1. Introduction

Surgical site infections (SSIs) are defined as infections anatomically associated with a surgical procedure performed in an operating room and not present prior to the operation. These infections represent an important problem for patients and a significant financial burden for the health care system.

There is evidence that optimized blood flow to the surgical incision decreases SSI rates through avoidance of hypothermia, hypoxia and decreased perfusion. Since 2000, several trials have been published on the use of high fractions of inspired oxygen concentration (FiO2) during the perioperative period and the potential association with lower rates of SSI. These studies include randomized controlled trials (RCTs), meta-analyses and the long-term survival follow-up of original cohorts.

The intervention consists of providing patients with 80% oxygen compared to the usual administration of 30% oxygen. Patients are routinely given 100% oxygen for 30 seconds to 2 minutes prior to intubation and then maintained on either “normoxia”, defined as oxygen at FiO2 30% or 35%, or “hyperoxia”, defined as oxygen at FiO2 80%. The arguments for providing oxygen levels beyond the standard 30% are largely based on two notions (1). The first is that the surgical incision may not be adequately perfused and might receive substantially higher oxygen if there is a higher partial pressure of oxygen in the blood (2). The other notion is that host defense systems might be further improved by higher oxygen partial pressures, particularly by enhancing neutrophil oxidative killing (3).

The argument regarding enhanced killing devolves down to the affinity of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase for oxygen. The Km (Michaelis constant) for the enzyme for oxygen is 5-20 μM Hg O2 (4, 5). It has been shown that oxygen tension at infected sites is greatly reduced compared with most uninfected tissues, with P02 approximating 25 mM of oxygen, equivalent to 3% oxygen (6).

SSI prevention bundles developed by the United Kingdom (UK) Department of Health High Impact Interventions and Health Protection Scotland, as well as guidelines from the Royal College of Physicians of Ireland and the UK-based National Institute for Health and Care Excellence (NICE), recommend maintaining a haemoglobin oxygen saturation of at least 95% (7-10). The SSI prevention guidelines of the Society for Healthcare Epidemiology of America (SHEA)/Infectious Diseases Society of America (IDSA) recommend optimizing tissue oxygenation by administering supplemental oxygen during and immediately following surgical procedures involving mechanical ventilation (11).
2. PICO question

How safe and effective is the perioperative use of increased FiO2 in reducing the risk of SSI?

- **Population**: patients of any age undergoing any type of surgical procedures
- **Intervention**: perioperative administration of increased FiO2 (80%)
- **Comparator**: perioperative administration of standard FiO2 (30-35%)
- **Outcomes**: SSI, SSI-attributable mortality

3. Methods

The following databases were searched: Medline (PubMed); Excerpta Medica Database (EMBASE); Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Central Register of Controlled Trials (CENTRAL); and WHO regional medical databases. The time limit for the review was between 1 January 1990 and 17 January 2014. There was no language restriction. A comprehensive list of search terms including Medical Subject Headings (MeSH) was used (Appendix 1).

Two independent reviewers screened titles and abstracts of retrieved references for potentially relevant studies. The full text of all potentially eligible articles was obtained. Two authors independently reviewed the full text articles for eligibility based on inclusion criteria. Duplicate studies were excluded.

Two authors extracted data in a predefined evidence table (Appendix 2) and critically appraised the retrieved studies using the Cochrane collaboration tool (12) for assessing risk of bias (Appendix 3). Any disagreements were resolved through discussion or after consultation of the senior author, when necessary. Publication bias was assessed using a funnel plot (13).

Meta-analyses of available comparisons according to type of anaesthesia and respiratory control and type of surgery were performed using Review Manager v5.3 (14) as appropriate (Appendix 4). Odds ratios (OR) and mean differences with 95% confidence intervals (CI) were extracted and pooled for each comparison with a random effects model. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (GRADE Pro software; http://gradepro.org/) (15, 16) was used to assess the quality of the body of retrieved evidence (Appendix 5).
4. Study selection

Flow chart of the study selection process

- Potentially relevant articles: 1071
  - Medline: 231
  - EMBASE: 495
  - CINAHL: 257
  - Cochrane CENTRAL: 61
  - WHO Global Library: 27

- Total articles after removal of duplicates: 674

- Excluded after title and abstract screening: 618

- Total articles screened: 674

- Full-text articles assessed for eligibility: 56

- Full-text articles excluded:
  - Review: 6
  - Retrospective/non-randomized controlled trial: 26
  - No SSI outcome: 9

- Randomized controlled trials included in the analysis: 15
5. Summary of the findings

We identified 15 randomized controlled trials (RCTs) (17-31) including a total of 7237 patients, which investigated the perioperative use of increased FiO2 and reported SSI as an outcome. All trials compared the administration of 80% FiO2 to 30-35% FiO2 (14 studies, 30%, and one study (23) 35%). The type of anaesthesia and respiratory control varied between neuraxial anesthesia with a facemask or nasal cannula (28-31) and general anaesthesia with endotracheal intubation and mechanical ventilation (17-27). Operative procedures differed also between colorectal surgery (17, 19, 20, 25), acute and elective abdominal surgery (21-23), gynaecological procedures and breast surgery (27), tibial fixation (26) and caesarean section (28-31).

Accordingly, the following comparisons and subgroup analyses were performed:

1) Administration of increased FiO2 vs. standard oxygenation

   a) Subgroup analysis according to type of anaesthesia and respiratory control

      i. Administration of increased FiO2 vs. standard oxygenation in patients undergoing procedures under neuraxial anaesthesia with nasal cannula or a facemask.

      ii. Administration of increased FiO2 vs. standard oxygenation in patients undergoing procedures under general anaesthesia with endotracheal intubation.

2) Administration of increased FiO2 vs. standard oxygenation in patients undergoing general anaesthesia with endotracheal intubation

   a) Subgroup analysis according to the type of surgery

      i. Colorectal surgery

      ii. Mixed surgical procedures

The results were as follows.

1) Administration of increased FiO2 vs. standard oxygenation

Fifteen studies (17-31) compared increased perioperative FiO2 (80%) with standard perioperative FiO2 (30-35%) in patients undergoing surgery. A meta-analysis of these studies showed that increased perioperative FiO2 had neither benefit nor harm compared to standard perioperative FiO2 (OR: 0.84; 95% CI: 0.66-1.06).

   a) Subgroup analysis according to the type of anaesthesia and respiratory control

      i. Neuraxial anaesthesia with nasal cannula or a facemask

      Among the 15 studies, 4 (28-31) compared increased perioperative FiO2 (80%) with standard perioperative FiO2 (30-35%) in patients having a caesarean section under neuraxial anesthesia with a facemask or nasal cannula. All studies showed no significant difference between the 2 groups. Subgroup analyses showed that increased perioperative FiO2 has neither benefit nor harm compared
to standard perioperative FiO2 (OR: 0.82; 95% CI: 0.59-1.13) (Appendix 4).

ii. General anaesthesia with endotracheal intubation
Eleven studies (17-27) compared increased perioperative FiO2 (80%) with standard perioperative FiO2 (30-35%) in patients undergoing surgery under general anaesthesia with endotracheal intubation. Subgroup analyses showed that increased perioperative FiO2 had a significant benefit when compared to standard perioperative FiO2 (OR: 0.72; 95% CI: 0.55-0.94) (Appendix 4).

Meta-regression
In meta-regression analysis, general anaesthesia with endotracheal intubation proved to be a significant covariate and independently modified the effect of hyperoxygenation (P=0.05).

2) Administration of increased FiO2 vs. standard oxygenation in patients undergoing general anaesthesia with endotracheal intubation
Eleven studies (17-27) compared increased perioperative FiO2 (80%) with standard perioperative FiO2 (30-35%) in patients undergoing surgery under general anaesthesia with endotracheal intubation. A meta-analysis showed that increased perioperative FiO2 had a significant benefit when compared to standard perioperative FiO2 (OR: 0.72; 95% CI: 0.55-0.94) (Appendix 4).

a) Subgroup analysis according to the type of surgery

i. Colorectal surgery
Among the 11 studies, 4 RCTs (17, 19, 20, 25) investigated the intervention (increased perioperative FiO2 [80%]) in patients undergoing exclusively colorectal procedures). Two studies (17, 19) reported a significant decrease in SSI among patients receiving increased perioperative FiO2 and the remaining 2 (20, 25) reported no statistically significant difference between the groups. Subgroup analysis of these 4 studies showed that increased perioperative FiO2 had a significant benefit compared to standard perioperative FiO2 (30-35%) (OR: 0.50; 95% CI: 0.33-0.74). (Appendix 4).

ii. Mixed surgical procedures
The remaining 7 RCTs (18, 21-23, 25-27) investigated the intervention in a mixture of surgical procedures (acute and elective abdominal surgery, gynaecological procedures, breast surgery and tibial fixation). Of these, one study (22) found a significant reduction in the intervention group. Five studies (18, 21, 25-27) reported ORs in favour of the intervention group, but found no statistically significant difference. One study (23) reported a significant increase in SSI in the intervention group. Subgroup analyses of the 7 studies showed that increased perioperative FiO2 (80%) has neither benefit nor harm compared to standard perioperative FiO2 (30-35%) (OR: 0.82; 95% CI: 0.59-1.13) (Appendix 4).

Meta regression
In meta-regression analysis, the type of surgery was not significantly associated with the effect of hyperoxygenation (P=0.101).
After careful appraisal of the included studies, the research team and the Guidelines Development Group decided to include only studies in which patients were under general anaesthesia with endotracheal intubation and mechanical ventilation (17-27) for the recommendation. Thus, studies using neuraxial anaesthesia with a facemask or nasal cannula were excluded (28-31). The type of anaesthesia proved to independently modify the effect of hyperoxygenation in the meta-regression analysis when introducing general anaesthesia with endotracheal intubation as a significant covariate (see above). In neuraxial anesthesia with nasal cannula or a facemask, control of ventilation, and thereby control of the actual administration of high FiO2 to the lungs, is limited and was considered to be different from the intervention with mechanical ventilation. No significant association was found between the type of surgery and the effect of hyperoxygenation.

In conclusion, the retrieved evidence can be summarized as follows.

Overall, a moderate quality of evidence shows that increased perioperative FiO2 (80%) is beneficial in reducing SSI when compared to standard perioperative FiO2 (30-35%) in patients undergoing surgical procedures under general anaesthesia with endotracheal intubation (OR: 0.72; 95% CI: 0.55-0.94). It resulted also in 36 fewer (from 7 fewer to 59 fewer) infections per 1000 treated patients (Appendix 4). The quality of the evidence for this comparison was moderate due to the risk of inconsistency (Appendix 5).

The benefit of hyperoxygenation tended to be greater in open colorectal surgery (OR: 0.50; 95% CI: 0.33-0.74) than in other types of surgery (OR: 0.82; 95% CI: 0.59-1.13), but no significant association was found between the type of surgery and the effect of hyperoxygenation.

Some limitations were observed in the available studies. It is unclear whether the administration of oxygen was consistently carried out postoperatively in all studies. Furthermore, in the context of the intervention, the additional benefit of postoperative hyperoxygenation with a facemask was not assessed. Other potential sources of heterogeneity were also discussed, including the age of the population (older patients may benefit more) and duration of surgery.

6. Other factors considered in the review

The systematic review team identified the following other factors to be considered.

Potential harms

None of the included studies showed a significant difference in pulmonary complications or other adverse events attributable to the intervention. There have been reports of atelectasis after administration of 100% oxygen before tracheal extubation and this has raised a concern regarding the administration of high FiO2 (32-34). However, this same increase in atelectasis has been described after the administration of 100% FiO2 compared to 80% FiO2 and showed a meaningful difference between the two concentrations (33). All included studies used a maximum FiO2 of 80%. Moreover, none of the clinical trials investigating the administration of 80% FiO2 that reported adverse events showed a significant difference in pulmonary complications or other adverse events (21, 22, 35, 36). In addition, there was a considerable variation in the exclusion criteria for underlying lung disease, especially when chronic obstructive pulmonary disease was diagnosed. Patients with chronic obstructive pulmonary...
disease should be evaluated preoperatively and their perioperative anesthesia needs to be designed to minimize complications as the risks of high inspiratory concentrations of oxygen may outweigh the benefits for these patients (37).

The long-term survival analysis of the trial by Meyhoff and colleagues seems to be in favour of normal oxygenation (38). However, the trial is underpowered for this purpose and a lower significance level is needed to avoid spurious statistical significance (39). For this reason, the presented $P$ value of 0.03 cannot be regarded as significant and may be considered as a type I error (40, 41). Shorter survival was predominantly observed in patients with malignant disease, but Cox regression analysis showed no association with new or recurrent cancer and a shorter survival time (42). Moreover, there is extensive experimental support of oxygen being a tumour suppressant (43-46). Finally, the long-term survival rate of the Enigma trial showed no difference between groups (22). Therefore, we conclude that there is no evidence of increased long-term mortality attributable to high FiO2 during the perioperative period at the present time.

A recent systematic review assessed the same PICO question (47). However, the conclusions by Wetterslev and colleagues differ substantially from those presented in this document. Although the same data were used in the analysis performed for this review, the authors did not conduct a subgroup analysis based on the type of anaesthesia (that is, general with endotracheal intubation vs. neuraxial with facemask or nasal cannula) as done here according to the strong suggestion by the Guidelines Development Group. In the review by Wetterslev and colleagues, general anaesthesia was not identified as a significant covariate and, consequently, it was not taken into account in the final analysis, thus resulting in a different outcome. The Guidelines Development Group strongly believes that the approach chosen here is superior and the difference in outcome is of critical importance for the presented recommendation.

7. **Key uncertainties and future research priorities**

The key uncertainty is the effect of the administration of high oxygen concentrations (80%) in other/mixed procedures under general anaesthesia with endotracheal intubation. Although there is no harm, a significant effect has not been shown. In addition, there is uncertainty about the time dependence for the effect. All studies reported a postoperative high oxygen flow, but this was not consistent and no study examined termination of high oxygen administration at extubation. Studies need to be conducted in low- and middle-income countries and to include different surgical procedures, while ensuring also that basic infection prevention and control measures are in place. Research investigating the benefit of post-extubation hyperoxaemia is also needed.
APPENDICES

Appendix 1: Search terms

PubMed (including Medline)


#2 #1 AND "oxygen/administration and dosage"[Mesh]
#3 #1 AND "oxygen inhalation therapy"[Mesh]
#4 #1 AND "oxygen"[TIAB]
#5 #1 AND "oxygenation"[TIAB]
#6 #1 AND "inspired oxygen fraction" [TIAB]
#7 #1 AND "FiO2"
#8 #1 AND "FiO(2)"
#9 #1 & #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8

EMBASE and CINAHL

’surgical wound infection'/exp OR 'surgical wound infection' OR surgical AND site AND infection* OR 'ssi' OR 'ssis' OR surgical AND ('wound'/exp OR wound) AND infection* OR surgical AND infection* OR 'post operative' AND ('wound'/exp OR wound) AND infection* OR postoperative AND ('wound'/exp OR wound) AND infection* OR 'wound'/exp OR wound AND infection* OR 'preoperative care'/exp OR 'preoperative care' OR 'perioperative care'/exp OR 'perioperative care' OR 'perioperative care' OR 'peri-operative care' OR 'perioperative' OR 'intraoperative' OR 'perioperative period'/exp OR 'perioperative period' OR 'intraoperative period'/exp OR 'intraoperative period' AND (‘infection’ OR ‘infection'/exp OR infection) AND [1990-2014]/py AND ("oxygen/administration and dosage" OR oxygen inhalation therapy OR oxygen OR oxygenation OR "inspired oxygen fraction" OR "FiO2" or "FiO(2)"")

Cochrane CENTRAL

((SSI) OR (surgical site infection) OR (surgical site infections) OR (wound infection) OR (wound infections) OR (postoperative wound infection)) AND oxygen

WHO Global Library

((SSI) OR (surgical site infection) OR (surgical site infections) OR (wound infection) OR (wound infections) OR (postoperative wound infection))

ti: title; ab: abstract.
Appendix 2: Evidence table
<table>
<thead>
<tr>
<th>Author, year, reference</th>
<th>Design, scope, setting, population type of surgery</th>
<th>SSI definition</th>
<th>Study methods</th>
<th>Intervention</th>
<th>Results</th>
<th>Risk of bias</th>
<th>Quality of evidence</th>
</tr>
</thead>
</table>

RCT of men and women undergoing elective open colorectal resection in 14 hospitals.

Spain, multicentre

Exclusion criteria: recent history of fever and/or infection; diabetes mellitus; HIV; serum albumin <3.0 gm/dL; white cell count of <2500 cells per cubic mm; or the loss of >20% of body weight within the past 3 months.

Elective colorectal resection, including abdomino-perineal resection.

**Mechanical bowel preparation:** electrolyte solution that did not contain antibiotics or antiseptics.

Antibiotic prophylaxis with metronidazole plus cefoxitin or a 3rd generation cephalosporin was administered 60-90 minutes before the surgical incision and continued postoperatively for up to 48 hours. Aminoglycosides were used as an alternative to beta-lactam antibiotics in patients who reported a history of cephalosporin allergy.

**Intraluminal antibiotics:** not specified.

**Intravenous antibiotics:** MTZ with 3rd generation cephalosporin or cefoxitin given 60-90 minutes before incision and continued for 48 hours.

**Skin antiseptics:** not specified.

**Warming:** maintained ≥ 36 °C.

**Maintenance fluids:** crystalloid solution administered IV at a rate of 15 mL per kg per hour throughout surgery. Fluids were administered at a rate of 3 mL per kg per hour for the first 6 hours.

**Randomization:** randomization was stratified by study centre. Computer-generated codes were maintained in sequentially numbered opaque envelopes. The randomization envelopes were opened in the operating department after induction of anaesthesia by the anaesthesiologist. Patients were assigned to an oxygen/air mixture with an FiO2 of 30% or 80%. The surgical team was blinded to group assignment. Patients were not informed of their group assignment.

<table>
<thead>
<tr>
<th>Infection (number (%))</th>
<th>Low</th>
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<tbody>
<tr>
<td>30%:</td>
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RCT (patients and observers blinded) of men and women >15 years of age undergoing open appendectomy between November 2006 and May 2009. All subjects were categorized as having an American Society of Anesthesiologists score of 1 or 2. Israel, single centre

Exclusion criteria: patients with COPD; severe malnutrition (serum albumin concentration 3 g/dL); or immunodeficiency disease.

Open appendectomy

A follow-up visit was conducted within 2 weeks after surgery.

**Intravenous antibiotics:** preoperative antibiotics against gram-negative and anaerobic bacteria were given to all patients, including intravenous aminoglycosides (gentamicin sulfate, 5 mg/kg) and metronidazole (500 mg). When intraoperative findings indicated a gangrenous or perforated appendicitis, antibiotic treatment lasted for 5 days.

**Skin antiseptics:** not specified.

**Warming:** “strictly maintained during the operation and convalescence”.

**Maintenance fluids:** hydration “strictly maintained during the operation and convalescence”.

**Randomization:** patients were randomized by an unspecified method. Patients, surgical teams and outcome assessors were blinded.

One group of patients received 30% oxygen and 70% nitrogen; the other group, 70% oxygen and 20% room air.

After extubation, the concentrations were returned to the previous levels as soon as deemed safe. During the first 2 hours of recovery, oxygen at either 10 L through a non-rebreathing mask or 4 L by nasal cannula were provided. Patients in both treatment groups subsequently breathed ambient air.

“The decision to conclude the study at this stage was made owing to recent major changes in professional personnel in the departments of surgery and anaesthesiology (avoiding strict adherence to the protocol) and the impression that statistical results had already been obtained.”

<table>
<thead>
<tr>
<th>Infection number (%)</th>
<th>30%: 14/103 (13.6)</th>
<th>80%: 6/107 (5.6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>0.04; OR: 0.38; 95% CI: 0.14-1.02</td>
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</tbody>
</table>
RCT of women who underwent scheduled or intrapartum caesarean delivery between 2006 and 2010.

USA, multicentre

Exclusion criteria: fever (temperature of 38°C or higher); chorioamnionitis (temperature of 38°C or higher with fetal or maternal tachycardia); patients who were group B streptococci-positive and had been started on antibiotics; immunocompromised or HIV-positive patients; planned general anaesthesia; age younger than 18 years; and incarcerated patients.

**Caesarean section**

The primary outcome was a composite of either SSI or endometritis.

According to the CDC definition.

Postpartum endometritis was diagnosed by the clinical finding of a temperature of more than 38°C associated with uterine tenderness without any other source of fever.

Patients were followed up to 2 weeks.

**Intravenous antibiotics:** cefazolin 2 g 60-90 minutes after cord clamping, and continued for 48 hours.

**Skin antiseptics:** not specified.

**Warming:** not specified.

**Maintenance fluids:** not described.

**Randomization:** a computer-generated randomization table was used to allocate eligible women to either 30% or 80% oxygen during surgery (after umbilical cord clamping) and for 1 hour postoperatively. Randomization was done after cord clamping. The anaesthesiologist was the only person aware of the concentration of oxygen given to the patient.

One group of patients received 30% oxygen and 70% room air; the other group, 80% oxygen and 20% room air, beginning after cord clamping and for 1 hour after wound closure. Patients in both treatment groups subsequently breathed ambient air unless additional oxygen was required to maintain an oxyhemoglobin saturation of more than 94%.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Infection number (%)</th>
<th>P</th>
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<tbody>
<tr>
<td>30%</td>
<td>35/425 (8.2)</td>
<td>0.89</td>
</tr>
<tr>
<td>80%</td>
<td>34/416 (8.2)</td>
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</table>
143 women undergoing caesarean delivery after the onset of labour or rupture of membranes under regional anaesthesia. Patients were randomly assigned to receive low- or high-concentration FiO2 via a non-rebreathing mask during the operation and for 2 hours after. USA, single centre

Study exclusion criteria randomization; caesarean delivery before the onset of labour or rupture of membranes; emergent caesarean delivery; general endotracheal anaesthesia (those who started with regional anaesthetic and converted to general anaesthesia were not excluded); clinical chorioamnionitis; and HIV infection.

Caesarean section

Administration of intravenous antibiotics for postpartum endometritis, or oral or intravenous antibiotics for wound infection during the initial hospital stay or within 14 days of surgery.

Postpartum endometritis was defined as fever equal to or greater than 38.5°C within the first 24 hours postpartum or greater than 38.0°C for at least 4 hours after the first 24 hours postpartum and associated with uterine tenderness greater than expected without other identified sources of fever.

Wound infection included cellulitis, as well as deeper incisional infections that required the wound to be opened.

Intravenous antibiotics: “all but one received prophylactic antibiotics”; timing, drug and dose not provided.

Skin antiseptics: “betadine scrub”.

Warming: not specified.

Maintenance fluids: not specified.

Randomization: an appropriate randomization technique using sequential sealed envelopes with allocation assigned by s random numbers table prior to sealing. Patients and surgical team were blinded.

An interim analysis using a formal stopping rule for both efficacy and futility was performed and the study was stopped after the planned analysis suggested futility.

Infection number (%)  
Low: 30%: 17/85 (14)  
High: 80%: 8/86 (9.3)  
P<0.05 ; RR 0.61;  
95% CI: 0.9-3.7 (favours low oxygen)
RCT of men and women undergoing elective open colorectal resection for middle or low rectal cancer. Austria and Germany, multcentre

Exclusion criteria: recent history of fever and/or infection; serious malnutrition (as indicated by a serum albumin concentration of <3.3 per dL; a white cell count of <2500 cells per cubic millimeter; or the loss of >20 % of body weight; and bowel obstruction.

Elective colorectal resection, including abdomino-perineal resection.

Wounds were considered likely to be infected when pus could be expressed from the incision or aspirated from a loculated mass within the wound. Pus was cultured, and wounds were considered infected when bacteria were cultured from the pus.

**Mechanical bowel preparation:** electrolyte solution.

**Intraluminal antibiotics:** not used.

**Intravenous antibiotics:** MTZ with cefazolin, cefamandole, amoxicillin/clavulanate or mezlocillin.

**Skin antiseptics:** not specified.

**Warming:** maintained ≥ 36°C.

**Maintenance fluids:** crystalloid solution administered IV at a rate of 15 mL per kg per hour throughout surgery. Fluids were administered at a rate of 3.5 mL per kg per hour for the first 24 hours after surgery and at a rate of 2 mL per kg per hour for the subsequent 24 hours.

**Randomization:** each patient was assigned through the use of a set of computer-generated random numbers. The assignments were stratified according to the participating hospital and were kept in sequential sealed envelopes. Randomization and allocation occurred after induction of anaesthesia.

One group of patients received 30% oxygen and 70% nitrogen; the other group, 80% oxygen and 20% nitrogen.

After extubation, the concentrations were returned to the previous levels as soon as deemed safe. During the first 2 hours of recovery, oxygen at the specified concentration was given through a non-rebreathing mask. Patients in both treatment groups subsequently breathed ambient air unless additional oxygen was required to maintain an oxyhemoglobin saturation of more than 92%.

<table>
<thead>
<tr>
<th>Infection number (%)</th>
<th>Low</th>
<th>Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>30%: 28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80%: 13</td>
<td></td>
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<tr>
<td>P=0.01</td>
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</tbody>
</table>
RCT of men and women undergoing elective open colorectal resection between January 2001 and January 2002. Israel, single centre

Exclusion criteria: American Society of Anesthesiologists class 3 or 4; body mass index > 35; diabetes mellitus; COPD; serious malnutrition (serum albumin < 3.3 g/dL, leukocyte count < 2500/mL, or loss of 20% or more of body weight); and preoperative immunosuppressive therapy. The study was designed to examine the benefits of reducing nitrous oxide-induced nausea and vomiting that would translate into a longer length of stay.

Elective colorectal resection, including abdomino-perineal resection.

<table>
<thead>
<tr>
<th>CDC criteria</th>
<th>Mechanical bowel preparation:</th>
<th>Intravenous antibiotics:</th>
<th>Infection number (%)</th>
<th>Low</th>
<th>Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients followed up each hospital day, at 1 week, and then at 1 month.</td>
<td>Electrolyte solution.</td>
<td>Choice of antibiotic prophylaxis according to institutional practice.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraluminal antibiotics: vancomycin and erythromycin.</td>
<td>Skin antiseptics: not specified.</td>
<td></td>
<td>30%: 2/19</td>
<td>(12.5)</td>
<td></td>
</tr>
<tr>
<td>Intravenous antibiotics:</td>
<td>Warming: maintained ≥ 36°C by forced-air covers.</td>
<td></td>
<td>80%: 3/19</td>
<td>(17.6)</td>
<td></td>
</tr>
<tr>
<td>Maintenance fluids: crystalloid solution administered IV at a rate of 15 mL per kg per hour throughout surgery. Fluids were administered at a rate of 30 mL per kg per day for the first 48 hours after surgery.</td>
<td>Randomization: a computer-generated code accessed via an automated telephone voice recognition service. Treatment assignment was stratified by site and elective/emergency status of the surgery using permuted blocks.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One group of patients received 30% oxygen and 70% nitrogen; the other group, 80% oxygen and 20% nitrogen. After extubation, the concentrations were returned to the previous levels as soon as deemed safe. During the first 2 hours of recovery, oxygen at the specified concentration was given through a non-rebreathing mask. Patients in both treatment groups subsequently breathed ambient air unless additional oxygen was required to maintain an oxyhemoglobin saturation of more than 92%.</td>
<td></td>
<td></td>
<td>30%: 2/19</td>
<td>(12.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>80%: 3/19</td>
<td>(17.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P=0.53</td>
<td></td>
</tr>
</tbody>
</table>
The PROXI trial

RCT (patients and observers blinded) of men and women undergoing elective and acute laparotomies in 14 hospitals between October 2006 and October 2008. Patients were eligible if they were 18 years or older and scheduled to undergo acute or elective laparotomy.

Denmark, multicentre

Exclusion criteria: operations under general anaesthesia within 30 days; chemotherapy for malignancy within 3 months; and preoperative arterial O2 saturation <90%.

Elective colorectal resection, including abdomino-perineal resection.

CDC criteria

A follow-up visit was conducted between postoperative days 13 and 30.

(See reference (48) for the rationale for each element of the protocol)

Mechanical bowel preparation: not done.

Intraluminal antibiotics: not specified.

Intravenous antibiotics: the protocol recommended cefuroxime (1.5 g) and metronidazole (1 g) given IV as the standard antibiotic choice, but ampicillin (2 g) or benzylpenicillin (2 million IU) in combination with gentamicin (0.240 g) and metronidazole (1 g) were also allowed.

“Timely” administration of the first and second antibiotic within 60 minutes prior to skin incision.

Skin antiseptics: not specified.

Warming: maintained ≥ 36°C with forced air.

Maintenance fluids: perioperative fluids were given only to replace measured or calculated deficits (no third space loss), aiming at a postoperative body weight increase of less than 1 kg.

Randomization: patients were randomized according to a computer-generated allocation list by a central interactive voice-response system at the central trial unit used as study centre, diabetes mellitus, acute or elective operations, and body mass index as stratification variables. Patients, surgical teams and outcome assessors were blinded.

One group of patients received 30% oxygen and 70% room air; the other group, 80% oxygen and 20% room air. However, a range of FiO2 concentrations (25–100%) was allowed if the anaesthesiologist had a strong preference, if medical air was unavailable or if clinically indicated.

After extubation, the concentrations were returned to the previous levels as soon as deemed safe. During the first 6 hours of recovery, oxygen at the specified concentration was given through a non-rebreathing mask. Patients in both treatment groups subsequently breathed ambient air unless additional oxygen was required to maintain an oxy-hemoglobin saturation of more than 92%.

Infection number (%)

| 30%: 141/701 (20.1) |
| 80%: 131/685 (19.1) |

P=0.64

OR: 0.94 (95% CI: 0.72-1.22)
RCT in patients over 17 years of age having major surgery expected to last at least 2 hours and expected to be in the hospital for >2 days after surgery were randomly assigned to nitrous oxide–free (80% oxygen, 20% nitrogen) or nitrous oxide–based (70% N2O, 30% oxygen) anaesthesia.

Australia and Hong Kong, multicentre trial with 19 sites. Administration commenced after induction of anaesthesia and was maintained until extubation.

Exclusion criteria: patients undergoing cardiac or thoracic surgery requiring one-lung ventilation. If the anaesthesiologist considered that nitrous oxide was contraindicated.

If the anaesthesiologist wanted to use supplemental oxygen for colorectal surgery.

Follow-up was for 30 days.

Mixed cases.

| Wound infection—if associated with purulent discharge, with or without a positive microbial culture; or pathogenic organisms isolated from aseptically obtained microbial culture |
| Intravenous antibiotics: “per institutional practice”. |
| Skin antiseptics: not specified. |
| Warming: “Anaesthesiologists were advised to avoid intraoperative hypothermia (<35.5°C)”. |
| Maintenance fluids: “…at the discretion of the attending anaesthesiologist.” |

Randomization: allocated using a computer-generated code accessed via an automated telephone voice recognition service. Treatment assignment was stratified by site and elective/emergency status of the surgery using permuted locks. Patients were randomly assigned to an oxygen/air mixture with an FiO2 of 30% (group 1) or 80% (group 2). Patients were not informed of their group assignments. The surgical team was blinded to the anaesthetic administered.

For patients assigned to nitrous oxide–free anaesthesia, anaesthesiologists were advised to administer a gas mixture of 80% oxygen with 20% nitrogen. However, a range of FiO2 concentrations (25–100%) was allowed if the anaesthesiologist had a strong preference, if medical air was unavailable or if clinically indicated.

For patients assigned to the nitrous oxide–based anaesthesia, anaesthesiologists were advised to administer a gas mixture of 70% nitrous oxide with 30% oxygen after induction of anaesthesia, and until completion of surgery.

<table>
<thead>
<tr>
<th>Infection number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low for 80%: 77/997 (7.7)</td>
</tr>
<tr>
<td>Moderate for 30%: 106/1015 (10.4)</td>
</tr>
</tbody>
</table>

P=0.036

OR: 0.72; 95% CI: 0.52–0.98
RCT of men and women over 18 years old undergoing a range of procedures in a metropolitan hospital between September 2001 and May 2003.

USA, single centre

Exclusion criteria: patients whose respiratory status required an FiO2 in excess of 35%; patients with severe COPD who were likely to experience respiratory depression at an FiO2 of 80%; patients who were haemodynamically unstable before surgery; patients who had received bleomycin at any time; and patients who had an American Society of Anesthesiologists class 5 or 5E.

Elective (right or left, hemi-colectomy and sigmoid) low anterior resection; abdominoperineal resection; gastrectomy; pancreatic-duodenectomy; exploratory laparotomy; large gynaecologic staging/debulking procedures in which the bowel or peritoneum was involved.

The criteria for SSI were:
(1) Surgical team-documented SSI.
(2) Infection precipitated by a management action such as the initiation or changing of antibiotics, opening of the wound, aspiration, drain placement or further surgery.
(3) At least 3 of the following:
   (a) White cell count >11 000/μL.
   (b) Temperature >38.5°C.
   (c) Radiological evidence of infection.
   (d) Extrusion of pus from the wound.
   (e) Positive culture result from the infected site.
   (f) Documentation of wound erythema and induration on physical examination.

Only infections diagnosed within 14 days after surgery were included in the analysis.

Mechanical bowel preparation: “most patients had undertaken a bowel preparation regimen…according to surgeon instructions”.

Intraluminal antibiotics: not specified.

Intravenous antibiotics: upon arrival to the operating room per surgeon’s usual practice.

Skin antiseptics: not specified.

Warming: not specified.

Maintenance fluids: not specified.

Randomization: an advance simple randomization without blocking or stratification. Before the recruitment phase of the study, 300 envelopes containing all protocol materials were prepared and numbered sequentially. A random-number table was used to assign each consecutively numbered envelope to either the 35% FiO2 group or the 80% FiO2 group. The surgical team was blinded to group assignment. Patients were not informed of their group assignment.

One group of patients received 35% oxygen and unspecified gas; the other group, 80% oxygen. Anaesthesiologists were permitted to increase the FiO2 as required to maintain oxygen SaO2 in excess of 94% at all times. After extubation, the concentrations were returned to the previous levels as soon as deemed safe. During the first 2 hours of recovery, oxygen at the specified concentration was given through nasal cannulae (35% group) or a non-rebreathing mask (80% group). Patients in both treatment groups had subsequent oxygen determined by the postanaesthesia/intensive care unit teams.

The low oxygen group had 65% of patients undergoing colon surgery and 75% in the high oxygen group.

Infection number (%)
35%: 9/80 (11.3)
80%: 20/80 (25)
P=0.02

OR: 2.63; 95% CI: 1.1 - 6.2; P=0.02
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Study Design</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schietroma 2013 (24)</td>
<td>RCT of 171 patients who underwent elective open esophago-jejunal anastomosis for gastric cancer between January 2009 and April 2012.</td>
<td>Administration commenced after induction of anaesthesia and was maintained for 6 hours after surgery.</td>
<td>One group of patients received 30% oxygen and 70% room air; the other group, 80% oxygen and 20% room air. After extubation, the concentrations were returned to the previous levels as soon as deemed safe. During the first 6 hours of recovery, oxygen at the specified concentration was given through a non-rebreathing mask.</td>
<td>Overall wound infection rate was 9.3% (16/171): 11 patients (12.9%) had a wound infections in the 30% FiO2 group, and 5 (5.8%) in the 80% FiO2 group ($P&lt;0.05$).</td>
</tr>
<tr>
<td></td>
<td>Italy, single centre</td>
<td>Exclusion criteria included: expected surgery time of less than 1 hour; fever or existing signs of infection; diabetes mellitus; known immunological dysfunction (advanced liver disease, HIV infection, hepatitis C virus, infection); loss of &gt;20% of body weight in the previous 3 months; serum albumin concentration of &lt;30 g/L; and a leukocyte count of &lt;2500 cells/mL.</td>
<td>Maintenance fluids: presumed from previous study by these authors: crystalloid solution administered IV at a rate of 20 ml per kg per hour throughout surgery. Fluids were administered at a rate of 3 mL per kg per hour for the first 24 hours.</td>
<td>Patients in both treatment groups subsequently breathed ambient air unless additional oxygen was required to maintain an oxyhemoglobin saturation of more than 92%.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intravenous antibiotics: cefotaxime (2 g) was administered 1 hour before surgery, followed postoperatively by 2 doses.</td>
<td>One group of patients received 30% oxygen and 70% room air; the other group, 80% oxygen and 20% room air.</td>
<td></td>
</tr>
</tbody>
</table>
RCT of men and women undergoing elective open colorectal resection for middle or low rectal cancer.

Italy, single centre

Exclusion criteria: fever and/or existing signs of infection; diabetes mellitus; known immunologic dysfunction; loss of >20% body weight in the previous 3 months; serum albumin concentration <3.0 g/L; or leukocyte count <2500 cells/mL.

Elective colorectal resection.

Ad hoc system defined in reference (49) and adding anastomotic leaks to the wound infections.

Wound infections were considered grade 1 with the presence of erythema, indurations and pain; grade 2, same as grade 1, but with serous fluid; grade 3, the presence of contaminated fluid in less than half of the wound; and grade 4, same as grade 3, but with contaminated fluid in more than half of the wound. Wound dehiscence was considered to be present when surgical closure of the cutaneous or subcutaneous tissue (superficial) or the fascia and muscular plane (deep) was necessary in the early postoperative period.

Mechanical bowel preparation: not performed.

Intraluminal antibiotics: not used.

Intravenous antibiotics: MTZ and ceftriaxone were given 1 hour prior to surgery, followed by 2 doses postoperatively

Skin antiseptics: not specified.

Warming: actively maintained normothermia.

Maintenance fluids: crystalloid solution administered IV at a rate of 20 ml per kg per hour throughout surgery. Fluids were administered at a rate of 3 mL per kg per hour for the first 24 hours.

Randomization: randomization scheme not defined. Randomization and allocation occurred after induction of anaesthesia; all participants were blinded, except the anaesthesiologist.

After induction of anaesthesia and endotracheal intubation, patients were assigned randomly to an oxygen/air mixture with FiO2 of 30% (group 1) or 80% (group 2). When the operation was finished, the inhaled anaesthetic was stopped, and FiO2 was increased to 100% during extubation. During the first 6 postoperative hours, all patients were administered non-rebreathing facemasks with a reservoir; oxygen was provided at the randomly designated concentration at a total flow of 16 L per minute. Subsequently, patients breathed ambient air, although supplemental oxygen was provided as necessary to maintain oxygen saturation as measured by pulse oxymetry (SpO2) of at least 92%.

<table>
<thead>
<tr>
<th>Infection number (%)</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>30%: 11/41 (26.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80%: 6/40 (2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P<0.05

OR: 2.08; 95% CI: 0.69-6.30

Anastomotic dehiscence: 30% oxygen: 9/41 (21.9)
80% oxygen: 4/40 (10)

P<0.05

RR: 0.63

95% CI: 0.42-0.98
RCT of women who underwent scheduled or intrapartum caesarean delivery between 2008 and 2010. Patients were assigned to receive either 2 L of oxygen by nasal cannula during caesarean delivery (standard care) or 10 L of oxygen by non-rebreather mask (intervention group) during and for 2 hours after delivery.

USA, single centre

Exclusion criteria: emergency surgery in which the participant was unable to provide informed consent; HIV infection; chronic corticosteroid therapy or other immunosuppressive therapy; general anaesthesia, and a diagnosis of extrauterine infection (that is, pyelonephritis or pneumonia) before caesarean delivery. Acute chorioamnionitis was not an exclusion criterion. The primary composite outcome was maternal infectious morbidity, which included endometritis and wound infection.

Caesarean section.

Endometritis was diagnosed if the patient had an oral temperature of ≥38°C after the first 24 hours following the procedure and either: (1) fundal or lower abdominal tenderness greater than expected; or (2) foul-smelling or purulent lochia and if other causes for the patient’s signs and symptoms were not identified. Patients had to be treated with IV antibiotics.

The diagnosis of wound infection required wound opening >1 cm or other surgical intervention (such as laparotomy or debridement of tissue) plus at least 1 of the following: (1) purulent drainage from the wound; (2) erythema or induration of the surrounding tissues; (3) maternal oral temperature ≥38°C; or (4) radiographic evidence of infection.

**Intravenous antibiotics:** cefazolin 60-90 minutes before incision and continued for 48 hours.

**Skin antiseptics:** not specified.

**Warming:** not specified.

**Maintenance fluids:** not described.

**Randomization:** sequence source not specified. The allocation envelopes were opened in the operating room after induction of anaesthesia by the anaesthesiologist. Patients were assigned to an oxygen/air mixture with a FIO₂ of 30% or 80%. The surgical team was blinded to group assignment. Patients were not informed of their group assignment.

One group of patients received 30% oxygen and 70% room air; the other group, 80% oxygen and 20% room air. After extubation, the concentrations were returned to the previous levels as soon as deemed safe. During the first 6 hours of recovery, oxygen at the specified concentration was given through a non-rebreathing mask. Patients in both treatment groups subsequently breathed ambient air unless additional oxygen was required to maintain an oxyhaemoglobin saturation of more than 94%.

### Infection number (%)

<table>
<thead>
<tr>
<th></th>
<th>30%: 26/297 (8.8)</th>
<th>80%: 35/288 (12.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>0.18</td>
<td>0.18</td>
</tr>
</tbody>
</table>

**RR:** 1.4; 95% CI: 0.9-2.3; P=0.18
| Stall 2013 (26) | RCT (parallel design, double-blind). Patients sustaining high-energy tibial plateau, tibial pilon and calcaneus fractures treated in a staged fashion were selected for enrollment as these injuries are associated with a high risk of infection. The study population included 222 patients with 235 fractures.
The study was conducted from April 2007 to November 2010. All adult patients (over 18 years) who sustained the above-mentioned fractures and undergoing open reduction and internal fixation were eligible for inclusion.
USA, single centre
Exclusion criteria included: evidence of infection at the fracture site before definitive fixation; preoperative arterial haemoglobin saturation less than 90% without supplemental oxygen; and a history of preexisting pulmonary disease that can be worsened by high-dose oxygen.
Distal leg trauma. | CDC criteria | Intravenous antibiotics: “per institutional practice”.
Skin antiseptics: not specified
Warming: “anaesthesiologists were advised to avoid intraoperative hypothermia (<35.5°C)”.
Maintenance fluids: “…at the discretion of the attending anaesthesiologist”.
Randomization: a random-number generator was used with injury type as a stratification variable. Assignments were kept in opaque, sealed, sequentially numbered envelopes until opened by the anaesthesiologist immediately before surgery. The surgical team was blinded to the anaesthetic administered.
Treatment group patients received 80% FiO2 intraoperatively and for 2 hours after. Control group patients received 30% FiO2 during the same period. After extubation, patients in the treatment group were placed on high flow non-rebreather masks at 15 L per minute for 2 hours postoperatively. Patients in the control group were placed on nasal cannulae at 4 L per minute to maintain oxygen saturation of at least 92% as determined by pulse oximetry for 2 hours. | Infection number (%) | Low | Moderate |
<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Design</th>
<th>Setting</th>
<th>Exclusion Criteria</th>
<th>Randomization</th>
<th>Results</th>
</tr>
</thead>
</table>
| Thibon 2012 (27) | RCT (assessor-blind, multicentre) comparing the effects of hyper-oxygenation (80% FiO2) with 30% FiO2 on the frequency of SSI in routine abdominal, gynaecological and breast surgery in 434 patients. | France, multicentre | recent history of fever and/or infection; chronic respiratory failure (oxygen PaO2 below 60 mmHg, 8.9 kPa at rest); and bleomycin treatment. | After the induction of anaesthesia and tracheal intubation, patients were assigned to one of two groups (30% or 80% FiO2) according to a computer-generated allocation list without blocking or stratification. Patients were not informed of their group assignments. The surgical team was blinded to the anaesthetic administered. We checked for evidence of SSI by having an investigator blinded to the randomization conduct a review of each patient’s medical records. | Intravenous antibiotics: according to surgeon practice. Skin antiseptics: not described. Warming: not described. Maintenance fluids: not described. Anesthesiologists administered a gas mixture of 80% or 30% FiO2. The admixture gas was not described. During the postoperative period, oxygen was administered at the physician’s discretion. Infection number (%): 30%: 15/208 (7.7) 80%: 15/226 (10.4) P=0.81 OR: 1.09; 95% CI: 0.52-2.30
RCT evaluating SSI following either 30% or 80% FiO2 during and 2 hours after caesarean delivery.

Anaesthesia providers administered FiO2 via a high-flow oxygen blender.

Study subjects included both term and preterm pregnancies and both labouring and non-labouring women. A single interim analysis (futility and stopping) was performed on the first 179 subjects recruited. The estimated conditional power was 0.0052.

CDC criteria with 30-day follow-up.

Assessments were made by the surgical team. Endometritis was considered to be an SSI and for the purpose of this study was defined as maternal temperature of 38°C or higher in the setting of uterine tenderness.

**Skin antiseptics** not described.

**Warming:** not described.

**Maintenance fluids:** not described.

**Randomization:** a random-number generator was used. Assignments were kept in opaque, sealed, sequentially numbered envelopes until opened by the anaesthesiologist immediately before surgery. Subjects, operating surgeons, and wound evaluation teams were blinded to the study arms.

Treatment group patients received 80% FiO2 intraoperatively and for 2 hours after. Control group patients received 30% FiO2 during the same period.

**Intravenous antibiotics:** a single prophylactic dose of cefazolin 2 g was administered IV at the time of umbilical cord clamping (clindamycin for allergy).

**Skin antiseptics** not described.

**Warming:** not described.

**Maintenance fluids:** not described.

**Randomization:** a random-number generator was used. Assignments were kept in opaque, sealed, sequentially numbered envelopes until opened by the anaesthesiologist immediately before surgery. Subjects, operating surgeons, and wound evaluation teams were blinded to the study arms.

Treatment group patients received 80% FiO2 intraoperatively and for 2 hours after. Control group patients received 30% FiO2 during the same period.

**Intravenous antibiotics:** a single prophylactic dose of cefazolin 2 g was administered IV at the time of umbilical cord clamping (clindamycin for allergy).

**Skin antiseptics** not described.

**Warming:** not described.

**Maintenance fluids:** not described.

**Randomization:** a random-number generator was used. Assignments were kept in opaque, sealed, sequentially numbered envelopes until opened by the anaesthesiologist immediately before surgery. Subjects, operating surgeons, and wound evaluation teams were blinded to the study arms.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Infection number (%)</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>30%: 10/77</td>
<td>(12.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80%: 12/83</td>
<td>(11.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P=0.7888</td>
<td>OR: 0.88; 95% CI: 0.36-2.18</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial; CDC: Centers for Disease Control and Prevention; FiO2: fraction of inspired oxygen; IV: intravenous; HIV: human immunodeficiency virus; MTZ: metronidazole; COPD: chronic obstructive pulmonary disease; USA: United States of America; RR: relative risk; CI: confidence interval; OR: odds ratio; SSI: surgical site infection
## Appendix 3: Risk of bias assessment of the included studies

<table>
<thead>
<tr>
<th>RCT, author, year, reference</th>
<th>Sequence generation</th>
<th>Allocation concealment</th>
<th>Participants blinded</th>
<th>Outcome assessors blinded</th>
<th>Incomplete outcome data</th>
<th>Selective outcome reporting</th>
<th>Other sources of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belda 2005 (17)</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>HIGH^1,2</td>
</tr>
<tr>
<td>Bickel 2011 (18)</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>HIGH</td>
<td>LOW</td>
<td>LOW</td>
</tr>
<tr>
<td>Duggal 2013 (28)</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
</tr>
<tr>
<td>Gardella 2008 (29)</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
</tr>
<tr>
<td>Greif 2000 (19)</td>
<td>LOW</td>
<td>LOW</td>
<td>UNCLEAR</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>HIGH^2</td>
</tr>
<tr>
<td>Mayzler 2005 (20)</td>
<td>UNCLEAR</td>
<td>UNCLEAR</td>
<td>UNCLEAR</td>
<td>UNCLEAR</td>
<td>LOW</td>
<td>LOW</td>
<td>HIGH^3</td>
</tr>
<tr>
<td>Meyhoff 2009 (21)</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>UNCLEAR</td>
<td>UNCLEAR</td>
<td>LOW</td>
</tr>
<tr>
<td>Myles 2007 (22)</td>
<td>LOW</td>
<td>HIGH</td>
<td>LOW</td>
<td>UNCLEAR</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
</tr>
<tr>
<td>Pryor 2004 (23)</td>
<td>LOW</td>
<td>LOW</td>
<td>UNCLEAR</td>
<td>LOW</td>
<td>LOW</td>
<td>UNCLEAR</td>
<td>LOW</td>
</tr>
<tr>
<td>Schietroma 2013 (24)</td>
<td>LOW</td>
<td>UNCLEAR</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>UNCLEAR</td>
<td>UNCLEAR</td>
</tr>
<tr>
<td>Schietroma 2014 (25)</td>
<td>UNCLEAR</td>
<td>UNCLEAR</td>
<td>LOW</td>
<td>LOW</td>
<td>UNCLEAR</td>
<td>LOW</td>
<td>HIGH^4</td>
</tr>
<tr>
<td>Scifres 2011 (30)</td>
<td>LOW</td>
<td>LOW</td>
<td>HIGH</td>
<td>HIGH</td>
<td>UNCLEAR</td>
<td>LOW</td>
<td>LOW</td>
</tr>
<tr>
<td>Stall 2013 (26)</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>UNCLEAR</td>
</tr>
<tr>
<td>Thibon 2012 (27)</td>
<td>UNCLEAR</td>
<td>UNCLEAR</td>
<td>HIGH</td>
<td>UNCLEAR</td>
<td>UNCLEAR</td>
<td>UNCLEAR</td>
<td>HIGH^3</td>
</tr>
<tr>
<td>Williams 2013 (31)</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>UNCLEAR</td>
<td>HIGH^6</td>
<td>LOW</td>
</tr>
</tbody>
</table>

1. Wounds only followed up to 14 days.
2. Trial was stopped early according to predefined stopping criteria ($P<0.012$).
3. Small sample size.
4. Included the same patients in 2 study reports.
5. Study ended prematurely because of elapsed time; other biases not declared.
6. Excluded women undergoing an emergency caesarean as these are a high-risk population. A "resident teaching service" population was used, thus creating a selection bias. The authors terminated the study early having met futility.
Appendix 4: Comparisons

1) Administration of increased FiO2 vs. standard oxygenation

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hyperoxia Events</th>
<th>Hyperoxia Total</th>
<th>Normoxia Events</th>
<th>Normoxia Total</th>
<th>Weight</th>
<th>Odds Ratio M−H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belda 2005</td>
<td>22</td>
<td>148</td>
<td>35</td>
<td>143</td>
<td>8.1%</td>
<td>0.54 [0.30, 0.97]</td>
</tr>
<tr>
<td>Bickel 2011</td>
<td>6</td>
<td>107</td>
<td>14</td>
<td>103</td>
<td>4.2%</td>
<td>0.38 [0.14, 1.02]</td>
</tr>
<tr>
<td>Duggal 2013</td>
<td>34</td>
<td>416</td>
<td>34</td>
<td>415</td>
<td>9.5%</td>
<td>1.00 [0.61, 1.64]</td>
</tr>
<tr>
<td>Gardella 2008</td>
<td>17</td>
<td>69</td>
<td>10</td>
<td>74</td>
<td>5.2%</td>
<td>2.09 [0.88, 4.96]</td>
</tr>
<tr>
<td>Grief 2000</td>
<td>13</td>
<td>250</td>
<td>28</td>
<td>250</td>
<td>6.9%</td>
<td>0.43 [0.22, 0.86]</td>
</tr>
<tr>
<td>Mavzler 2005</td>
<td>2</td>
<td>19</td>
<td>3</td>
<td>19</td>
<td>1.4%</td>
<td>0.63 [0.09, 4.26]</td>
</tr>
<tr>
<td>Mevhoft 2009</td>
<td>131</td>
<td>685</td>
<td>141</td>
<td>701</td>
<td>13.4%</td>
<td>0.94 [0.72, 1.22]</td>
</tr>
<tr>
<td>Myles 2007</td>
<td>77</td>
<td>997</td>
<td>106</td>
<td>1015</td>
<td>12.6%</td>
<td>0.72 [0.53, 0.98]</td>
</tr>
<tr>
<td>Fryor 2004</td>
<td>20</td>
<td>80</td>
<td>9</td>
<td>80</td>
<td>5.2%</td>
<td>2.63 [1.11, 6.20]</td>
</tr>
<tr>
<td>Schietroma 2013</td>
<td>5</td>
<td>86</td>
<td>11</td>
<td>85</td>
<td>3.6%</td>
<td>0.42 [0.14, 1.25]</td>
</tr>
<tr>
<td>Schietroma 2014</td>
<td>6</td>
<td>40</td>
<td>11</td>
<td>41</td>
<td>3.6%</td>
<td>0.48 [0.16, 1.46]</td>
</tr>
<tr>
<td>Scifres 2011</td>
<td>35</td>
<td>288</td>
<td>26</td>
<td>297</td>
<td>8.9%</td>
<td>1.44 [0.84, 2.46]</td>
</tr>
<tr>
<td>Stall 2013</td>
<td>14</td>
<td>119</td>
<td>19</td>
<td>116</td>
<td>6.3%</td>
<td>0.68 [0.32, 1.43]</td>
</tr>
<tr>
<td>Thibon 2012</td>
<td>15</td>
<td>226</td>
<td>15</td>
<td>208</td>
<td>6.3%</td>
<td>0.91 [0.44, 1.92]</td>
</tr>
<tr>
<td>Williams 2013</td>
<td>10</td>
<td>77</td>
<td>12</td>
<td>83</td>
<td>4.9%</td>
<td>0.88 [0.36, 2.18]</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

|                | 3607 | 3630 | 100.0% | 0.84 [0.56, 1.06] |

**Total events:**

|                | 407  | 474  |

Heterogeneity: Tau² = 0.09; Chi² = 28.31, df = 14 (P = 0.01); I² = 51%

Test for overall effect: Z = 1.47 (P = 0.14)

M−H: Mantel-Haenszel (test); CI: confidence interval
a) Subgroup analysis according to the type of anaesthesia and respiratory control

i. Administration of increased FiO2 vs. standard oxygenation in patients undergoing procedures under neuraxial anesthesia with nasal cannula or a facemask (→ in forest plot 1.2.7)

ii. Administration of increased FiO2 vs. standard oxygenation in patients undergoing procedures under general anesthesia with endotracheal intubation (→ in forest plot 1.2.1)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hyperoxia Events</th>
<th>Normoxia Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>M+H, Random, 95% CI</th>
<th>Odds Ratio M+H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.2.1 General anesthesia with endotracheal tube</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belca 2005</td>
<td>22</td>
<td>148</td>
<td>170</td>
<td>8.1%</td>
<td>0.54 [0.30, 0.97]</td>
<td></td>
</tr>
<tr>
<td>Bokel 2011</td>
<td>6</td>
<td>107</td>
<td>113</td>
<td>4.2%</td>
<td>0.38 [0.14, 1.02]</td>
<td></td>
</tr>
<tr>
<td>Grief 2000</td>
<td>13</td>
<td>250</td>
<td>263</td>
<td>6.9%</td>
<td>0.43 [0.22, 0.86]</td>
<td></td>
</tr>
<tr>
<td>Maytner 2005</td>
<td>2</td>
<td>19</td>
<td>21</td>
<td>1.4%</td>
<td>0.63 [0.09, 4.26]</td>
<td></td>
</tr>
<tr>
<td>Mook-Jones 2009</td>
<td>131</td>
<td>668</td>
<td>799</td>
<td>13.4%</td>
<td>0.94 [0.72, 1.22]</td>
<td></td>
</tr>
<tr>
<td>Myles 2007</td>
<td>22</td>
<td>997</td>
<td>1019</td>
<td>12.6%</td>
<td>0.72 [0.53, 0.98]</td>
<td></td>
</tr>
<tr>
<td>Phipp 2004</td>
<td>20</td>
<td>80</td>
<td>100</td>
<td>5.2%</td>
<td>2.63 [1.11, 6.20]</td>
<td></td>
</tr>
<tr>
<td>Schierma 2013</td>
<td>5</td>
<td>86</td>
<td>91</td>
<td>3.6%</td>
<td>0.42 [0.14, 1.25]</td>
<td></td>
</tr>
<tr>
<td>Schierma 2014</td>
<td>6</td>
<td>40</td>
<td>46</td>
<td>3.6%</td>
<td>0.48 [0.16, 1.46]</td>
<td></td>
</tr>
<tr>
<td>Stull 2013</td>
<td>14</td>
<td>119</td>
<td>133</td>
<td>6.3%</td>
<td>0.68 [0.32, 1.43]</td>
<td></td>
</tr>
<tr>
<td>Tribon 2012</td>
<td>15</td>
<td>226</td>
<td>241</td>
<td>6.3%</td>
<td>0.91 [0.44, 1.92]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2757</strong></td>
<td><strong>2761</strong></td>
<td><strong>5518</strong></td>
<td></td>
<td>71.6%</td>
<td>0.72 [0.55, 0.94]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>311</td>
<td>392</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \tau^2 = 0.08; \ Chi^2 = 18.51, df = 10 (P = 0.05); I^2 = 46\%

Test for overall effect: \( Z = 2.44 (P = 0.01) \)

| **1.2.7 Procedure under neuroxia without endotracheal intubation** |
|-------------------|------------------|----------------|--------------|--------|---------------------|-------------------------------|
| Duggal 2013       | 24               | 416            | 440          | 9.5%   | 1.00 [0.61, 1.64]   |                               |
| Giardelli 2008    | 17               | 69             | 86           | 5.2%   | 2.09 [0.88, 4.96]   |                               |
| Sifred 2011       | 35               | 298            | 333          | 8.5%   | 1.44 [0.99, 2.36]   |                               |
| Williams 2003     | 10               | 77             | 87           | 4.9%   | 0.88 [0.36, 2.38]   |                               |
| **Subtotal (95% CI)** |
| **850**           | **869**          | **1719**       |             | 28.4%  | 1.23 [0.90, 1.69]   |                               |
| Total events      | 96               | 82             |              |        |                     |                               |

Heterogeneity: \( \tau^2 = 0.06; \ Chi^2 = 3.00, df = 3 (P = 0.39); I^2 = 0\%

Test for overall effect: \( Z = 1.30 (P = 0.19) \)

| **Total (95% CI)** |
|-------------------|------------------|----------------|--------------|--------|---------------------|-------------------------------|
| **3607**          | **3630**         | **7237**       |             | 100.0% | 0.84 [0.66, 1.06]   |                               |
| Total events      | 407              | 474            |              |        |                     |                               |

Heterogeneity: \( \tau^2 = 0.09; \ Chi^2 = 28.31, df = 14 (P = 0.01); I^2 = 51\%

Test for overall effect: \( Z = 1.47 (P = 0.14) \)

Test for subgroup differences: \( \chi^2 = 6.61, df = 1 (P = 0.01); I^2 = 84.9\%

M-H: Mantel-Haenszel (test); CI: confidence interval
**Funnel plot comparison 1:** Administration of increased FiO2 vs. standard oxygenation

- **Subgroups:**
  - ○ General anesthesia with endotracheal tube
  - ⚫ Procedure under neuroxia without endotracheal intubation
2) Administration of increased FiO2 vs. standard oxygenation in patients undergoing general anaesthesia with endotracheal intubation

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hyperoxia Events</th>
<th>Hyperoxia Total</th>
<th>Normoxia Events</th>
<th>Normoxia Total</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belda 2005</td>
<td>22</td>
<td>148</td>
<td>35</td>
<td>143</td>
<td>0.54 [0.30, 0.97]</td>
<td></td>
</tr>
<tr>
<td>Bickel 2011</td>
<td>6</td>
<td>107</td>
<td>14</td>
<td>103</td>
<td>0.38 [0.14, 1.02]</td>
<td></td>
</tr>
<tr>
<td>Grief 2000</td>
<td>13</td>
<td>250</td>
<td>28</td>
<td>250</td>
<td>0.43 [0.22, 0.86]</td>
<td></td>
</tr>
<tr>
<td>Mayziöer 2006</td>
<td>2</td>
<td>19</td>
<td>3</td>
<td>19</td>
<td>0.63 [0.09, 4.26]</td>
<td></td>
</tr>
<tr>
<td>Mayhoff 2009</td>
<td>131</td>
<td>685</td>
<td>141</td>
<td>701</td>
<td>0.94 [0.72, 1.22]</td>
<td></td>
</tr>
<tr>
<td>Myles 2007</td>
<td>77</td>
<td>997</td>
<td>106</td>
<td>1015</td>
<td>0.72 [0.53, 0.98]</td>
<td></td>
</tr>
<tr>
<td>Pryor 2004</td>
<td>20</td>
<td>80</td>
<td>9</td>
<td>80</td>
<td>2.63 [1.11, 6.20]</td>
<td></td>
</tr>
<tr>
<td>Schietroma 2013</td>
<td>5</td>
<td>86</td>
<td>11</td>
<td>85</td>
<td>0.42 [0.14, 1.25]</td>
<td></td>
</tr>
<tr>
<td>Schietroma 2014</td>
<td>6</td>
<td>40</td>
<td>11</td>
<td>41</td>
<td>0.48 [0.16, 1.46]</td>
<td></td>
</tr>
<tr>
<td>Stall 2013</td>
<td>14</td>
<td>119</td>
<td>19</td>
<td>116</td>
<td>0.68 [0.32, 1.43]</td>
<td></td>
</tr>
<tr>
<td>Thibon 2012</td>
<td>15</td>
<td>226</td>
<td>15</td>
<td>208</td>
<td>0.91 [0.44, 1.92]</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 2757 2761 100.0% 0.72 [0.55, 0.94]

Total events 311 392

Heterogeneity: Tau² = 0.08, Chi² = 18.51, df = 10 (P = 0.05); I² = 46%
Test for overall effect: 2 = 2.44 (P = 0.01)

M-H: Mantel-Haenszel (test); CI: confidence interval
a) Subgroup analysis according to the type of surgery

i. Administration of increased FiO₂ vs. standard oxygenation in patients undergoing colorectal surgery under general anaesthesia with endotracheal intubation (→ in forest plot 1.1.1)

ii. Administration of increased FiO₂ vs. standard oxygenation in patients undergoing other or mixed surgical procedures under general anaesthesia with endotracheal intubation (→ in forest plot 1.1.3)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hyperoxia</th>
<th>Normoxia</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.1.1 Colorectal Procedures (Open)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beida 2005</td>
<td>22</td>
<td>148</td>
<td>35</td>
<td>143</td>
</tr>
<tr>
<td>Cref 2000</td>
<td>13</td>
<td>250</td>
<td>28</td>
<td>250</td>
</tr>
<tr>
<td>Mauder 2005</td>
<td>2</td>
<td>19</td>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td>Schietroma 2014</td>
<td>6</td>
<td>40</td>
<td>11</td>
<td>41</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>457</td>
<td>453</td>
<td>27.3%</td>
<td>0.50 [0.33, 0.74]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>43</td>
<td>77</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.03; Chi² = 3.08; df = 3; P = 0.56; I² = 0%
Test for overall effect: Z = 3.39 (P = 0.0007)

<table>
<thead>
<tr>
<th><strong>1.1.3 Other / Mixed</strong></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bickel 2011</td>
<td>6</td>
<td>107</td>
<td>14</td>
<td>103</td>
</tr>
<tr>
<td>Heyl 2009</td>
<td>13</td>
<td>685</td>
<td>14</td>
<td>710</td>
</tr>
<tr>
<td>Myles 2007</td>
<td>77</td>
<td>937</td>
<td>106</td>
<td>1015</td>
</tr>
<tr>
<td>Pryor 2004</td>
<td>20</td>
<td>80</td>
<td>9</td>
<td>80</td>
</tr>
<tr>
<td>Schietroma 2014</td>
<td>5</td>
<td>86</td>
<td>11</td>
<td>85</td>
</tr>
<tr>
<td>Stoll 2013</td>
<td>14</td>
<td>119</td>
<td>19</td>
<td>116</td>
</tr>
<tr>
<td>Thibon 2012</td>
<td>15</td>
<td>226</td>
<td>15</td>
<td>208</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>2300</td>
<td>2308</td>
<td>72.7%</td>
<td>0.82 [0.59, 1.13]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>268</td>
<td>315</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.09; Chi² = 12.86; df = 6; P = 0.05; I² = 53%
Test for overall effect: Z = 1.20 (P = 0.23)

**Total (95% CI)**

| **Total events** | 2757 | 2761 | 100.0% | 0.72 [0.55, 0.94] |
| **Total events** | 211 | 392 | | |

Heterogeneity: Tau² = 0.08; Chi² = 18.51; df = 10; P = 0.05; I² = 46%
Test for overall effect: Z = 2.44 (P = 0.01)
Test for subgroup differences: Chi² = 5.64; df = 1; P = 0.06; I² = 72.6%

M-H: Mantel-Haenszel (test); CI: confidence interval
Funnel plot 2: Administration of increased FiO2 vs. standard oxygenation in patients undergoing general anaesthesia with endotracheal intubation.
Appendix 5: GRADE table

Comparison 1: Hyperoxygenation vs. standard oxygenation in patients undergoing general anaesthesia with an endotracheal tube

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Nº of patients</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Nº of studies</td>
<td>Safety</td>
<td>Risk of bias</td>
</tr>
<tr>
<td>Surgical site infection</td>
<td>11</td>
<td>RCT</td>
<td>Not serious</td>
</tr>
</tbody>
</table>

1. High heterogeneity, $I^2 = 46%$; one study (Pryor and colleagues) contributed to heterogeneity – the other studies reported opposite results.

SSI: surgical site infection; RCT: randomized controlled trial; CI: confidence interval; OR: odds ratio
References


