.16, 95% CI 1.00–1.33), cardiac (OR 1.148, 95% CI 1.003–1.313), colorectal (OR 2.9, 95% CI 1.1–7.9) and vascular (risk ratio [RR] 7.0, 95% CI 2.8–17.2) surgery.⁹² Patients with undiagnosed diabetes undergoing cardiac surgery also have an increased risk for 30-day mortality (OR 1.53, 95% CI 1.24–1.91).¹¹⁰ Using NSQIP data for patients without known diabetes, Wang and colleagues¹⁰⁸ found that those with elevated preoperative random blood glucose levels (5.5–8 mmol/L and 8–10 mmol/L) had significantly higher postoperative infection rates than those with normal random blood glucose levels (9.33% and 10.16% v. 5.62%; $p < 0.001$).

A robust association exists between postoperative hyperglycemia and postoperative morbidity and mortality in general surgery patients, which makes preoperative identification of patients at risk essential for effective perioperative planning. Kwon and colleagues¹¹⁴ used data from the Surgical Care and Outcomes Assessment Program to assess the outcomes of 11 633 patients who underwent colon, rectal or bariatric surgery and had their blood glucose level monitored postoperatively. Those with hyper-

glycemia were found to have an increased risk of infection (OR 2.0, 95% CI 1.63–2.44), reoperation (OR 1.8, 95% CI 1.41–2.30) and death (OR 2.71, 95% CI 1.72–4.28). Patients with hyperglycemia who received insulin did not have an increased risk of infection (OR 1.01, 95% CI 0.72–1.42), reoperation (OR 1.29, 95% CI 0.89–1.89) or death (OR 1.21, 95% CI 0.61–2.42) compared to patients with blood glucose levels within the normal range.

A systematic review of papers published from 2001 to 2013 assessing preoperative testing identified a benefit in screening patients undergoing orthopedic and vascular procedures but not other procedures.¹¹⁵ However, none of the studies in the review reported on changes in clinical management based on preoperative screening. Also, patients with diabetes and patients with undiagnosed diabetes were considered together. This review, therefore, has limited utility but is helpful in identifying some benefit of screening.

Although there is insufficient evidence to show that patients with hyperglycemia (both those with known diabetes and those with previously undiagnosed diabetes) benefit from preoperative treatment, screening identifies patients who would benefit from intra- and postoperative treatment of hyperglycemia, which has been proven to reduce postoperative morbidity and mortality.⁹⁵ With routine screening, the effect of treatment can also be studied properly.

2. Measurement of the HbA_{1c} level is the most appropriate screening test for hyperglycemia.

Although there is debate regarding the ideal test to diagnose diabetes, an HbA_{1c} test is easier and more convenient for patients than a fasting blood glucose or oral glucose tolerance test, and the result is less affected by day-to-day variability.^{85,86} An HbA_{1c} test will also show the level of control over the previous 2–3 months.⁸⁷ Care must be taken to ensure that an HbA_{1c} assay that has been standardized by the National Glycohemoglobin Standardization Program to the Diabetes Control and Complications Trial reference is used, as considerable variation may exist between different HbA_{1c} assays.^{85,86}

Existing guidelines vary in their recommendations for screening. The Strong for Surgery program (American College of Surgeons) recommends screening all patients without a previous diagnosis of diabetes by means of a fasting blood glucose test on the morning of surgery if their body mass index is greater than 30 or they are older than 45 years. Patients with diabetes who have an HbA_{1c} level greater than 7.0% should be referred for optimization. The National Institute for Health and Care Excellence recommends obtaining an HbA_{1c} level for patients with diabetes but not screening patients with no prior history of diabetes.¹¹⁶ In their guidelines for primary care physicians evaluating patients preoperatively, Feely and colleagues¹¹⁷ state that, in patients with known diabetes,

the preoperative HbA_{1c} value is more likely to be useful if results would change perioperative management. Preoperative random glucose measurement could be considered in patients at very high risk for undiagnosed diabetes and in those with signs or symptoms of undiagnosed diabetes.¹¹⁷

3. A preoperative HbA_{1c} level less than 6.0% does not require any further action or preoperative optimization.

As per Diabetes Canada guidelines, an HbA_{1c} level less than 6.0% is generally considered to be normal and therefore does not require preoperative optimization.⁸⁵

4. A preoperative HbA_{1c} level of 6.0%–6.9% in a patient with no history of diabetes does not require preoperative optimization. However, it may represent prediabetes or a new diagnosis of diabetes, and the patient should be referred to a family physician, internist or endocrinologist for follow-up and confirmation.

Patients with a preoperative HbA_{1c} level of 6.0%–6.4% are at increased risk for diabetes (prediabetic). These patients are also at higher risk for postoperative complications and should have their blood glucose monitored while in hospital¹⁰⁰ (see recommendation 8).

Patients with confirmed or suspected diabetes (HbA_{1c} level \geq 6.5%) are at increased risk for postoperative complications, even if their HbA_{1c} level is within the target range.^{97,102,118} After identification of a preoperative HbA_{1c} level of 6.5% or higher, a second confirmation test is required to diagnose diabetes unless clear symptoms are present.^{85,86} These patients should be referred to their family physician, an internist or an endocrinologist for confirmation.⁸⁵ In addition, they should be referred to a community diabetes education program for ongoing support. They should receive glycemic monitoring intra- and postoperatively, and should be treated as indicated (see recommendation 8).

5. A preoperative HbA_{1c} level of 7.0%–8.4% requires preoperative optimization, and these patients should be referred to their family physician, an internist or an endocrinologist for optimization to a target blood glucose level of 5–10 mmol/L.

Patients with suboptimal glycemic control are at increased risk for postoperative complications. The ADA and Diabetes Canada recommend an HbA_{1c} target of less than 7% (blood glucose level $<$ 8.5 mmol/L) for most nonpregnant patients with diabetes.^{85,118} Diabetes Canada also recommends a postprandial glycemic target of 5–10 mmol/L for patients with diabetes. It has also been shown that an HbA_{1c} level higher than 8% increases hospital length of stay from 5.2 to 6.7 days ($p = 0.02$),¹¹⁹ and a recent systematic review and meta-analysis showed a decrease in SSI

rates (OR 0.43, 95% CI 0.29–0.64) with an intensive protocol aimed at strict intra- and postoperative blood glucose control ($<$ 8.3 mmol/L), with no increase in rates of death or stroke related to hypoglycemia.⁹⁵ Patients with suboptimal glycemic control should receive optimization of their glycemic control regardless of whether or not they are having surgery. They should receive glycemic monitoring intra- and postoperatively, and should be treated as indicated (see recommendation 8).

6. A preoperative HbA_{1c} level of 8.5% or greater indicates poor glycemic control and requires preoperative optimization, and these patients should be referred to an internist or endocrinologist for preoperative optimization.

An HbA_{1c} level of 8.5% or greater is substantially above target. Postoperative complication rates have been shown to increase with increasing HbA_{1c} levels.^{100,101} Optimization may be expedited and enhanced by the involvement of an internist or endocrinologist, and preoperative involvement may be helpful for postoperative management. These patients should receive glycemic monitoring intra- and postoperatively, and should be treated as indicated (see recommendation 8).

7. Patients with known diabetes with a preoperative HbA_{1c} level less than 7.0% do not require preoperative optimization.

Diabetes Canada and the ADA recommend a target HbA_{1c} level of less than 7.0% for most nonpregnant patients with diabetes in order to reduce the risk of microvascular complications.^{85,118} Below 7.0%, it is a balance among smaller incremental benefits, polypharmacy and harm from hypoglycemia. These patients should receive glycemic monitoring intra- and postoperatively, and should be treated as indicated (see recommendation 8).

8. All patients (both with and without diabetes) with a preoperative HbA_{1c} level greater than 6.0% should undergo intra- and postoperative blood glucose monitoring, with a target blood glucose level of 6–10 mmol/L, to reduce the risk of postoperative complications.

Hyperglycemia increases the risk of postoperative complications. A large NSQIP study of 55 408 patients with diabetes undergoing noncardiac surgery showed an increased risk of postoperative infections (incidence rate ratio 1.22, 95% CI 1.04–1.43).¹²⁰ Data from the Surgical Care and Outcomes Assessment Program also confirmed an increased risk of morbidity and mortality for patients with hyperglycemia.¹¹⁴ There is conflicting evidence regarding intensive versus conventional glucose control postoperatively. A recent systematic review and meta-analysis showed a reduction in SSI rates (OR 0.43, 95% CI 0.29–0.64) with an intensive protocol aimed at stricter intra- and

postoperative blood glucose control (< 8.3 mmol/L), with no increase in mortality or strokes related to hypoglycemia.⁹⁵ However, a previous Cochrane review did not show any difference in infectious complications or mortality, but did show an increase in hypoglycemic episodes.¹²¹ Diabetes Canada recommends a target blood glucose level of 6–10 mmol/L for critically ill patients and those undergoing major surgery.⁸⁵ To meet this target, it is recommended that a basal bolus insulin regimen be used rather than a correctional sliding scale.^{85,96}

Preoperative management of diabetic medications

All patients with diabetes should be assessed in a pre-admission clinic to help with the preoperative management of their medications. The ADA suggests holding all oral hypoglycemic agents the morning of surgery and giving 50% of the dosage of NPH insulin, or 60%–80% of the dosage of long-acting analogues or basal pump insulin.⁹⁶ Hypoglycemia is a serious preventable condition that patients may experience while they are fasting and are receiving insulin or other diabetic medications, such as sulphonylureas; these patients should be monitored for hypoglycemia and treated if it develops.⁹⁶ Sodium–glucose cotransporter-2 inhibitors should be avoided during fasting owing to an association with diabetic ketoacidosis.^{96,122}

Special considerations

Diabetes Canada and the ADA recommend personalized HbA_{1c} targets, which may translate to less stringent HbA_{1c} targets for older or frail patients.^{85,123} It is important to consider this when such patients are presenting for surgery, as they may have higher HbA_{1c} levels than expected. Regardless, it is still important to assess and treat them for hyperglycemia perioperatively to decrease the risk of associated complications.

Conclusion

Surgical patients with preoperative hyperglycemia are at increased risk for postoperative complications regardless of surgical specialty. There is a lack of evidence regarding screening for hyperglycemia and optimization of preoperative hyperglycemia. In the absence of high-quality prospective studies assessing the benefits of preoperative management of hyperglycemia, it would be appropriate to treat patients undergoing major surgical procedures according to guidelines that address the management of diabetes in the general population. Given the high rate of undiagnosed diabetes and prediabetes in surgical patients, patients undergoing major surgery should be screened so that treatment may be initiated, as there is a clear benefit of proper intra- and postoperative control of hyperglycemia.

SMOKING

Tobacco smoking remains highly prevalent in North America, and, despite decreased rates in recent decades, it remains the leading cause of preventable disease and death in Canada.¹²⁴ In 2016, 16.9% of Canadians aged 13 years or older (roughly 5.2 million people) were reported to be smokers.¹²⁵ The prevalence of smoking in clinical populations is even higher (> 20%).¹²⁶

Clinicians may not appreciate the adverse effect of smoking on postsurgical outcomes.¹²⁷ For example, a retrospective cohort study of more than 600 000 patients who underwent noncardiac surgery showed that preoperative smoking was associated with a 40% increase in 30-day mortality (OR 1.38, 95% CI 1.11–1.72) and a 70% increase in major morbidity (OR 1.72, 95% CI 1.67–1.78).¹²⁸

Several systematic reviews and meta-analyses have shown that interventions that help patients quit smoking before surgery lead to reductions in adverse surgical outcomes, including wound, pulmonary and overall complications.^{129,130} The following clinical practice guideline summarizes the current evidence informing the recommendations within the proposed diagnostic and treatment algorithm for preoperative smoking (Figure 3).

Recommendations

1. Tobacco smoking is associated with increased adverse postoperative outcomes, and all patients undergoing major surgery should have their smoking status identified and documented at every preoperative clinic visit.

A retrospective review of 400 000 patients who underwent noncardiac surgery showed that, compared to nonsmokers, smokers had a 29% increase in 30-day mortality (OR 1.29, 95% CI 1.20–1.39) and a 55% increase in 1-year mortality (OR 1.55, 95% CI 1.50–1.61).¹³¹ One-year postoperative mortality decreased significantly for prior smokers who had not smoked in the previous year (OR 1.14, 95% CI 1.10–1.19).¹³¹

A meta-analysis of 107 studies published since 2000 showed preoperative smoking to be significantly associated with general morbidity (RR 1.52, 95% CI 1.33–1.74), wound complications (RR 2.15, 95% CI 1.87–2.49), pulmonary complications (RR 1.73, 95% CI 1.35–2.23), neurologic complications (RR 1.38, 95% CI 1.01–1.88) and intensive care unit admission (RR 1.60, 95% CI 1.14–2.25).¹³⁰ Smoking is a demonstrated risk factor in most surgical procedures, increasing rates of incisional hernia after laparotomy (OR 3.93, 95% CI 1.82–8.49),¹³² spinal fusion nonunion (OR 2.01; $p < 0.02$),¹³³ disease recurrence (HR 1.25; $p = 0.02$) and metastasis (HR 2.64; $p = 0.03$) after radical prostatectomy,¹³⁴ anastomotic leakage after anterior resection for rectal cancer (OR 1.88, 95% CI 1.02–3.46)¹³⁵ and fracture after shoulder arthroplasty (HR 3.63; $p = 0.02$).¹³⁶ Smoking also leads to increased wound

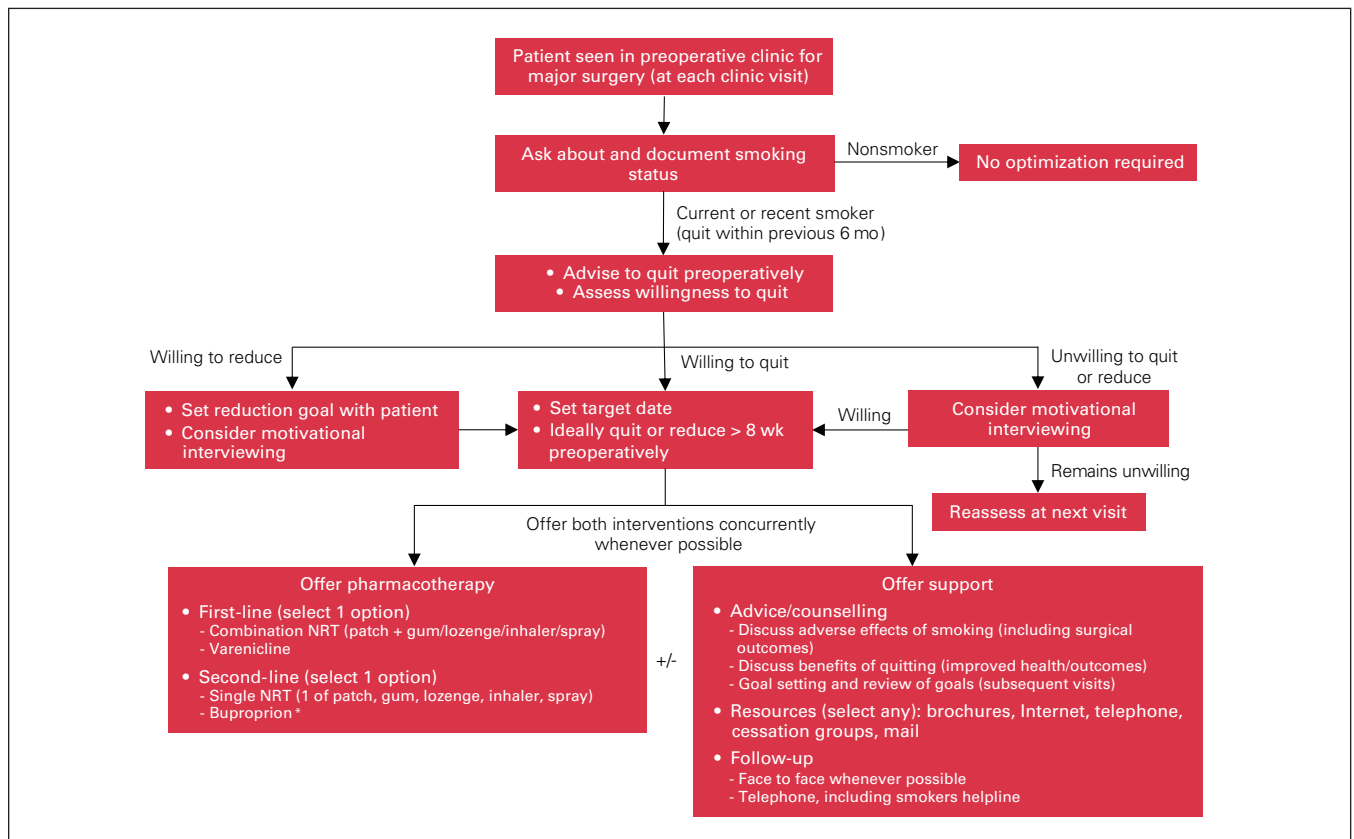


Fig. 3. Algorithm for diagnosis and treatment of smoking in patients undergoing major elective surgery. *Use with caution in patients older than 65 years of age. NRT = nicotine replacement therapy.

complication rates after both laparoscopic (OR 1.20; $p = 0.02$) and open (OR 1.28; $p = 0.01$) cholecystectomy, and results in a longer average postoperative length of stay, by 2–4 days ($p < 0.001$).¹³⁷

Although roughly 25% of surgical patients are smokers,¹²⁸ more than half of patients undergoing elective outpatient procedures report not having been informed about the adverse effects of smoking before surgery.¹³⁸ Of 116 consecutive patients surveyed after a surgical clinic appointment at a Canadian tertiary care centre, less than 10% had been asked about smoking status, and none had been asked about quitting or offered any form of intervention.¹³⁹ Smoking status should be documented systematically in all patients undergoing surgery. Combining clinician training with a charting system has been shown to increase the rates of assessing tobacco use, setting a quit date, providing materials and arranging for follow-up.¹⁴⁰

2. All surgical patients who smoke should be advised to quit smoking preoperatively and have their willingness to quit assessed to guide next steps. Because of the high risk of relapse, those who have quit within the previous 6 months should be treated as active smokers.

More than 70% of all tobacco smokers report wanting to quit.¹⁴⁰ Half of Canadian smokers try to quit each year,¹⁴¹

but patient-driven smoking cessation is ineffective: 80%–90% of self-quitters relapse within 3 months of cessation, and less than 5% achieve long-term success.¹⁴¹ However, patients often view surgery as a “wake-up call” regarding their health and are more likely to be receptive to advice offered by health care professionals, particularly regarding the perioperative risks of smoking, at this time.^{142–144} A recent systematic review and meta-analysis suggested that cessation rates almost doubled (from 24.5% to 46.2%; effect size $g = 0.56$, 95% CI 0.32–0.80) before surgery with proactive, clinician-driven behavioural interventions.¹⁴⁵ The preoperative period is therefore an ideal time to intervene.

All patients who smoke should be advised to quit preoperatively in a clear, strong and personalized way, and have their willingness to quit assessed.¹⁴⁰ It is important to stratify patients by willingness to quit to determine the best management approach (see recommendations 3–5). Those who are willing to quit should set a quit date, and can choose between abrupt cessation or gradual reduction leading up to their quit date, which were shown to be equally effective in a meta-analysis of quit approaches (RR 0.94, 95% CI 0.79–1.13).¹⁴⁶ Among those who are unwilling to quit but willing to reduce the amount smoked per day, the use of pharmacotherapy should be encouraged to assist with smoking reduction.¹⁴⁷ Increased cessation rates have been reported after motivational

interviewing (a patient-centred approach focusing on the “5 Rs” strategy: relevance, risks, rewards, roadblocks and repetition at every visit¹⁴⁰) among patients who were initially unwilling to quit.¹⁴⁰

Smoking relapse most frequently occurs early after quitting but can occur as late as months to years later.¹⁴⁸ A Cochrane review of 63 RCTs showed that multiple behavioural techniques used by patients to prevent relapse failed to show any benefit but that success rates may be improved with pharmacotherapy.¹⁴⁹ Given the high relapse rate, we recommend treating patients who have quit within the previous 6 months as active smokers. This provides them with the best available evidence-based cessation treatments to promote sustained abstinence.

3. A quit date should be set more than 8 weeks preoperatively to achieve the most substantial improvements in postoperative outcomes; however, outcome benefits may still be seen with cessation as late as the day of surgery.

In a meta-analysis of 25 RCTs and cohort studies (combined $n > 21\,000$), smoking cessation more than 8 weeks before surgery significantly reduced rates of postoperative pulmonary complications compared to active smoking (RR 0.53, 95% CI 0.37–0.76), with rates approaching those among nonsmokers (RR 1.16, 95% CI 0.76–1.77).¹⁵⁰ Cessation 4 weeks preoperatively had a smaller but significant effect on pulmonary complication rates (RR 0.77, 95% CI 0.61–0.96), but the risk remained higher than that among nonsmokers (RR 1.39, 95% CI 1.18–1.65). There was no significant pulmonary benefit to cessation 2–4 weeks or less than 2 weeks preoperatively (RR 1.14, $p = 0.3$; and RR 1.20, $p = 0.1$, respectively).¹⁵⁰

The same meta-analysis also showed that smoking cessation more than 3–4 weeks preoperatively reduced wound complication rates (RR 0.69, 95% CI 0.56–0.84), with rates approaching those among nonsmokers (RR 1.44, 95% CI 0.97–2.15).¹⁵⁰ A retrospective cohort study of 188 patients with head or neck cancer with flaps showed a similar reduction in wound failure rates among smokers who quit 3–6 weeks (RR 0.17, 95% CI 0.04–0.75) or more than 6 weeks (RR 0.17, 95% CI 0.05–0.60) before surgery.¹⁵¹

Two landmark RCTs involving behavioural interventions and nicotine replacement therapy (NRT) showed improved postsurgical outcomes with smoking cessation programs 4 weeks or less before surgery.^{152,153} Møller and colleagues¹⁵² found that a program with a target quit date of 4 weeks before surgery led to significant reductions in rates of overall (18% v. 52%; $p < 0.001$) and wound-related (5% v. 31%; $p = 0.001$) complications. Lindström and colleagues¹⁵³ reported that a program with a target quit date of 3 weeks before surgery was associated with a significant reduction in any postoperative complication (21% v. 41%; RR 0.51; $p = 0.03$).

A recent observational nested matched case-control study showed benefit to quitting as late as the day of surgery, showing a significant decrease in SSI rates (OR 1.96, 95% CI 1.23–3.13).¹⁵⁴ However, 2 prior studies showed no significant reduction in wound complication rates with cessation less than 3 weeks before surgery.^{150,151}

4. In patients who are unwilling to quit smoking, motivational interviewing techniques can be used to increase motivation to quit, thereby increasing quit rates.

An RCT involving 616 patients who were unmotivated to quit smoking showed that motivational interviewing based on the US Public Health Service 2008 smoking cessation guideline¹⁴⁰ led to a quit rate of 23% at 6 months and an average reduction of 30% in the amount smoked per day.¹⁵⁵ Motivational interviewing is a specialized skill, and interested clinicians can learn more¹⁴⁰ or consider referral to a specialist. Even patients unwilling to quit should be encouraged to abstain from smoking at least 24 hours before surgery, as this may reduce the occurrence of SSI.¹⁵⁴

5. In patients who are unwilling to quit smoking but willing to reduce, clinicians should offer full cessation treatment to support reduction goals.

In a meta-analysis of RCTs involving smokers who did not intend to quit, smoking-reduction support with pharmacotherapy versus no intervention was found to be beneficial in achieving complete cessation (RR 1.93, 95% CI 1.41–2.64).¹⁴⁷ Of note, the authors used only long-term follow-up (> 6 mo) data, and, to our knowledge, no similar shorter-term data exist. Although the data are limited, pharmacotherapy is likely a major contributor to the success of smoking-reduction plans. Reduction counselling and support alone versus no intervention did not significantly increase abstinence (RR 1.49, 95% CI 0.56–3.93). Both reduction counselling and support with varenicline therapy (RR 2.66, 95% CI 2.10–3.36) and reduction counselling and support with NRT (RR 1.94, 95% CI 1.26–3.00) were far superior to reduction support with placebo.

Although there is currently no good evidence that preoperative smoking reduction without cessation improves surgical outcomes,¹⁵² supporting surgical patients who are interested in smoking reduction preoperatively has no adverse consequences, improves long-term quit rates and may lead to preoperative cessation.¹⁴⁷

6. All surgical patients who smoke should be offered the combination of counselling and pharmacotherapy preoperatively. When this is not possible, they should still be offered either intervention individually.

Both pharmacotherapy and cessation counselling are effective alone^{145,156,157} and should be provided even if a patient is not interested in combined therapy. Whenever

possible, patients who are willing to quit should be provided both interventions: a meta-analysis showed that combining therapies has increased efficacy compared to pharmacotherapy (OR 1.4, 95% CI 1.2–1.6) or behavioural therapy (OR 1.7, 95% CI 1.3–2.1) alone.¹⁴⁰

7. All surgical patients who smoke should be offered combination nicotine replacement therapy (NRT) preoperatively. Prescribers capable of follow-up may consider varenicline as a first-line agent. Second-line options include single-agent NRT and bupropion.

Three therapies approved in Canada have been shown to increase smoking cessation rates in the general population: varenicline, NRT and bupropion.¹⁵⁸ Combination NRT (combining daily use of a nicotine patch with a short-acting adjunct [gum, lozenge, inhaler or spray, according to patient preference]) is more effective than NRT patch (OR 1.43, 95% CI 1.08–1.91), NRT gum (OR 1.63, 95% CI 1.21–2.20), or NRT lozenge/inhaler/spray (OR 1.34, 95% CI 1.00–1.80) alone. Varenicline is superior to any single-agent NRT (OR 1.57, 95% CI 1.29–1.91) and to bupropion (OR 1.56, 95% CI 1.26–1.93). Bupropion is less effective than combination NRT (OR 0.68, 95% CI 0.50–0.91).¹⁵⁶ Nicotine replacement therapy options are sold over the counter, whereas both varenicline and bupropion require a prescription.¹⁵⁶

We recommend combination NRT and varenicline as first-line treatments, as they are the most effective smoking-cessation interventions (Appendix 1), with no significant difference between them in direct comparison (OR 1.06, 95% CI 0.75–1.48).¹⁵⁶ Combination NRT has no absolute contraindications¹⁵⁶ or required follow-up, and was associated with reduced postoperative complication rates in 2 RCTs.^{152,153} It can easily be prescribed by surgeons, who can place patient concerns about the cost of patches (\$20/wk) and adjuncts (\$15–\$40/wk) in the context of savings from cigarette purchases¹⁵⁹ and overall health benefits.

Varenicline is the most effective monotherapy for smoking cessation (OR 2.89, 95% CI 2.40–3.48)¹⁵⁶ but has not been as well studied in the perioperative setting as NRT. Wong and colleagues¹⁶⁰ reported that 12 weeks of varenicline therapy initiated 1 week preoperatively significantly increased cessation rates 1 year after surgery (RR 1.45; $p = 0.04$). Given its efficacy, we consider varenicline a first-line treatment.

Bupropion is an atypical antidepressant that has been shown to improve smoking cessation rates versus placebo (OR 1.85, 95% CI 1.63–2.10).¹⁵⁶ It is contraindicated in patients with increased seizure risk. As it has not been well studied in the perioperative setting and is less effective than both combination NRT and varenicline, we consider it a second-line option.

Randomized controlled trials across 140 centres in 16 countries have shown no evidence that any of these 3 therapies are associated with an increased risk of adverse

cardiovascular¹⁶¹ or neuropsychiatric¹⁶² events. A 2012 systematic review showed no clinical evidence of a detrimental effect of NRT on postoperative wound or tissue healing.¹⁶³

8. All surgical patients who smoke should be given brief counselling on the consequences of smoking and the benefits of smoking cessation preoperatively. When possible, counselling should be face to face, frequent and of sufficient duration, all of which increase cessation rates.

Physician counselling to quit smoking has been shown to increase the likelihood of short-term abstinence by 30% (OR 1.3, 95% CI 1.1–1.6), and even interventions as brief as 3 minutes can increase cessation rates significantly (OR 1.3, 95% CI 1.01–1.60).¹⁴⁰

A meta-analysis of 22 studies in patients scheduled to undergo elective surgery showed 6 behaviour-change techniques leading to higher rates of smoking abstinence: provision of information on the consequences of smoking and smoking cessation; facilitation of goal setting; prompt review of cessation goals; regular monitoring by others (e.g., friends or family members); options for additional and later support; and provision of information on withdrawal symptoms.¹⁴⁵ Of these, providing information on the consequences of smoking and smoking cessation was the most significant predictor of quitting ($\beta = 0.69$, $p = 0.01$). Counselling interventions may be delivered (in order of most to least effective) face to face, by telephone, over the Internet¹⁶⁴ or in print. Higher cessation rates have been shown with increased duration ($\beta = 0.01$, $p = 0.02$) and frequency ($\beta = 0.22$, $p = 0.002$) of intervention sessions,¹⁴⁵ which is reflected in the US and Canadian guidelines.^{140,165}

Several other techniques have been attempted in perioperative RCTs, without evidence of increased preoperative cessation rates. These include a decision aid with laminated graphics to facilitate discussion,¹⁶⁶ a behavioral tapering regimen (scheduled reduced smoking) via handheld computer¹⁶⁷ and planned checks of carbon monoxide levels on the day of surgery.¹⁶⁸

9. All surgical patients who smoke should be offered clinical follow-up.

Offering follow-up provides cessation support after the initial intervention, and follow-up interventions with increased frequency are more effective.¹⁴⁰ Lindström and colleagues¹⁵³ reported that a weekly face-to-face or telephone intervention of smoking cessation therapy with individual counselling and NRT delivered by a trained nurse starting 4 weeks preoperatively led to both increased perioperative cessation rates (39.6% v. 1.9%) and decreased postoperative complication rates (21% v. 41%, $p = 0.03$) compared to standard care.

A meta-analysis of RCTs or quasi-randomised controlled trials in which telephone counselling was offered to smokers or recent quitters to assist smoking cessation

showed an increase in smoking cessation rates when used as the primary intervention (RR 1.34, 95% CI 1.22–1.46), when following a face-to-face intervention (RR 1.41, 95% CI 1.20–1.66) and when used as an adjunct to NRT or varenicline (RR 1.14, 95% CI 1.03–1.27).¹⁶⁹ Having 3 or more follow-up telephone calls showed additional benefit (RR 1.32, 95% CI 1.23–1.42). In busy surgical clinics, repeat preoperative visits and follow-up with specialized nurses may not always be feasible or cost-effective. Lee and colleagues¹⁷⁰ conducted an RCT in which patients seen at least 3 weeks preoperatively received either no specific smoking-cessation intervention, or an intervention consisting of brief counselling by the preadmission nurse, brochures on smoking cessation, referral to a smokers helpline (available at no cost in all Canadian provinces) and a free 6-week supply of NRT. Significantly reduced smoking rates were observed in the intervention group at the time of surgery (14.3% v. 3.6%; $p = 0.03$).

Conclusion

Smoking is the most important risk factor for postoperative complications and should be routinely identified, documented and treated preoperatively according to the patient's willingness to quit. By targeting a quit date of at least 8 weeks before surgery and offering a combination of brief counselling with pharmacotherapy and follow-up, clinicians can reduce perioperative smoking rates and postoperative complication rates. Given the minimal time and resources required, along with the substantial benefits of cessation, a preoperative smoking-cessation program should be offered in all surgical clinics.

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