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A Major Paper Presented

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Abstract

Surgical site infections (SSIs) are among the most preventable infections acquired in the healthcare setting today. The potential for improved patient care and reduced healthcare spending by decreasing SSIs could save millions of US healthcare dollars and at the same time lead to better patient outcomes. The purpose of this systematic review was to explore whether high concentration oxygen delivered to surgical patients undergoing intraabdominal surgery decreases SSI. A systematic review was conducted to determine if high concentration oxygen decreases surgical site infection. Databases were searched, and inclusion and exclusion criteria were applied to select the articles for this systematic review. The PRISMA framework was used to guide the review and a total of six studies were critically analyzed. Two data collection tables were created for each article, one that illustrated the design of the study and one that illustrated the results. The CASP checklist was utilized to appraise each article critically. Finally, a cross-study analysis was conducted to compare the studies. Of the six studies, two were statistically significant 1and showed a decrease in SSI, contradicting earlier findings. Based on all the available research at this time, the use of high concentration oxygen during the intraoperative phase to decrease SSI should be followed if patient specifics and facility resources allow. Further studies will need to focus on standardized protocols specific to each abdominal surgery.

Table of Contents

Does High Concentration Oxygen Decrease Surgical Site Infections?

Background/Statement of the Problem

According to the Centers for Disease Control (CDC), 16 million surgeries were performed in the United States during 2011 (2018). Of those patients, 157,000 developed a surgical site infection (SSI). Surgical site infections are among the most preventable infections acquired in the healthcare setting today. The time frames of pre-operation, intra-operation, and post-operation all have specific risk factors that can lead to the development of an SSI, potentially lengthening hospitalization (CDC). Expenditure for SSI is estimated at 10,000 - 100,000 dollars for each occurrence and more then 4 billion dollars total, annually (CDC). This results in burgeoning health care costs, as well as an increase in morbidity and mortality (Reichman & Greenberg, 2009). The annual number of surgeries are expected to rise along with a growing US population; therefore, decreasing the number of SSIs is paramount.

Organizations, such as the Institute for Healthcare Improvement (IHI), have suggested dynamic initiatives that aim to decrease spending in the healthcare field. The IHI's *Triple Aim for Populations* recommends three areas in healthcare where improvement is needed. These include the restructuring of health care through integrated approaches such as the improvement of patient care, improvement of population health, and reduction in costs per capita (IHI, 2018). The Affordable Care Act (ACA) also has three improvement objectives: increase the number of insured; improve the quality of patient care; and reduce the cost of health care (Blumenthal, Abrams, & Nuzum, 2015). Lastly, the Center for Medicare and Medicaid Services (CMS) incorporated the Innovation Center to come up with new and innovative ways to decrease health care

spending through payment initiatives (CMS, 2017). This societal push for cost-effective, innovative healthcare has led to a 19% decrease in SSI between 2008 and 2013 (CDC, 2018). The potential for better patient care and reduced healthcare spending by reducing SSIs could save millions of healthcare dollars and lead to better patient outcomes.

The World Health Organization (WHO) and the CDC (Berrios-Torres et al., 2017) have released guidelines on ways to decrease SSI. One recommended guideline put forth by the WHO is the use of high concentration oxygen (O_2), defined as greater than 80% fraction of inspired oxygen (FiO2 ≥ 80%), perioperatively to reduce the risk of surgical site infections (2016). Evidence in the surgical literature (Al-Niaimi & Safdar, 2009; Belda, et al., 2005; Greif, Akça, Horn, Kurz & Sessler, 2000) has suggested that intra-abdominal surgical patients who received high concentration O_2 had a lower incidence of SSI post-operatively. There is, however, opposing literature (Gottrup, 2004; Pryor, Iii, Lien, & Goldstein, 2004) which indicated that similar surgical patients who received high concentration O_2 had a higher risk of SSI.

The WHO's recommendation comes from years of evaluating evidence-based research and is a guideline to help aid clinicians all over the world in their practice. But does the WHO's suggested guideline related to use of high concentration O_2 to decrease SSI come at an increased risk of patient harm from O_2 toxicity? The juxtaposing outcomes of clinical studies suggest that additional research that examines high concentration O_2 use in the perioperative phase is needed in order for clinicians to make best evidence-based decisions.

The purpose of this systematic review was to explore whether high concentration oxygen delivered to surgical patients undergoing intraabdominal surgery decreases SSI.

According to Polit and Beck (2017), most evidence-based practice guidelines use the acronym PICO (patient intervention comparison outcome) to help develop a research question. Using the PICO format, this systematic review attempted to answer the question: Does the delivery of high concentration oxygen to surgical patients perioperatively effect the incidence of SSI compared to surgical patients that receive normal concentration oxygen perioperatively?

Next, a review of the current literature will be presented.

Literature Review

A comprehensive literature search was accomplished using electronic bibliographic databases CINHAL, PUBMED, Cochrane, Up to Date, and Google Scholar. The search utilized the keywords: “SSI”, “oxygen”, “high concentration oxygen”, “perioperative”, “anesthesia”, “oxygen free radical”, “oxygen toxicity”, and “hyperoxia”. This literature review also utilized anesthesia textbooks and published guidelines.

Surgical Site Infections

The CDC defines SSI as an infection occurring at the incision site, or space the surgery occupied, that occurs within 90 days of surgery (CDC, 2018). Reichman and Greenberg (2009) published a review on reducing SSI and noted that SSIs lead to an increase in morbidity and mortality. They explained the most common infections originate from bacterial, viral, or fungal sources. Hospitalized patients are often exposed to a multitude of such infectious agents, and when these patients develop an infection, it is termed a nosocomial infection. While there are many types of infections, and many sources of infections, only nosocomial SSI are addressed in this review. Providers, equipment, or even a patient’s natural skin flora can potentially be the source of a nosocomial SSI. Surgical site infections account for 15-30% of all nosocomial infections, are the most common infection related to surgery, and lead to increased length of hospital stay and higher rates of hospital readmissions (Reichman & Greenberg). The authors estimated that SSI increases the length of stay at a hospital by 9.7 days, with an average cost of $20,842 per admission and a yearly total of $900 million in healthcare. Hospital readmissions due to SSIs are estimated to cost upwards of $700 million a year. Both of

these factors accelerate health care costs while placing the patient at a higher risk for poor outcomes (Reichman & Greenburg).

According to the 2018 CDC guidelines regarding SSI prevention, an intra-abdominal SSI must meet the following criteria: the infection must be within 30-90 days of the surgery and involve any part of the intra-abdominal area that was opened and manipulated during the surgery. It must contain at least one of the following: purulent drainage from a drain in the intra-abdominal region; an organism identified from fluid to be infectious; or an abscess in the intra-abdominal region. Surgical site infections are the number one healthcare-associated infection (HAI), reported to be as high as 31% of all hospitalized infections. They are associated with a 3% increase in mortality; of all the SSI deaths reported 75% of them are directly due to the infection (CDC).

Nearly half of all SSIs in the US can be prevented, which could help lower the burden of unnecessary national healthcare spending (Berrios-Torres et al., 2017). The United States has one of the only health care systems in the world that is built upon a free market design and also one of the most expensive health care systems of any nation. All the different sections of the US healthcare system are attempting to make a profit, partially explaining why health care costs are so incredibly high in the US. Insurance companies have recently started to decline payments for SSI and the extra care associated with SSI. Preventable infections now receive much attention because hospital reimbursement rates for nosocomial infections have either decreased or become nonexistent. Surgical site infections cost an average of $10,433 per infection and could exceed $90,000 when a prosthetic is involved (Berrios-Torres et al.). It is in the best interest of any health care facility to implement the most efficient practices to reduce SSI.

Surgical Site Infection Risk Factors

Barie and Eachempati (2005) presented a state of science publication on SSI and risk factors, which described a surgical incision as ischemic, injured tissue susceptible to infection. The authors used the National Nosocomial Infections Surveillance System (NNIS) to list the most common risk factors for SSI. These factors are separated into three categories: patient factors; environmental factors; and treatment factors. Patient factors are any physical condition that lowers a patient's ability to fight off an infection and are listed as ascites, chronic inflammation, corticosteroid therapy (controversial), obesity, diabetes, extremes of age, hypocholesterolemia, hypoxemia, peripheral vascular disease (especially for lower extremity surgery), postoperative anemia, prior site irradiation, recent operation, remote infection, skin carriage of staphylococci, skin disease in the area of infection (eg, psoriasis), and undernutrition (Barie & Eachempati). Environment factors are any risk from the external world and are listed as contaminated medications, inadequate disinfection/sterilization, inadequate skin antisepsis, and inadequate ventilation (Barie & Eachempati). Treatment factors are any risk involved with the actual surgery and are listed as an emergency procedure, hypothermia, inadequate antibiotic prophylaxis, oxygenation (controversial), prolonged preoperative hospitalization, and prolonged operative time (Barie & Eachempati). Barie and Eachempati stated that with strict adherence to the established guidelines, SSIs can be reduced by as much as 27% (2005).

Critical Practice Guidelines: Overview

Evidence-based clinical practice guidelines are an attempt to review large bodies of evidence and convert the evidence into manageable clinical guidelines for practice

(Polit & Beck, 2017). Evidence-based clinical guidelines have four features. First, they are usually based on systematic reviews, and they give some form of a recommendation for a decision-making process. Second, they attempt to balance benefit with risk. Third, they are developed to guide clinical practice. Fourth they are typically developed by a group made up of researchers, clinicians, and experts (Polit & Beck).

Guidelines are available for a variety of clinical decisions. Typically, guidelines "define a minimum set of services and actions appropriate for certain clinical conditions" (Polit & Beck. 2017, p. 28). Most guidelines are developed by an organization such as the WHO or the CDC who have sponsored the research of these clinical conditions, and most will post their guidelines on their website (Polit & Beck). There is no one central guideline hub to find the most current guidelines, but Polit and Beck recommend the National Clearinghouse (www.guideline.gov) for nursing and healthcare guidelines in the United States. With the increasing amounts of clinical guidelines being released, there is a greater chance of multiple guidelines which can lead to conflicting recommendations (Polit & Beck). When there are multiple guidelines, Polit and Beck recommend to critically appraise each organization's recommendation and choose the one with the "strongest and the most-up-to-date evidence" (p. 29) that best fits with one's clinical practice.

The WHO guidelines. The WHO sponsored and released guidelines on decreasing SSI (2016). The objectives were to provide comprehensive evidence, and expert-based recommendations and to support health care settings and clinicians develop infection prevention programs. The prevention of SSI is a WHO global priority in patient safety. The WHO panel of international experts came together with relevant evidence to

develop a global set of guidelines that could be followed by any institution worldwide. The WHO developed SSI guidelines specifically to increase awareness of the "global burden" associated with SSI in the healthcare settings and mobilize the anesthetist who provides direct patient care (2016).

The WHO (2016) expert panel based their recommendation on 11 randomized control trials (RCT) that compared the administration of high versus low concentration oxygen, in the perioperative phase, in the adult population with an endotracheal tube that could measure and deliver a set amount of oxygen. Using evidence-based and expert-based recommendations, the WHO created a guideline of preventive measures to decrease SSI in the perioperative phase. These global guidelines take into account the balance between benefit and harm, cost and resource implications, and patient values and preference across the world (WHO). The WHO guideline noted that SSIs are a significant cost burden to the world and especially the low and middle-income countries. The WHO recommended 16 ways to decrease the incidence of SSI. The first recommendation notes that the adult patients undergoing general anesthesia with endotracheal intubation for surgical procedures should receive 80% FiO_2 intraoperatively. If feasible, this should be initiated in the immediate preoperative period and continued into the postoperative period for two to six hours. As this recommendation is central to the purpose of this paper, it will be examined in detail in this systematic review.

The WHO "strong guideline recommendations" to reduce SSI include patients with known nasal carriage of *S. aureus* should receive intranasal applications of mupirocin 2% ointment with or without a combination of chlorhexidine gluconate body wash. It is recommended that mechanical bowel preparation alone (without the

administration of oral antibiotics) should not be used in adult patients undergoing elective colorectal surgery. In patients undergoing any surgical procedure, hair should not be removed or, if absolutely necessary, should only be removed with a clipper. Shaving is strongly discouraged at all times, whether preoperatively or in the operating room. Surgical antibiotic prophylaxis (SAP) should be administered before surgical incision, when indicated. Surgical antibiotic prophylaxis should be administered within 120 min before incision, while considering the half-life of the antibiotic. Surgical hand preparation should be performed either by scrubbing with a suitable antimicrobial soap and water or using a suitable alcohol-based hand rub before donning sterile gloves. Alcohol-based antiseptic solutions based on CHG for surgical site skin preparation should be used in patients undergoing surgical procedures. Surgical antibiotic prophylaxis administration should not be prolonged after completion of the operation (WHO).

Other Guidelines for Reducing SSIs. The CDC used research conducted by Berrios-Torres et al. (2017) as the foundation for their guidelines on SSI. Berríos-Torres et al. undertook a targeted systematic review of the literature to find clinically relevant studies that were current and involved the theme of SSI. In the initial search, the authors found 5,759 studies that met the criteria for inclusion. Using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) critical appraisal tool, they refined their full-text review studies to 896. In addition, they hired two independent reviewers to appraise the 896 studies, and from that pool of studies, they selected 170 to be included in the review. They narrowed their research to five studies that specifically examined the effects of supplemental high concentration oxygenation during the perioperative phase of intraabdominal surgery.

When Berrios-Torres et al. (2017) narrowed their search to three studies specific to elective colorectal surgery and the effects of supplemental high concentration oxygenation during the perioperative phase, they found no significant ($p = 0.07$) benefit to the use of high concentration O_2 ($FiO2 > 80\%$) during surgery. They attributed the any significant decrease in SSI that the authors of the studies may have had, to the addition of other protocols used in the perioperative phase such as maintaining normothermia and generous fluid replacement. They suggested that a multitude of therapies used together can decrease SSI, including parenteral antimicrobial prophylaxis, non-parenteral antimicrobial prophylaxis, glycemic control, normothermia, oxygen, antiseptic prophylaxis, and biofilm (Berrios-Torres et al.).

Most of these recommendations have already been put in place and are viewed less as guidelines and more as standards of care for the operative phase. Berrios-Torres et al. (2017) stated that when therapies are combined, they can have a synergistic effect. The notion to combine therapies is similar to the recommendation by Aga et al. (2015) to account for all risk factors before surgery and use a multimodal approach to decrease the incidence of SSI.

Abdominal Surgical Site Infection Risk Factors.

Abdominal SSIs, in particular, have been shown to occur in up to 17.4 % of intra-abdominal surgeries (Razavi, Ibrhimpoor, Kashani & Jafarian, 2005). Kalakouti et al. (2018) reported that abdominal SSI can range from 3% to 30%, and up to 40%, without proper antibiotics. Abdominal surgery is especially prone to surgical wound infections due to the nature of visceral handling intra-operatively and dissemination of microorganisms from the bowel (Kalakouti et al.).

In a prospective cohort study conducted by Aga et al. (2015), researchers looked at the incidence and risk factors of SSI after abdominal surgery that lead to increased health care spending, along with morbidity and mortality. In their study of 302 patients who had intraabdominal surgery between 2005-2007, the total SSI rate was 22.2%. Aga et al. estimated that for every SSI, at least six additional days of hospitalization are required, and each day significantly increases spending on health care. The increased risk can be related to the fact that the abdominal cavity and intestines have higher concentrations of bacteria than the rest of the body. Numerous patient-specific risk factors were identified, including advanced age, malnutrition, diabetes mellitus, smoking, morbid obesity, and an impaired immune system. A univariate analysis of intra-abdominal surgeries demonstrated additional risk factors for SSI including increased length of hospital stay, an ASA score greater then 2, long duration of surgery, quality of patients' skin preparation, preoperative hair removal, prophylactic antibiotic, operating room ventilation, sterilization of surgical equipment, presence of a surgical drains, and surgical technique. While an increased stay can be related to an SSI, it was also identified by Aga et al. as a risk factor for those very infections.

Oxygen and Surgery

Oxygen is the third most abundant element in the universe and is the most vital for life (Hall, 2014). The body uses O_2 as a fuel in cellular respiration to produce the energy needed for life. For O_2 to reach the lungs, it needs to travel through the airway. The airway is made up of the nasal and oral pharynx, upper pharynx, lower pharynx, trachea, bronchi, bronchioles, alveolar sacs, and finally the individual alveoli where O_2 diffuses across the cell membrane and is absorbed into the blood (Hall, 2014). Once O_2

has diffused in the blood, it can travel to where the body needs it most (Hall). During intra-abdominal surgery, the oxygen-rich blood can travel into the intra-abdominal compartment to promote wound healing.

Oxygen can be a liquid, solid, or a gas depending on the atmospheric pressure and temperature. Oxygen under normal conditions is a gas. The air that surrounds earth the same air we breathe is made up of 20.95 percent O_2 commonly rounded up to 21%. Oxygen makes up only a partial pressure of the total pressure in the atmosphere since there are other gasses, mainly nitrogen (Hall, 2014; Nagelhout & Plaus 2014). Dalton's Law that states the total pressure expressed as P, is made up of all the elements in the air, (nitrogen, oxygen, argon) this can also be said as the partial pressures of nitrogen = Pn, Oxygen = Po, and Argon = Pa together. The equation can be expressed as P = Pn + Po + Pa (Hall, 2014).

An essential aspect of a patient when under an anesthetist's care is their airway. The airway delivers O_2 to the lungs in exchange for carbon dioxide. During the perioperative phase, the anesthetist is in control of the airway and the amount of O_2 a patient receives. Typically, a patient that undergoes surgery with general anesthesia will first be intubated with an endotracheal tube (ETT) to secure and protect a patient's airway (Nagelhout & Plaus, 2014). The ETT is connected to a mechanical ventilator that is part of the anesthesia machine.

The anesthesia machine is a fundamental piece of equipment to the anesthetist, and on the most basic level, it is used to control a patient's ventilation and O_2 delivery (Butterworth, Mackey, Wasnick, Morgan, & Mikhail, 2013). Anesthesia machines in the US must adhere to standards promulgated by the American Society for Testing and

Materials F1850 (ASTM F1850). One such standard is that every anesthesia machine must have a continuous pipeline supply O_2 and a spare tank of O_2 behind the machine in case of pipeline failure. This standard sadly is not a global standard and many undeveloped countries have minimal resources, and a tank of O_2 may be hard to obtain. From the anesthesia machine, the percentage of O_2 can be adjusted with a turn of a dial. The anesthetist can adjust the fraction of inspired oxygen (FiO2) in the lungs from 21% FiO2 (low concentration O_2, also referred to as room air) to 85% FiO2 (high concentration O_2) (2014). The correct amount of O_2 administered to a patient has many co-factors such as the length of the procedure, the patients co-existing diseases, and the patients baseline arterial oxygen saturation (SpO2) to name a few. The American Society of Anesthesiologists (ASA) standards do not indicate the amount of O_2 a patient receives during surgery (2015). During a short procedure, an anesthetist may administer 100% FiO2 for the entire procedure with the thought that it is better to have the patient maximally oxygenated.

Clinicians can continuously monitor oxygenation in a patient using pulse oximetry. The ASA standards for basic monitoring during delivery of anesthetics includes “a quantitative method of assessing oxygenation” such as pulse oximetry (2015). The pulse oximeter should include a pitch pulse tone that is variable, meaning a low pitch sound is heard with low saturated O_2 levels, and a high pitch sound is heard with high-saturated O_2 levels, and should alarm with a low saturated O_2 (ASA). The SpO2 can be used to estimate of the amount of O_2 in the blood. Every anesthesia machine has a monitor that displays the SpO2. During induction and intubation, the anesthetist is looking directly at the patient and the airway and is unable to focus on the monitor. The

variable pitch pulse tone assigned to the SpO2 provides the anesthetist the ability to monitor SpO2 and heart rate audibly while visually looking directly at a patient throughout the case (Nagelhout & Plaus 2014).

Preoxygenation. During elective surgery the anesthesia provider has the ability to provide adequate preoxygenation by administering 100% O_2 for 3 minutes (Pandey, Ursekar, & Aphale, 2014). Effective preoxygenation with 100% O_2 eliminates nitrogen from the lungs and replaces it with O_2 (Nagelhout & Plaus, 2014). The increase in PaO2 allows the anesthetist time to secure the airway after the induction of anesthesia, when a patient is no longer breathing and thereby avoid hypoxia.

To avoid hypoxia and its deleterious effects during the induction of anesthesia, preoxygenation is crucial (Pandey et al., 2014). However, there are numerous ways to preoxygenate a patient. Pandey et al. conducted an RCT examining two popular methods used for preoxygenation to determine if preoxygenation was best achieved by administration of 100% O_2 for three minutes with normal respiratory tidal volumes prior to induction versus four maximal inspirations with 100% O_2The study examined 100 surgical patients and the time it took for an apneic patient's SpO2 to decrease to 90%.

Study results were statistically significant ($P < 0.05$) and found that the mean time to desaturation in four maximal breaths method was 110.40 ± 30.27 seconds. The mean time to desaturation the three minutes method was 281.70 ± 18 seconds. The authors concluded that the administration of 100% O_2 over three minutes with normal tidal volumes prior to induction of anesthesia is an effective and safe method of preoxygenation (Pandey et al., 2014).

Hypoxia. Hypoxia is defined as a SpO2 of less than 90%, or a PO2 of less than 60 mmHg (Hall, 2016). When looking at the oxygen disassociation curve (Figure 1) provided by Creative Commons Attribution-Non-Commercial-Share Alike 3.0 License, a SpO2 of 100% can be correlated with a PO2 of 100 milligrams of mercury (mmHg). However, a slight decrease in SpO2 can be a significant decrease in PO2. If SpO2 is decreased by 10% to a SpO2 of 90% the correlated PO2 decreases to 60 mmHg, which is a 40% decrease in the total amount of O_2.

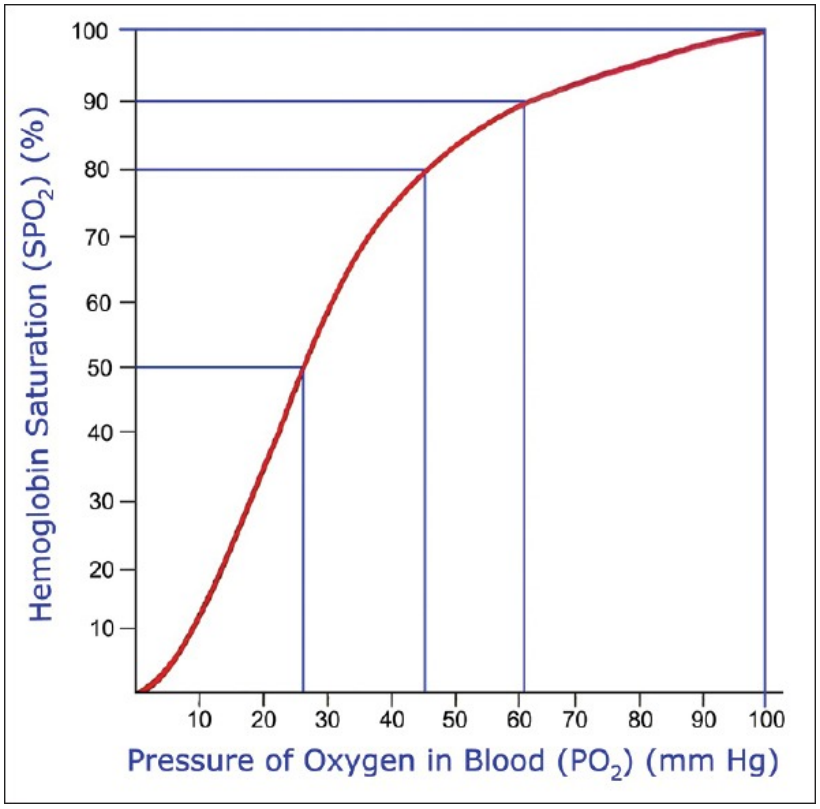

Figure 1. Oxygen disassociation curve

Hypoxia is a lack of oxygen. According to Hall (2016), there are five types of hypoxia. There is inadequate oxygenation of the blood in the lungs because of extrinsic factors, pulmonary diseases, venous-to-arterial shunts, inadequate O_2 transport to the tissues by the blood, and inadequate tissue capability of using O_2 (Hall). Inadequate

oxygenation of the blood in the lungs because of extrinsic factors is of significant concern for anesthetists. The extrinsic factors can be subdivided into a deficiency of O_2 or hypoventilation. Both of these extrinsic factors are managed by anesthetists and can be controlled by the anesthesia machine. If not treated, hypoxia can cause the death of the cells throughout the entire body including the epidermis (skin layer), intra-abdominal tissue, and cardiac cells, which can result in cardiac arrest (Hall). Medical professions learn early in their training to avoid the perils of hypoxia. Even the basic first responder is taught that oxygenation is crucial to life. The treatment for hypoxia is O_2. Hypoxia can be treated with 100 percent O_2, or high concentration O_2 therapy, which will deliver five times as much O_2 into the lungs with each breath, compared to a patient breathing room air (Hall).

Oxygen Toxicity. Oxygen toxicity or hyperoxia is when cells, tissues, and organs are exposed to an excess supply of O_2 or higher than the average partial pressure of O_2. Hyperoxia, or the delivery of high concentration O_2 greater than 21% room air, has only been achievable with modern advances in the medical field of O_2 tanks and hyperbaric chambers. The advancements over the past century have enabled humans to breath greater than 21% O_2. The ability to now provide hyper oxygenation has created a new set of risk factors stemming from O_2 toxicity (Nagelhout & Plaus, 2014).

The pathophysiology behind O_2 toxicity is related to an increase in the highly reactive O_2 free radicals that are products of O_2 metabolism (Chawla & Lavani. 2011). An increase in O_2 creates an increase in O_2 free radicals, and if antioxidants do not counteract the O_2 free radicals in the body, toxicity can occur. Oxygen can be metabolized into free radicals such as superoxide anion, hydrogen peroxide, and hydroxyl

radicals when there is an abundance of O_2 build up. As metabolites increase in the body and exert their toxic effects, they cause abnormal functioning of the body (Chawla & Lavani). The toxic O_2 free radicals can act on the cells and organelle membranes and interfere with cellular functions like enzyme and protein transport and permanently stop cellular growth (Malhotra, Schwartz, Schwartzstein, Manaker, & Finlay, 2015). Other than the concentration along with the duration of FiO2, there are other risk factors for O_2 toxicity. Advanced age, radiation therapy, and chemotherapy all alter the healthy development of antioxidants and predispose a person to O_2 toxicity (Nagelhout & Plaus, 2014).

Since the very discovery of oxygen, the debate of just how much oxygen is a good thing was started and continues today. Joseph Priestly is the scientist credited with the discovery of oxygen in 1775 (Ford, 2004). Priestly noted that a candle that burned in pure oxygen burned faster and brighter than a candle that burned in room air. Priestly hypothesized at the time of discovery that too much oxygen might also be toxic and accelerate the lifespan of man. Priestly's hypotheses started the debate about how much oxygen do we actually need (Ford).

With technological advances, O_2 can now be concentrated and stored in tanks and delivered in higher than atmospheric concentrations to a patient undergoing surgery. A high concentration of O_2 delivered to a patient can have adverse effects. Nagelhout and Plaus (2014) detail in their textbook that the prolonged (greater than 24 hours) use of high concentration O_2, defined as 50 percent FiO2, is potentially toxic and can result in permanent and irreversible damage to the lungs. Also, "deleterious effects" can result from shorter periods of time, even under 24 hours (p.648). The amount of lung damage

can be directly correlated to higher concentrations of FiO2 and a longer duration of exposure to the higher concentration FiO2 (Nagelhout & Plaus).

Physical symptoms related to high concentration O_2 and its toxic effects develop in as early as six hours. The early signs and symptoms related to high concentration O_2 exposure include substernal chest pain that is felt more with inspiration, tachypnea, and a non-productive cough (Nagelhout & Plaus, 2014). Signs and symptoms that can be seen within 24 hours of O_2 exposure include paresthesia, anorexia, nausea, and headache.

According to Malhotra et al., oxygen toxicity is essentially an overdose of oxygen (2015). Oxygen toxicity / hyperoxia on a biological chemical level is not yet clearly understood (Malhotra et al.). The leading theory is that an overabundance of O_2 in the body is transformed into free radicals and other toxic substances. Oxygen greater than 21 percent atmospheric pressure (a normal oxygen level) can cause injury (Malhotra et al.). Clinical consequences of O_2 toxicity are known to include cellular injury, absorptive atelectasis, accentuation of hypercapnia, airway injury, parenchymal injury, potentiation by bleomycin, extrapulmonary toxicity, and augmentation of antioxidants and extrapulmonary toxicity. Suggested methods to prevent or reduce injury from O_2 toxicity include prevention of over oxygenation by reducing FiO2 to as low as a patient can tolerate and using arterial oxygen saturation (SaO2) as a guide to prevent O_2 toxicity (Malhotra et al.).

Oxygen's Role in Decreasing SSI.

Administration of high concentration O_2 has the ability to raise the partial pressure of oxygen (PaO2) in the body while decreasing the partial pressure of the other elemental gases (Hall, 2016). When the partial pressure of oxygen is increased in the

lungs, it diffuses into the blood in higher concentrations (Hall). The higher concentrations then travel throughout the body. Gottrup (2004) explained that a continuous supply of O_2 rich blood from the lungs to the wound is vital for wound healing, and resistance from postoperative SSI is only possible when microcirculation of nutrition is able to reach the tissue. "The main component of the nutrition is O_2, which is critically important for healing a wound by the production of granulation tissue and for ensuring resistance against infection" (p.312).

Oxygen's role in decreasing SSI and wound healing continues throughout the entire wound healing process. Oxygen is continuously needed in the production of energy during cellular respiration. The energy produced is then used throughout the body. The cells of the different organs in the body use O_2 to heal itself (Smet et al., 2017). A detailed look at the role of O_2 on the microscopic level shows that O_2 is responsible for the synthesis of collagen, proliferation, and defense against infection-causing bacteria. Oxygen-derived peroxides, such as hydrogen peroxide, are byproducts of O_2 reactions in the body (Smet et al.). These peroxides stimulate reactive oxygen species (ROS), and they are super-oxides that are bacterio-toxic. The ROS are also potent stimulators of angiogenesis that form new blood vessels, which in turn can deliver more oxygen-rich blood and remove waste.

Smet et al. (2017) conducted a systematic review which evaluated 65 studies that investigated O_2 usage in wound healing. Using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) as a guideline, they evaluated and categorized studies according to the type of O_2 therapy. These categories included topical O_2 therapy, oxygen-dressing therapy, hyperbaric O_2 therapy, and supplemental inspired

O_2. Smet et al. reviewed six experimental animal studies that used O_2 dressing therapy. They found that O_2 dressing therapy in wound healing accelerated wound healing as evident by faster wound closure, and less inflammation. Also reviewed were three RCTs that tested topical O_2 therapy, which delivers high flow O_2 to a wound bed. In the review, the authors examined venous ulcers over a 12-week period using topical O_2 therapy versus a conventional compression dressing. Smet et al. found that with the use of O_2 to a wound bed, patients had a faster to wound closure time. The proportion of completely healed ulcers at the 12-week mark with 80% with topical O_2 therapy was improved compared to 35% O_2 therapy with a compression dressing.

High Concentration Oxygen

The use of high concentration O_2 in surgery to reduce SSI has been an ongoing area of study. The meta-analysis conducted by the WHO (2016) showed that high concentration O_2 given perioperatively was beneficial in reducing SSI when compared to low concentration O_2. The expert panel noted that this effect was only observed when the patient was intubated during surgery and delivery and continuous measurement of high concentration O_2 was achievable. The amount of oxygenation to optimize wound healing without over oxygenating is still being debated and more research is needed.

There is increased confusion regarding the use of oxygenation during surgery related to differing guidelines released by the CDC (2018) and WHO (2016) for SSI prevention. The CDC recognizes the use of high concentration O_2 during the perioperative phase as a possible therapy to decrease SSI but states “no recommendation” as their guidelines. The CDC stated that while there have been studies that show a reduction in SSI with the use of high concentration O_2, the evidence is not conclusive,

and the risk of high concentration O_2 may be more deleterious than any benefit of receiving high concentration O_2 during the perioperative phase (CDC, 2018). The WHO (2016) published guidelines for use high concentration O_2 during the perioperative phase of intraabdominal surgery to reduce the incidence of SSI. The WHO stated that there is no significant risk of harm from the use of high concentration O_2 and adult patients undergoing general anesthesia with endotracheal intubation for surgical procedures should receive 80% fraction of inspired O_2 intraoperatively to reduce SSI and, if feasible, in the immediate postoperative period for 2–6 hours (2016).

Barie and Eachempati (2005) suggested that the use of high concentration O_2 may have an antibacterial effect and its use in the perioperative phase would be beneficial. In their state of science review of SSI, they examined patients undergoing intraabdominal surgery who had received high concentration O_2 (80% FiO2) perioperative and continued to receive high concentration O_2 for two hours post operation versus low concentration O_2 (30% FiO2) perioperative. When they examined a study of over 500 patients, they found that those who received the high concentration O_2 peri-operatively had a 50% decrease in SSI (5.2% versus 11.2%). However, a separate study that included 165 patients examined the same criteria and found that the SSI rate doubled (25% versus 11.3%). The authors concluded that the use of perioperative oxygen O_2 should be considered as a treatment factor, but with the caveat that it is still controversial. Barie and Eachempati also raised the question of inconsistencies and inaccuracy of data on SSI, especially since not all SSI are reported. It should be noted that currently, a higher number of surgical procedures are done on an outpatient basis, making these procedures more difficult to monitor for SSI.

While evidence from studies on supplemental high concentration oxygenation during the perioperative phase of intraabdominal surgery looks promising, Berrios-Torres et al. cautioned that it is inconclusive at this time (2017). The use of O_2 is listed in their guidelines as "no recommendation/unresolved" (p. E4). They stated that a patient with normal pulmonary function may benefit from receiving high concentration O_2 perioperatively to reduce SSI, but it is a tradeoff between the benefit and harm of O_2 (2017). The lack of a formal recommendation and suggestion of a tradeoff between benefit and harm reaffirms that further studies are needed to address the use of high concentration O_2 during the perioperative phase.

Therefore, the purpose of this systematic review was to explore whether high concentration O_2 delivered to surgical patients undergoing intraabdominal surgery decreases SSI.

Next, the theoretical framework used to guide this project will be presented.

Theoretical Framework

Two frameworks were used to guide this paper: Pasteur's Germ Theory and PRISMA.

Germ Theory

Louis Pasteur's Germ Theory from 1858 stated that a specific organism or germ is capable of causing an infectious disease (McEwen & Wills, 2014). The idea that a germ could cause infection or disease was unique at that time. Before Pasteur's germ theory, the leading theory was the theory of miasma. The miasma theory proposed that disease came from bad air sometimes referred to as night air. This bad air was thought to be a product of the bad environment. It was thought that the decomposing matter or miasmata would fill the air and disease would spread. Though the theory of miasma has since been disproved, it guided Pasteur in his development of the germ theory (Smith, 2012).

Pasteur was studying how to prevent wine from spoiling when he developed the Germ Theory. According to the miasma theory in use at the time, the air caused the wine to spoil. Pasteur hypothesized that it was not the air, but instead, a microorganism in the air that caused the spoiling. Through better scientific instruments, like the microscope, Pasteur was able to isolate yeast, the organism responsible for fermentation. Pasteur was also able to detect the growth of microorganisms that he deemed responsible for the spoiling of wine (Smith, 2012). Pasteur extended his theory to many other types of mediums in an attempt to replicate his findings. The Germ Theory became accepted, and other great discoveries, like pasteurization and the concept of sterility, arose from it. Thanks to the theory of germs, hand washing, sterile gowns, gloves, surgical fields, and equipment are now the gold standard in surgical operating rooms.

Pasteur's Germ Theory is theoretically sound and easy to understand. The concepts that the theory relies on are common knowledge today. One example of this is Pasteur's concept of a microorganism. When Pasteur first theorized about germs, a microorganism was a radical idea, yet today the microorganism is proven. Germ theory is not overly complicated and in fact is so simple that even young children can understand it. One of the first lessons preschool children learn is how to wash their hands before eating or after using the restroom to get rid of any germs that might be on their hands. The theory and assumptions that microorganisms can cause infectious disease are adequately explained and still hold true today. The microscope helped proved the concept of a microorganism, and through many experiments and studies, one can safely say that some microorganisms can cause infectious disease. The Germ Theory continues to be an essential theory and has been shared by many different disciplines, as it has excellent generalizability. Health care workers, scientists, food service industry workers, and preschool teachers have embraced the germ theory. The knowledge gained from Germ Theory helped the profession of nursing tremendously in infectious disease prevention.

The Germ Theory was used to guide a recent study about hand washing. The researchers wanted to examine the role that hand hygiene of the surgical patient might play in SSIs. They proposed that by following the principles from the Germ Theory, effective hand hygiene would decrease or eliminate any organism on the hands and thereby decrease SSIs caused by the spread of infectious organisms from surgical patients' hands. Ardizzone, Smolowitz, Kline, Thom, and Larson (2013) found that the medical staff believed they offered the opportunity for hand hygiene to patients, but it was observed that only 14 of 81 patients were provided hand hygiene opportunities

(17.3%). After an in-service education on the importance of hand hygiene, nursing staff assisted by offering the patient the opportunity to wash hands in the sink with soap and water or with an alcohol based hand cleansing solution and they observed an increase of 37 out of 83 opportunities (44.6%). The authors concluded that "efforts to increase hand hygiene should be directed toward patients as well as healthcare workers" (p.490). Hand washing and compliance to universal protocols of infection prevention result in lower incidence of SSI and ultimately saves lives (Ardizonne et al.). The Germ Theory provides the foundation for understanding bacteria and its transmission.

PRISMA Framework

The framework used to specifically guide this systematic review was the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher, Liberati, Tetzlaff, & Altman, 2015). The PRISMA-P statement contains a 17-question checklist (Figure 2, next page) that examines administrative information, introduction, and methods of a systematic review. PRISMA also contains a flow diagram that provides a conceptual visualization of how the articles appraised in a systematic review are selected. The criteria in the PRISMA checklist should be followed to present a clear and concise systematic review. The PRISMA statement was developed to help guide authors in reporting the necessities while conducting a systematic review and can also help appraise a journal article.

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale	6	Describe the rationale for the review in the context of what is already known
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesized
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

Figure 2. PRISMA-P checklist (Moher et al., 2015)

The methodology guiding this systematic review will be presented next.

Method

Purpose

The purpose of this systematic review was to determine whether high concentration O_2 delivered to surgical patients undergoing intraabdominal surgery decreases SSI.

Research Question

Does the delivery of high concentration oxygen to surgical patients perioperatively effect the incidence of SSI compared to surgical patients that receive normal concentration oxygen perioperatively?

Design

The design of this paper was a systematic review that aimed to review and analyze the outcome variable of SSI with the use of high concentration O_2 vs. low concentration O_2 perioperatively during intraabdominal surgery.

Search Strategy

A comprehensive literature search was conducted using electronic bibliographic databases, including CINHAL, PUBMED, Cochrane, and Google Scholar. The search utilized the keywords: “RCT”, “SSI”, “high concentration oxygen”, “perioperative”, “anesthesia”. The PRISMA flow diagram (Figure 3, next page) was used to display the search path and how the articles appraised for this systematic review were selected. The number of articles diminishes based on identification, screening, eligibility and inclusion.

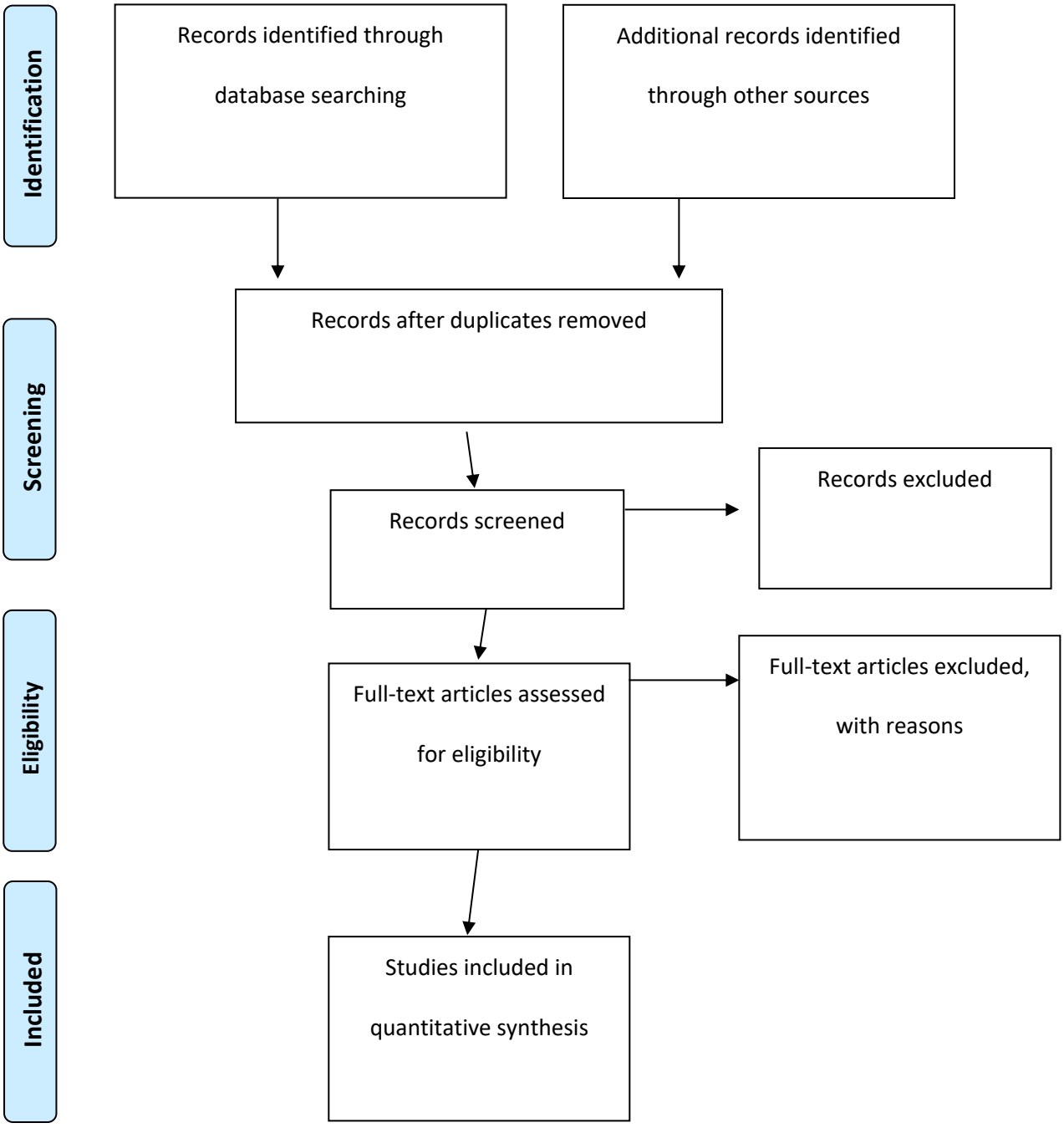

Figure 3. PRISMA Flowchart (Moher et al., 2009)

Inclusion/Exclusion Criteria

To meet the inclusion criteria for this systematic review, the sample studies needed the following criteria: (a) adults 15 year of age or older; (b) patients undergoing intra-abdominal surgery, (c) patients who received general anesthesia, (d) use of normal concentration oxygen during intraoperative phase (FiO2 < 35%), (e) use of high concentration oxygen during the intraoperative phase (FiO2 > 80%), (f) monitoring of SSI, (g) studies must be an RCT, or control trial. The literature search was limited to full-text electronic Journal articles written after the year 2000 and written in English, or that have been translated. There were no limitations of race, ethnicity, primary language, socio-economic status, or gender.

Exclusion criterion of this systematic review was the pediatric population (less than 15 years of age) and meta-analysis studies.

Data Collection

The data collected for this systematic review included the variables of: design, sample size, the procedure performed, and the concentration of O_2 used during surgery. The outcome variables identified were the incidence of postoperative SSI related to high concentration oxygen vs. normal concentration oxygen and the average length of stay. The data collection template also included any limitations in the study. The data collection templates used are labeled Table 1 and Table 2.

Table 1. *Study Specific Data*

Method/ Design	Sample	Type of Surgical procedure performed	Anesthesia and airway used during surgery	Post-operative oxygen delivery

Table 2. *Outcome Data Collection*

Incidence of postoperative SSI	Outcome / mortality	Limitations

Critical Appraisal

Each journal article was appraised with the Critical Appraisal Skills Programme (CASP, 2017). The CASP appraisal tool for randomized controlled trials (Table 3) is a 10-question checklist to help appraise literature to determine if it has reliable and relevant evidence. The CASP appraisal tool for case controlled trials, similar to the CASP appraisal tool for randomized control trails listed above, is a 11-question checklist to help appraise literature to determine if it has reliable and relevant evidence (Table 4). Both CASP appraisal tools question three essential aspects of a study: Is the study valid? What are the results? Are the results useful? The CASP checklist was used to evaluate the scientific integrity of the studies. The use of the CASP appraisal tools and clinical judgment helped determine if the journal article was of clinical importance to this systematic review. The CASP checklist is free to use under the Creative Commons license, and no approval was needed for its use.

Table 3. *CASP Checklist for Randomized Controlled Trials* (CAPS, 2017)

Question	Yes	Can't Tell	No
Did the trial address a clearly focused issue?			
Was the assignment of patients to treatments randomized?			
Were all of the patients who entered the trial properly accounted for at its conclusion?			
Were patients, health workers and study personnel blinded?			
Were the groups similar at the start of the trial?			
Aside from the experimental intervention, were the groups treated equally?			
How large was the treatment effect?			
How precise was the estimate of the treatment effect?			
Can the results be applied in your context? (Or to the local population?)			
Were all clinically important outcomes considered?			
Are the benefits worth the harms and costs?			

Table 4. *CASP Checklist for Case Controlled Study* (CAPS, 2017)

Question	Yes	Can't Tell	No
Did the trial address a clearly focused issue?			
Did the authors use an appropriate method to answer their question?			
Were the cases recruited in an acceptable way?			
Were the controls selected in an acceptable way? The study			
Was the exposure accurately measured to minimize bias?			
Aside from the experimental intervention, were the groups treated equally			
Have the authors taken account of the potential confounding factors in the design and/or in their analysis?			
How large was the treatment effect?			
How precise was the estimate of the treatment effect?			
Do you believe the results?			
Can the results be applied to the local population?			
Do the results of this study fit with other available evidence?			

Next, the results will be presented.

Results

A comprehensive literature search was conducted using electronic bibliographic databases as described in the search strategy section. The PRISMA Flowchart was used for a visual display of the search conducted and the results can be seen on the next page. The first search resulted in 1,510 journal articles. After duplicates were removed there was 135 journal articles identified. All 135 articles abstracts were read for relevance and 127 were excluded for not being relevant to this systematic review. Of the eight remaining articles, two were excluded for being meta-analysis articles. One article was identified using the reference list of an article that was included in this systematic review (Figure 4).

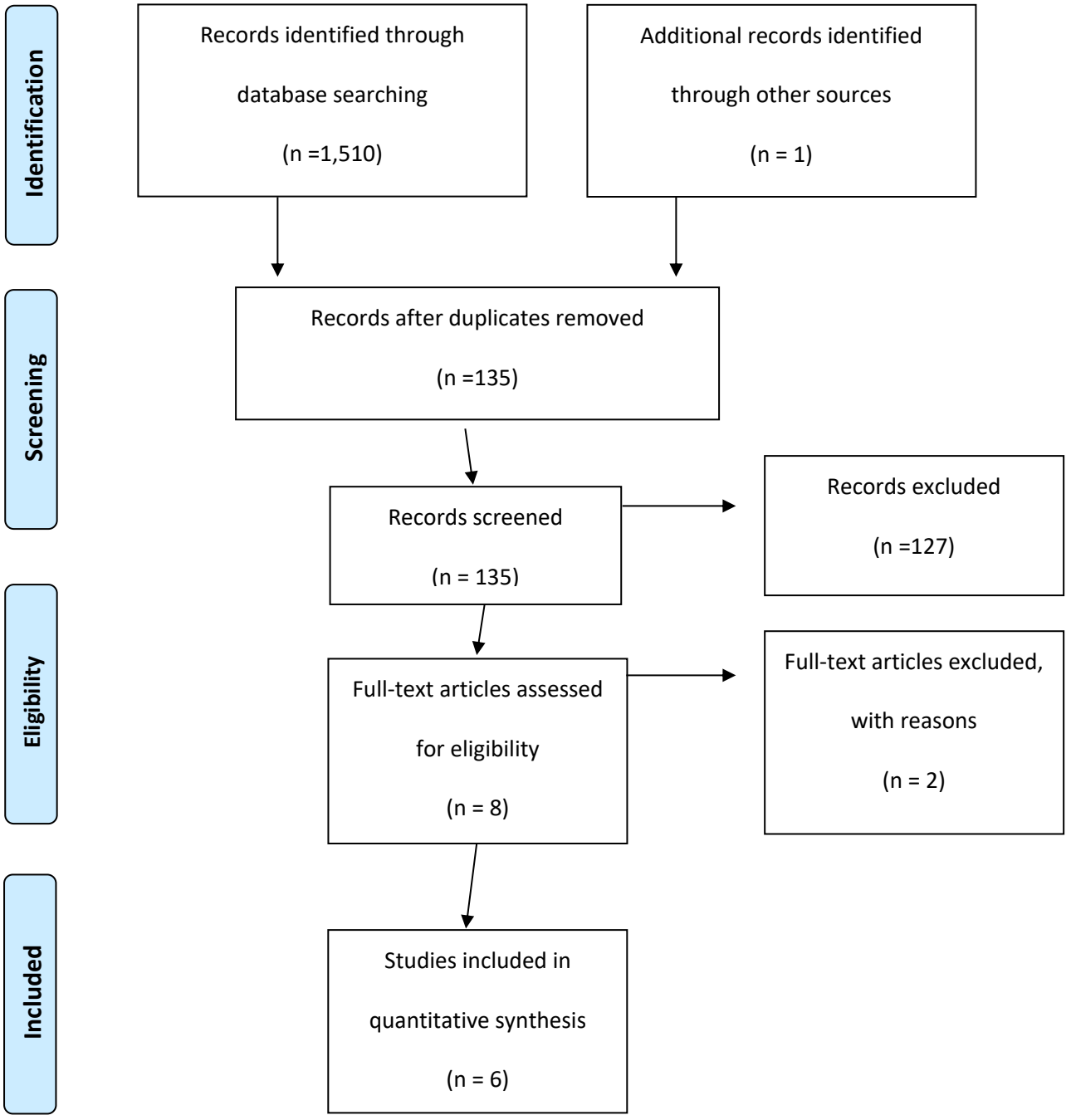

Figure 4. PRISMA Flowchart (Moher et al., 2009)

Review of Included Studies

A study by Greif et al. (2000) (Appendix A-1) tested the hypothesis that supplemental administration of oxygen during the perioperative phase would decrease the incidence of SSI. The RCT included 500 adults aged 18-80 undergoing elective open colorectal resection with general inhalational anesthesia via an ETT. The groups were split into a control group and a treatment group by a computer-generated random assignment. The two groups were then blinded from all but the anesthesia provider. The control group consisted of 250 patients assigned to receive 30% O_2 intraoperative vs. the treatment group that consisted of 250 patients assigned to receive 80% O_2 intraoperative. Once the intraoperative phase was complete, both groups received a sealed non-rebreathing face mask for two hours postop and O_2 was titrated to maintain an O_2 saturation of 92%.

Outcomes for this study (Appendix B-1) showed that 28 patients (11.2%) in the control group developed a SSI vs. 13 patients (5.2%) in the treatment group (P = 0.01). Greif et al. (2000) also examined the average length of hospital stay and found that the control group had an average stay of 11.9 ($\pm$ 4.0) days in the hospital vs. the treatment group with an average stay of 12.2 ($\pm$ 6.1) days in the hospital (P = 0.26). The authors also examined the mortality rate at 15 days postoperative and found that the control group had six patients (2.4%) that died within the 15 days after surgery vs. the treatment group which had one patient (0.4%) die within the 15 days after surgery (P= 0.13). Limitations to this study were patients that enrolled in the study who had a smoking history, low preoperative hemoglobin concentration, co-existing systemic disease, or drug therapy, all of which could have influenced wound healing.

When evaluating the study utilizing CASP (Appendix C-1), the RCT addressed a clearly focused issue, all patients involved in the study were randomized and both groups were similar at the start of the trial. Aside from the experimental intervention, both groups were treated equally throughout the study. The treatment effect was not explicitly mentioned in this study. A limitation of this study was not all of the patients were accounted for at the 30-day follow up visit. Three patients did not return for follow up visits; however, the authors stated that the patients had no known infections at discharge from the hospital and were considered uninfected in the analysis. The results of the study can be applied to intraabdominal surgery that requires general anesthesia with an ETT.

A study by Pryor et al. (2004) (Appendix A-2) examined whether the routine use of high O_2 during the perioperative period would alter the incidence of SSI in general surgical patients. The RCT consisted of 160 adults over the age 18 undergoing major intra-abdominal surgical procedures including colectomy (right, left, hemicolectomy, and sigmoid), lower anterior resection, abdominoperineal resection, gastrectomy pancreatico-duodenectomy, exploratory laparotomy, and extensive gynecological procedures. All surgeries were done under general anesthesia with an ETT. The RCT was blinded to all involved except the anesthesia provider who was aware of the percent of O_2 being delivered. The groups were made up of a treatment group that received 80% O_2 intraoperative and a control group that received 35% O_2 intraoperative. Patients in the treatment group were transported from the operating room with either a closed reservoir bag-mask system or a Jackson-Rees modified Mapleson E circuit at an O_2 flow rate of 10 liters per minute. Once in the PACU, the treatment group was fitted with a non-rebreather mask and 80% O_2 was administered for the next two hours. Patients in the control group

were transported from the OR with nasal cannula at an O_2 flow rate of 4 liters per minute. Once in the PACU, the control group was fitted with a non-rebreather mask and 35% O_2 was administered for the next two hours.

Outcomes for the study (Appendix B-2) showed that 20 patients (25%) in the treatment group developed a SSI vs. nine patients (11.3%) in the control group ($P = 0.02$). While this study is statically significant, the findings are limited to a difference of only 11 patients. Pryor et al. (2004) also examined the average length of hospital stay and found that the treatment group had an average of 8.3 days vs. the control group that had an average of 6.4 days ($P = 0.07$). The authors did not measure mortality. Limitations to this study were numerous patient conditions that could affect wound healing, including a smoking history, ASA physical class status, vital signs, lab values, and the presence of a significant co-morbidity (diabetes, asthma, hypertension, coronary artery disease, obesity, chronic obstructive pulmonary disease, end-stage renal disease or immunosuppression). This study deliberately permitted variation in their anesthetic and surgical management to model routine practice. This study also used a very heterozygous surgical population. The small sample size, varying anesthetic management, and heterozygous surgical population may be the reason for their contradictory results.

When evaluating the study utilizing CASP (Appendix C-2), the RCT addressed a clearly focused issue, all patients involved in the study were randomized, and both groups were similar at the start of the trial. This study accounted for variability and a variety of anesthetic management and deliberately permitted variation in anesthetic and surgical management to model routine practice. The treatment effect included 300 patients using the Lan-Demets α spending function approach, with an interim analysis of the first 160

patients. The analysis assessed an overall risk of 0.05 for type I error and 0.20 for type II error and a detectable treatment effect of 40%. This study demonstrated that a higher O_2 concentration might be damaging to a patient and have adverse effects. The results of the study can be applied to intraabdominal surgery that requires general anesthesia.

A study by Belda et al. (2005) (Appendix A-3) tested the hypothesis that supplemental O_2 would reduce infection risk in patients following colorectal surgery. The RCT consisted of 300 patients aged 18-80 undergoing elective colorectal surgery with general inhalational anesthesia via an ETT. The RCT was a double blinded study to all those involved except the anesthesia provider that was aware of the percent of O_2 being delivered. The groups were randomly assigned by computer-generated codes to receive either 30 or 80% O_2 intraoperatively and for six hours after surgery. The groups were made up of a treatment group that had 148 patients that received 80% O_2 intraoperative and a control group with 143 patient that received 30% O_2 intraoperative. All patients received 100% O_2 during the extubation. Following extubation, during the 6-hour post-operative period, patients in the control group received 30% O_2 while the treatment group received 80% O_2 via a non-rebreathing face mask at a flow of 16 liters per minute.

Outcomes for the study (Appendix B-3) showed that 22 patients (14.9%) in the treatment group developed a SSI vs. 35 patients (24.4%) in the control group (P=0.4). The risk of SSI was 39% lower in the treatment group (RR, 0.61; 95% confidence interval [CI], 0.38 – 0.98) vs. the control group. The authors also examined how many patients required hospitalization after surgery and found that 11.7 patients (7.0%) in the treatment group required hospitalization vs. 10.5 patients (4.4%) in the control group (P= 0.9). Two patients died during the study, and they were both in the control group.

Limitations to this study were the small sample size, lack of a diagnostic tool used to define SSI, and SSI was only examined for the first 15 days postoperatively unlike other studies that followed the patient for 30 days.

When evaluating the study utilizing CASP (Appendix C-3), the RCT addressed a clearly focused issue, all patients involved in the study were randomized, and both groups were similar at the start of the trial. Aside from the experimental intervention, both groups were treated equally throughout the study. The treatment effect was not explicitly mentioned in this study. Not all the clinically important outcomes were considered. The study failed to look at 30-day post-operative SSI and mortality. While the sample size was less than similar studies and the follow-up evaluation for SSI was at 15 days as compared to most other studies at 30 days, the findings can still be applied to patients undergoing intraabdominal surgery with general anesthesia.

A study by Meyhoff et al. (2009) (Appendix A-4) examined whether the use of 80% O_2 during surgery reduced the frequency of SSI without increasing the frequency of pulmonary complication in patients undergoing abdominal surgery. The RCT included 1400 adults over the age of 18 who underwent an acute or elective laparotomy with inhalational or total intravenous anesthesia that required an ETT. The treatment group consisted of 685 patients assigned to receive 80% O_2 during the intraoperative phase. The control group consisted of 701 patients assigned to receive 30% O_2 during the perioperative phase. Both groups were placed on a non-rebreather mask for two hours during the postoperative phase. The groups did differ in their O_2 delivery during the next two hours in the Post-Anesthesia Care Unit (PACU). The treatment group received 14L

of O_2 and 2L of air per minute in the PACU vs. the control group that received 2L of O_2 and 14L of air per minute for two hours postoperative.

The outcomes for this study (Appendix B-4) showed that 131 patients (19.1%) in the treatment group developed SSI vs. 141 patients (20.1%) in the control group (P= 0.64) ([CI]0.94). The authors also found that 30 patients (4.4%) in the treatment group died before the 30-day follow up period vs. 20 patients (2.9%) control group (P = 0.15).

Limitations to this study included the lack of an optimized regimen of antibiotics and the prevention of hypothermia could not be controlled for in all of the patients during the trial. Also, 51 of the 701 (7.3%) patients that received 30% O_2 required a FiO_2 of 0.60 or greater for more than an hour to maintain O_2 saturations above 94% during surgery, which should have excluded them from this subset. The study did exclude patients who had surgery within 30 days, were taking chemotherapy for malignancy within the past three months, or O_2 saturations below 90% in the preoperative phase.

When evaluating the study utilizing CASP (Appendix C-4), the RCT addressed a clearly focused issue, all patients involved in the study were randomized, and both groups were similar at the start of the trial. Aside from the experimental intervention, both groups were treated equally throughout the study. The treatment effect was not explicitly mentioned in this study. A limitation of this study was not all of the patients were accounted for at the 30-day follow up visit. One hundred fifty-seven of the 1386 (11.3%) did not have a follow-up visit between the 13^{th} and 30^{th} postoperative day. The results of the study can be applied to intraabdominal surgery that requires general anesthesia with an ETT.

A study Bickel et al. (2011) (Appendix A-5) examined the influence of hyperoxygenation on surgical site infection by using a homogenous study population. The RCT consisted 210 adults, defined as 15 years of age or older, undergoing intra-abdominal surgery homogenous for open appendectomy, which is a type of intraabdominal surgery to treat an acute appendicitis. The surgery was performed under general inhalational anesthesia with an ETT. The RCT was double blinded. The two groups were made up of 107 patients in the treatment group assigned to receive 80% O_2 intraoperative and 103 patients in the control group assigned to receive 30% O_2 intraoperative. The treatment group received high flow O_2 (O_2 flow rate of 10 liters per minute) via a non-rebreather mask with a reservoir for two hours while in PACU while the control group received O_2 at a flow rate of 4 liters per minute via nasal cannula.

Outcomes for the study (Appendix B-5) showed that six subjects (5.6%) in the treatment group developed a SSI vs. 14 (13.6%) in the control group ($P = 0.04$). The authors also examined the mean length of hospital stay and found the treatment group had an average stay of 2.51 days ($\pm$0.88) vs the control group that had an average length of hospital stay 2.92 ($\pm$1.51) ($P = 0.01$). This study didn't not measure mortality rates. Limitations to this study included patients in PACU didn't have the anesthesia provider closely monitoring the delivery of O_2, as they had been doing intra-operatively. Also, patients with a smoking history, low preoperative hemoglobin concentration, co-existing systemic disease, and drug therapy could influence wound healing.

When evaluating the study utilizing CASP (Appendix C-5), the RCT addressed a clearly focused issue, all patients involved in the study were randomized, and both groups were similar at the start of the trial. Aside from the experimental intervention, both

groups were treated equally throughout the study. The treatment effect was not explicitly mentioned in this study. The results of the study can be applied to intraabdominal surgery that requires general anesthesia with an ETT.

A study by Kurz et al. (2018) (Appendix A-6) tested the hypothesis that supplemental O_2 would reduce the risk of a 30-day composite of deep tissue or organ-space SSI, healing-related wound complications, and mortality. The controlled trial took place at a colorectal surgery center and consisted of 5749 colorectal surgeries lasting over two hours, on adults over the age of 18 that received general inhalational anesthesia with an ETT. Qualifying colorectal operations included 2843 colorectal resections, 1866 lower GI therapeutic procedures, 373 small bowel resections, and 667 other colorectal procedures. The controlled trial consisted of 2896 patients in the treatment group assigned to receive 80% O_2 intraoperative and 2853 patients in the control group assigned to receive 30% O_2 intraoperative. The first two weeks of the study, the groups were randomized by a statistician, but the subsequent 38 months were not randomized, and the provider decided the concentration of 0_2 delivered.

Outcomes for the study (Appendix B-6) showed that 118 patients (4.1%) in the treatment group developed SSI vs. 112 patients (3.9%) in the control group (P = 0.77, [CI] 1.04 (0.74-1.46). While examining mortality, the authors found that 20 patients (0.7%) died within the 30 days after surgery in the treatment group vs.10 patients (0.4%) in the control group (P = 0.85, [CI] 1.97 (0.71-5.47). The outcomes for this study were abstracted from a billing department using medical records rather than evaluation by the investigators. Limitation of this study included the evaluation of SSI via chart review; “a small fraction” (Kurz et al., 2018) of the patients could not be accounted at 30 days post-

operative because they had follow-up care at other facilities not included in this study. Also, the use of positive end-expiratory pressure (PEEP) by the anesthesia provider was not accounted.

When evaluating the study utilizing CASP (Appendix C-6), this controlled trial clearly addressed a focused issue. The authors used appropriate methods to answer their question and the cases were selected from a colorectal center that performed many intraabdominal surgeries daily. The treatment effect was not explicitly mentioned in this study. The authors failed to minimize bias when they discontinued the randomization of groups after two weeks. A statistician randomized the first two weeks of the study, but the subsequent 38 months were not randomized and the concentration of 0_2 delivered was decided by the provider to maximize patient safety rather than randomization. Aside from experimental intervention, the two groups were treated equally. The authors didn't take into account the use of positive end expiratory pressure (PEEP) by the anesthesia provider in the design. The study allowed the control group to receive more than 30% O_2 when a patient's O_2 saturation fell below 95% to maximize patient safety, creating the potential for confounding factors in the analysis. For these reasons, concerns about confidence in study findings exist and findings should not be applied to the general population. The results of this study are in opposition to most other studies. Also, findings do not fit with other available evidence and research completed by the same group a couple of years earlier.

Cross-Study Analysis

For this systematic review, the central elements of each journal article were extracted to analyze critical variables across the different studies (Appendix D). The

elements and data collected included the specific treatment used, including the percent of O_2 each group was administered, the SSI rate by group, and the mortality rate. All of the studies used in this systematic review were similar in that the treatment groups all received 80% O_2, and the control groups received 30-35% O_2 during intraabdominal surgery under general anesthesia with an ETT. All the studies differed in many ways including the number of patients, whether the research was blinded, the amount of time spent collecting patient data and outcomes, the specific outcomes examined, and the method of O_2 delivery in the PACU all varied amongst the studies. The one finding that all the studies reviewed was whether an increase in O2 during the perioperative phase resulted in an increase or decrease in SSI.

The studies by Greif et al. (2000), Meyhoff et al. (2000), Belda et al. (2005), and Bickel et al. (2011) all showed a decrease in SSI ($P = 0.01$; $P= 0.64$; $P=0.4$; and $P = 0.04$ respectively) in their treatment groups that received 80% O_2 intraoperative during intraabdominal general surgery. Conflicting studies by Pryor et al. (2004), and Kurz et al. (2018) found their treatment groups had an increased risk of SSI ($P = 0.02$; $P = 0.77$ respectively). The statistically significant studies by Greif et al. (2000) and Bickel et al. (2011) showed a decrease in SSI, contradicting the findings by Pryor et al. (2004) that showed an increase in SSI. The two fundamental differences in these studies were the size of the patient population and the type of surgery performed. Greif et al. (2000) studied 500 patients undergoing elective open colorectal resection, and Bickel et al. (2011) studied 210 patients undergoing open appendectomy for acute appendicitis. Pryor et al. (2004) studied 160 undergoing major intra-abdominal surgical procedures including colectomy (right, left, hemicolectomy, and sigmoid), lower anterior resection,

abdominoperineal resection, gastrectomy pancreaticoduodenectomy, exploratory laparotomy, and extensive gynecological procedures. Meyhoff et al. (2000) and Bickel et al. (2011) both had a larger population compared to Greif et al. (2000). Meyhoff et al. (2000) and Bickel et al. (2011) also studied only one specific type of intra-abdominal surgery, making their making studies generalizable only to that type of surgery.

A second variable examined across a majority of the studies was mortality. A direct causal relationship between SSI and mortality is difficult to examine because there are many variables involved with mortality such as co-existing diseases, patient age, patient health prior to surgery, and the availability to quality health care to name a few. Studies by Greif et al. (2000) ($P= 0.13$) and Belda et al. (2005) (no P value given) reported a decrease in mortality in their treatment groups whereas studies by Meyhoff et al. (2000) and Kurz et al. (2018) reported an increase in the mortality rate in the treatment groups ($P = 0.15$; $P = 0.85$ respectively). There was no level of significance amongst the studies in regard to mortality. Bickel et al. (2011) and Pryor et al. (2004) both chose not to examine mortality in their studies, perhaps due to the fact that mortality has many variables and it would be difficult to account for them all.

Next, the summary and conclusions will be presented.

Summary and Conclusions

Surgical site infections cost billions of dollars a year to treat and put a strain on patients and the health care system (CDC, 2017). The potential for improved patient care and reduced healthcare spending by decreasing SSIs could save millions of US healthcare dollars and at the same time lead to better patient outcomes. The WHO (2016) recommended the use of high concentration oxygen throughout the intraoperative phase to decrease SSI. The correct concentration of O_2 to administer during surgery is influenced by many factors such as the patient condition, the provider's preference, and perhaps an unwritten standard at a facility. Some facilities, due to varying standards of equipment, may not have O_2 piped into the anesthesia machines, forcing them to rely pre-filled canisters during surgery. In the US it is typical for an Advanced Practicing Registered Nurse (APRN) CRNA to titrate the concentration of O_2 down to a minimum while maintaining an O_2 saturation of 94% or better during surgery. Because current practice regarding O_2 use differs from the WHO guidelines, and the evidence they used to make this recommendation can be considered inconclusive, there has been a discussion amongst anesthesia providers as to whether this is the best practice to follow.

The focus of this systematic review was to determine whether high concentration oxygen delivered to surgical patients undergoing intra-abdominal surgery decreases SSI. Pasteur's Germ Theory and PRISMA were used to guide this systematic review. A total of six studies were identified and used for this review which can be visualized with the PRISMA flow sheet. All six studies were then evaluated using the CASP tool and data extraction tables were created. Comparison tables were also created, and a cross study analysis of data was completed.

Studies by Greif et al. (2000), Meyhoff et al. (2000), Belda et al. (2005), and Bickel et al. (2011) all showed a decrease in SSI, but only the studies by Greif et al., and Bickel et al. reported statistical significance with a P value of less than 0.05. Contradictory to these studies was a smaller, but well-designed review by Pryor et al. (2004) that showed a statically significant increase in SSI. This study is often referenced in other works as the outlier and the reason why more studies are needed before a strong recommendation can be given endorsing the use of high concentration O_2. The WHO (2016) did not include this study in their meta-analysis of evidence-based research.

Limitations to this systematic review included the most current available evidence, moderate sample size of studies, time limitations to conduct this review, and the novice status of the researcher who conducted it. Articles that were not controlled trials available in full text or in a foreign language was excluded. The six studies used for this systematic review had a combined total sample of 8296 patients. Two thirds of the total sample (n = 5749) came from the Kurz et al. (2018) study alone. The other five studies had a combined total of 2547 subjects. More large-scale studies like the Kurz et al. study are needed to further examine the use of high concentration O_2. With more time, perhaps articles not in full text could have been obtained and included in this review.

The WHO (2016) guideline recommending the use of high concentration oxygen during intraabdominal surgery to decrease SSI will inevitably generate more research that will test the guideline. Addition studies will generate new hypothesis and more raw data to be used in the continued evaluation of this guideline. Based on all the available research at this time, the WHO's (2016) recommended guideline related to use of high concentration oxygen during the intraoperative phase to decrease SSI should be followed

if patient specifics and facility resources allow. Further studies will need to focus on standardized protocols specific for each abdominal surgery.

Next, the recommendations and implications for advanced nursing practice will be presented.

Recommendations and Implications for Advanced Nursing Practice

Prevention of SSI requires timely interventions by multiple clinicians during a patient's care to prevent infection. One of the best and simplest ways to prevent infection is the act of washing germs off one's hands. The practice of hand washing originated from Pasteur's Germ Theory which demonstrated that germs cause infection. When handwashing was utilized prior to surgical dressing changes by bedside RNs, infection rates significantly decreased. In addition, surgeons can decrease SSI by scrubbing their hands and wearing sterile gloves, gowns and a mask during surgery. The CRNA may have the greatest opportunity to prevent SSI with the administration of the appropriate antibiotics just prior to skin incision.

Over a century has passed since the introduction of the Germ theory and medicine continues to improve strategies for decreasing bacteria and thus infection. The WHO has implemented guidelines to help decrease SSI and subsequently reducing health care costs. Following these recommendations could potentially save billions of dollars. Not only will the APRN CRNAs need to adopt this change in practice but they will also need to inform other members of the interdisciplinary team of the current evidence-based practice recommendations. The APRN is an integral part of the interdisciplinary team, which includes the surgeon and anesthesiologist. There are times when APRN must follow the surgeon, and/or the anesthesiologist's order regarding O_2 concentration administration during surgery. The APRN can confidently include evidence-based studies in their decision-making process, which is generally well-received by the interdisciplinary team. This systematic review yielded evidence-based results that can be utilized specifically by the APRN CRNA to help guide the decision related to the correct O_2 concentration to use

during intra-abdominal surgery. Research has shown that the use of high concentration O2 does have benefits and the APRN CRNA will be in a position to share the evidence-based research to the interdisciplinary team.

The American Association of Nurse Anesthetists (AANA) provides CRNAs access to unparalleled professional resources. Membership in AANA includes live and online continuing education as well as a bi-monthly professional journal of trending topics. The AANA annual conference is the ideal arena to inspire association involvement. Presentation of well-designed meta-analysis on high concentration oxygen use could have unmatched opportunities to reach the most extensive collection of CRNAs. The AANA online continuing education classes could incorporate the most up to date research and recommended guidelines on this topic. The bi- monthly journal could help publicize the topic by publishing the newest RCTs that examine high concentration O2 use perioperatively. It will be the responsibility of the CRNA to disseminate and promote this evidence-based research in their daily practice. The CRNAs in developed countries such as the U.S. have an abundance of available recourses compared to undeveloped parts of the world and they will be in a critical position to guide this ongoing research.

The pendulum of evidence is starting to swing towards the use of high concentration O2 to help decrease the rate of SSI. Guidelines are meant to guide practice not dictate it. With the current evidence available, it would be premature to institute a policy that dictates the use of high concentration O2 during intra-abdominal surgery. Any policy that dictates and limits the autonomy of practice will be a hard sell to a practicing CRNA. Until more meta-analysis and evidence-based research demonstrate decreased

SSI with the use of high concentration O_2, the recommended guidelines are precisely that: guidelines not policy. Clearly, further research is needed to explore this important topic. Specifically, research that examines toxicity related to high concentration oxygen.

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Appendix A

Table A-1. *Study Specific Data*
Greif, R., Akça, O., Horn, E., Kurz, A., & Sessler, D. I. (2000). Supplemental perioperative oxygen to reduce the incidence of surgical-wound nfection. *New England Journal of Medicine*, *342(3)*, 161-167.

Method/ Design	Sample	Type of Surgical procedure performed	Anesthesia and airway used during surgery	Post-operative oxygen delivery
RCT, computer generated random assignment of groups. Blinded study from all but the anesthesia provider. Independent physicians (not part of the surgical team) evaluated the wounds daily.	500 adults aged 18-80: 250 assigned to receive 80% O_2 intraoperative; 250 assigned to receive 30% O_2 intraoperative.	Elective open colorectal resection	General inhalational anesthesia with an ETT	All patients received a sealed non-rebreathing face mask for two hours postop. Oxygen was titrated to maintain O_2 saturation of 92% in both groups.

Appendix A

Table A-2. *Study Specific Data*
Pryor, K. O., Iii, T. J., Lien, C. A., & Goldstein, P. A. (2004). Surgical site infection and the routine use of perioperative hyperoxia in a general surgical population. *JAMA*, 291(1*)*, 79-87.

Method/ Design	Sample	Type of Surgical procedure performed	Anesthesia and airway used during surgery	Post-operative oxygen delivery
Randomized control trial, double blinded; only the anesthesia provider was aware of the groups.	160 adults over the age 18: 80 assigned to receive 80% O_2 intraoperative; 80 assigned to receive 35% O_2 intraoperative.	Major intra-abdominal surgical procedures including colectomy (right, left, hemicolectomy, and sigmoid), lower anterior resection, abdominoperineal resection, gastrectomy pancreatico-duodenectomy, exploratory laparotomy, and large gynecological procedures	General inhalational anesthesia with an ETT	Patients in the 80% O_2 group were transported from the operating room with either a closed reservoir bag-mask system or a Jackson-Rees modified Mapleson E circuit at an oxygen flow rate of 10 liters per minute; once in the PACU the group was fitted with a non-rebreather mask and 80% O_2 was administered for the next two hours. Patients in the 35% O_2 group were transported from the OR with nasal cannula at an oxygen flow rate of 4 liters per minute; once in the PACU the group was fitted with a non-rebreather mask and 35% O_2 was administer for the next two hours.

Appendix A

Table A-3. *Study Specific Data*
Belda, F. J., Aguilera, L., García de la Asunción, J., Alberti, J., Vicente, R., Ferrándiz, L., . . . Ortí, R. (2005). Supplemental perioperative oxygen and the risk of surgical wound infection a randomized controlled trial. *JAMA*, *294(16)*, 2035-2042.

Method/ Design	Sample	Type of Surgical procedure performed	Anesthesia and airway used during surgery	Post-operative oxygen delivery
Double blind randomized control trial; patients were randomly assigned by computer generated codes to receive either 30 or 80% O_2 intraoperatively and for 6 hours after surgery Blinded study from all but the anesthesia provider.	300 patients aged 18-80: 143 patients received 30% O_2; 148 patients received 80% O_2.	Elective colorectal surgery	General inhalational anesthesia with an ETT	All patients received 100% O_2 during the extubation. During the 6-hour postoperative period, patients received either a 30% O2 or 80 % O_2 via a non-rebreathing face mask at a flow of 16 liters per minute.

Appendix A

Table A-4. *Study Specific Data*
Meyhoff, C. S., Wetterslev, J., Jorgensen, L. N., Henneberg, S. W., Høgdall, C., Lundvall, L., Group, F. T. (2009). Effect of high perioperative oxygen fraction on surgical site infection and pulmonary complications after abdominal surgery. *JAMA*, *302(14),* 1543-1550.

Method/ Design	Sample	Type of Surgical procedure performed	Anesthesia and airway used during surgery	Post-operative oxygen delivery
PROXI trial: patient and observer-blinded randomized clinical trial	Adults over the age of 18; 1400 patients: 685 assigned to receive 80% O_2; 701 assigned to receive 30% O_2.	Acute or elective laparotomy	Inhalational or total intravenous anesthesia with an ETT	Both groups were placed on a non-rebreather mask for two hours post op. 80% O_2 group received 14L of oxygen and 2L of air per minute; 30% O_2 group received 2L of oxygen and 14L of air per minute.

Appendix A

Table A-5. *Study Specific Data*
Bickel, A. (2011). Perioperative hyperoxygenation and wound site infection following surgery for acute appendicitis. *Archives of Surgery*,146(4), 464-470.

Method/ Design	Sample	Type of Surgical procedure performed	Anesthesia and airway used during surgery	Post-operative oxygen delivery
Randomized double blinded controlled trial; homogenous for one specific type of intra-abdominal surgery	210 adults (defined as 15 years of age or older): 107 assigned to receive 80% O_2 intraoperative; 103 assigned to receive 30% O_2 intraoperative.	Open appendectomy for acute appendicitis	General inhalational anesthesia with an ETT	Patients in the 80% O_2 group received high flow O_2 (O_2 flow rate of 10 liters per minute) via a non-rebreather mask with a reservoir for 2 hours. Patients in the 30% O_2 group received O_2 at a flow rate of 4 liters per minute via nasal cannula.

Appendix A

Table A-6. *Study Specific Data*
Kurz, A., Kopyeva, T., Suliman, I., Podolyak, A., You, J., Lewis, B., . . . Sessler, D. (2018). Supplemental oxygen and surgical-site infections: An alternating intervention controlled trial. *British Journal of Anaesthesia,120(1*), 117-126.

Method/ Design	Sample	Type of Surgical procedure performed	Anesthesia and airway used during surgery	Post-operative oxygen delivery
Controlled trial at a colorectal surgery center; evaluation by staff via chart review. First two weeks of the study were randomized by a statistician, but the subsequent 38 months were not randomized and the concentration of 0_2 delivered was decided by the provider.	5749 colorectal surgeries on adults aged over 18years old: 2896 assigned to receive 80% O_2 intraoperative; 2853 assigned to receive 30% O_2 intraoperative.	Major intestinal surgery lasting at least two hours: qualifying operations included 2843 colorectal resections, 1866 lower GI therapeutic procedures, 373 small bowel resections, 667 other colorectal procedures.	General inhalational anesthesia with an ETT	Not addressed

Appendix B

Table B-1. *Outcome Data Collection*
Greif, R., Akça, O., Horn, E., Kurz, A., & Sessler, D. I. (2000). Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. *New England Journal of Medicine*, *342(3*), 161-167.

Incidence of postoperative SSI	Outcome / mortality	Limitations
13 (5.2%) in the 80% O_2 group developed SSI; 28 (11.2%) in the 30% O_2 group developed SSI (P = 0.01)	Length of hospital stay 12.2 ($\pm$ 6.1) for the 80% O_2 group; Length of hospital stay 11.9 ($\pm$ 4.0) for the 30% O_2 group (P = 0.26); 1 patient (0.4%) died within the 15 days after surgery in the 80% O_2; 6 patients (2.4%) died within the 15 days after surgery in the 30 % O_2. (P= 0.13)	Patients with a smoking history, low preoperative hemoglobin concentration, co-existing systemic disease, and drug therapy could have influenced wound healing. Follow up evaluations of wounds were not completed in three patients at the 30-day follow up visit. They had no known infections and were considered uninfected in the analysis.

Appendix B

Table B-2. *Outcome Data Collection*
Pryor, K. O., Iii, T. J., Lien, C. A., & Goldstein, P. A. (2004). Surgical site infection and the routine use of perioperative hyperoxia in a general surgical population. *JAMA*, *291(1)*, 79-87.

Incidence of postoperative SSI	Outcome / mortality	Limitations
20 (25%) in the 80% O_2 group developed SSI; 9 (11.3%) in the 35% O_2 group developed SSI. (P = 0.02)	Length of hospital stay 8.3 days for the 80% O_2 group; Length of hospital stay 6.4 day for the 35% O_2 group. (P = 0.07) Mortality was not measured.	Numerous conditions could affect wound healing including a smoking history, ASA physical class status, vital signs, lab values, the presences of a major co-morbidity (diabetes, asthma, hypertension, coronary artery disease, obesity, chronic obstructive pulmonary disease, end stage renal disease or immunosuppression). Unable to detect if other elements of anesthetic management might affect SSI. This study deliberately permitted variation in anesthetic and surgical management to model routine practice.

Appendix B

Table B-3. *Outcome Data Collection*
Belda, F. J., Aguilera, L., García de la Asunción, J., Alberti, J., Vicente, R., Ferrándiz, L., . . . Ortí, R. (2005). Supplemental perioperative oxygen and the risk of surgical wound infection a randomized controlled trial. *JAMA*, *294(16)*, 2035-2042.

Incidence of postoperative SSI	Outcome / mortality	Limitations
22 (14.9%) in the 80% O_2 group developed SSI; 35 (24.4%) in the 30% O_2 group developed SS. (P=0.4) The risk of SSI was 39% lower in the 80% O_2 group (RR, 0.61; 95% confidence interval [CI], 0.38 – 0.98) vs the 30% O_2 group.	11.7 (7.0%) required hospitalization after surgery in the 80% O_2 group; 10.5 (4.4%) required hospitalization after surgery in the 30% O_2 group (P= 0.9); only 2 patients died during the study and they were both in the 30% O2 group.	Small sample size; Diagnostic tool used to define SSI included purulent drainage whether or not it was tested for organisms. Only looked at SSI for the first 15 days post operatively unlike other studies that followed the patient for 30 days.

Appendix B

Table B-4. *Outcome Data Collection*
Meyhoff, C. S., Wetterslev, J., Jorgensen, L. N., Henneberg, S. W., Høgdall, C., Lundvall, L., Group, F. T. (2009). Effect of high perioperative oxygen fraction on surgical site infection and pulmonary complications after abdominal surgery. *JAMA*, *302(14)*, 1543-1550.

Incidence of postoperative SSI	Outcome / mortality	Limitations
131 (19.1%) in the 80% O_2 group developed SSI; 141 (20.1%) in the 30% O_2 group developed SSI. (P= 0.64) ([CI]0.94)	30 (4.4%) in the 80% O_2 group died before the 30-day follow up period; 20 patients (2.9%) in the 30% O_2 group died before the 30-day follow up period (P = 0.15).	Excluded patient who had surgery within 30 days, taking chemo therapy for malignancy within the past 3 months, oxygen saturations below 90% in the pre-operative phase. An optimized regimen of antibiotics and the prevention of hypothermia could not be controlled for in all of the patients during the trial. 51 of the 701 (7.3%) patients that received 30% O_2 required an FiO_2 of 0.60 or greater for more than an hour to maintain O_2 saturations above 94% during the trial, which would should have excluded them from this subset.

Appendix B

Table B-5. *Outcome Data Collection*
Bickel, A. (2011). Perioperative hyperoxygenation and wound site infection following surgery for acute appendicitis. *Archives of Surgery,146(4)*, 464-470.

Incidence of postoperative SSI	Outcome / mortality	Limitations
6 (5.6%) in the 80% O_2 group developed SSI; 14 (13.6%) in the 30% O_2 group developed SSI (P = 0.04)	Mean length of hospital stay 2.51 ($\pm$0.88) in the 80% O_2 group; Length of hospital stay 2.92 ($\pm$1.51) of the 30% O_2 group (P = 0.01). Mortality was not measured.	Patients in PACU didn't have the anesthesia provider closely monitoring the delivery O_2, as they did intra-operatively. Patients with a smoking history, low preoperative hemoglobin concentration, co-existing systemic disease, and drug therapy could influence wound healing

Appendix B

Table B-6. *Outcome Data Collection*
Kurz, A., Kopyeva, T., Suliman, I., Podolyak, A., You, J., Lewis, B., . . . Sessler, D. (2018). Supplemental oxygen and surgical-site infections: An alternating intervention controlled trial. *British Journal of Anaesthesia,*120(1*)*, 117-126.

Incidence of postoperative SSI	Outcome / mortality	Limitations
118 (4.1%) patients in the 80% O_2 group developed SSI; 112 (3.9%) patients of the 30% O_2 group developed SSI. (P = 0.77, [CI] 1.04 (0.74-1.46)	20 patients (0.7%) died within the 30 days after surgery in the 80% O_2; 10 patients (0.4%) died within the 30 days after surgery in the 30% O_2 (P = 0.85, [CI] 1.97 (0.71-5.47)	Outcomes were abstracted from a billing department rather than evaluation by investigators; some patients could not be accounted for because they had follow-up care in other facilities not included in this study. The use of PEEP was not accounted for. Randomization of groups was discontinued after two weeks. The first two weeks of the study were randomized by a statistician, but the subsequent 38 months were not randomized and the concentration of 0_2 delivered was decided by the provider for added safety to the patient.

Appendix C

Table C-1. *Critical Appraisal Skills Programme (CASP) Randomized Control Trials Checklist*
Greif, R., Akça, O., Horn, E., Kurz, A., & Sessler, D. I. (2000). Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. *New England Journal of Medicine*, *342(3)*, 161-167.

Question	Yes	Can't Tell	No
Did the trial address a clearly focused issue?	X		
Was the assignment of patients to treatments randomized?	X		
Were all of the patients who entered the trial properly accounted for at its conclusion? **The authors state "most patients returned for the follow up visit at 14 days"**	X		
Were patients, health workers and study personnel blinded? **Except the Anesthesia provider due to safety concerns they had to know.**	X		
Were the groups similar at the start of the trial?	X		
Aside from the experimental intervention, were the groups treated equally?	X		
How large was the treatment effect?		X	
How precise was the estimate of the treatment effect?		X	
Can the results be applied in your context? (Or to the local population?)	X		
Were all clinically important outcomes considered?	X		
Are the benefits worth the harms and costs? **The benefits of extra oxygen resulted in a reduction in SSI and length of stay which was estimated to cost 12,500 per case. The cost of extra oxygen is pennies.**	X		

Appendix C

Table C-2. *Critical Appraisal Skills Programme (CASP) Randomized Control Trials Checklist*
Pryor, K. O., Iii, T. J., Lien, C. A., & Goldstein, P. A. (2004). Surgical site infection and the routine use of perioperative hyperoxia in a general surgical population. *JAMA*, *291(1)*, 79-87.

Question	Yes	Can't Tell	No
Did the trial address a clearly focused issue?	X		
Was the assignment of patients to treatments randomized?	X		
Were all of the patients who entered the trial properly accounted for at its conclusion?	X		
Were patients, health workers and study personnel blinded? **Except the Anesthesia provider due to safety concerns they had to know.**	X		
Were the groups similar at the start of the trial?	X		
Aside from the experimental intervention, were the groups treated equally? **This study deliberately permitted variation in anesthetic and surgical management to model routine practice.**		X	
How large was the treatment effect? **300 patients using the Lan-Demets α spending function approach, with an interim analysis of the first 160 patients.**	X		
How precise was the estimate of the treatment effect**? The analysis assessed an overall risk of 0.05 for type I error and 0.20 for type II error and a detectable treatment effect of 40%**	X		
Can the results be applied in your context? (Or to the local population?)	X		
Were all clinically important outcomes considered?	X		
Are the benefits worth the harms and costs? **The authors suggest that the negative effects of a higher O_2 concentration may be damaging to a patient.**			X

Appendix C

Table C-3. *Critical Appraisal Skills Programme (CASP) Randomized Control Trials Checklist.*
Belda, F. J., Aguilera, L., García de la Asunción, J., Alberti, J., Vicente, R., Ferrándiz, L., Ortí, R. (2005). Supplemental perioperative oxygen and the risk of surgical wound infection a randomized controlled trial. *JAMA*, *294(16)*, 2035-2042.

Question	Yes	Can't Tell	No
Did the trial address a clearly focused issue?	X		
Was the assignment of patients to treatments randomized?	X		
Were all of the patients who entered the trial properly accounted for at its conclusion?	X		
Were patients, health workers and study personnel blinded? **Yes except for the anesthesia provider**	X		
Were the groups similar at the start of the trial?	X		
Aside from the experimental intervention, were the groups treated equally?	X		
How large was the treatment effect?		X	
How precise was the estimate of the treatment effect?		X	
Can the results be applied in your context? (Or to the local population?)	X		
Were all clinically important outcomes considered? **They didn't examine death rates, or 30-day infection rates**			X
Are the benefits worth the harms and costs?	X		

Appendix C

Table C-4. *Critical Appraisal Skills Programme (CASP) Randomized Control Trials Checklist*
Meyhoff, C. S., Wetterslev, J., Jorgensen, L. N., Henneberg, S. W., Høgdall, C., Lundvall, L., Group, F. T. (2009). Effect of high perioperative oxygen fraction on surgical site infection and pulmonary complications after abdominal surgery *JAMA*, *302(14)*, 1543-1550.

Question	Yes	Can't Tell	No
Did the trial address a clearly focused issue?	X		
Was the assignment of patients to treatments randomized?	X		
Were all of the patients who entered the trial properly accounted for at its conclusion? **157 of the 1386 (11.3%) did not have a follow up visit between the 13th and 30th day**			X
Were patients, health workers and study personnel blinded?	X		
Were the groups similar at the start of the trial?	X		
Aside from the experimental intervention, were the groups treated equally?	X		
How large was the treatment effect		X	
How precise was the estimate of the treatment effect?		X	
Can the results be applied in your context? (Or to the local population?)	X		
Were all clinically important outcomes considered?	X		
Are the benefits worth the harms and costs? **There was no increase in pulmonary complication with the use of high O2 concentration.**	X		

Appendix C

Table C-5. *Critical Appraisal Skills Programme (CASP) Randomized Control Trials Checklist*
Bickel, A. (2011). Perioperative hyperoxygenation and wound site infection following surgery for acute appendicitis. *Archives of Surgery,146(4)*, 464-470.

Question	Yes	Can't Tell	No
Did the trial address a clearly focused issue?	X		
Was the assignment of patients to treatments randomized?	X		
Were all of the patients who entered the trial properly accounted for at its conclusion?	X		
Were patients, health workers and study personnel blinded? **Except for the anesthesia provider**	X		
Were the groups similar at the start of the trial?	X		
Aside from the experimental intervention, were the groups treated equally?	X		
How large was the treatment effect?		X	
How precise was the estimate of the treatment effect?		X	
Can the results be applied in your context? (Or to the local population?)	X		
Were all clinically important outcomes considered?	X		
Are the benefits worth the harms and costs?	X		

Appendix C

Table C-6. *Critical Appraisal Skills Programme (CASP) Checklist for Case Controlled Study.*
Kurz, A., Kopyeva, T., Suliman, I., Podolyak, A., You, J., Lewis, B., . . . Sessler, D. (2018). Supplemental oxygen and surgical-site infections: An alternating intervention controlled trial. *British Journal of Anaesthesia,120(1)*, 117-126.

Question	Yes	Can't Tell	No
Did the trial address a clearly focused issue?	X		
Did the authors use an appropriate method to answer their question?	X		
Were the cases recruited in an acceptable way?	X		
Were the controls selected in an acceptable way? The study	X		
Was the exposure accurately measured to minimize bias? **No, the study had no blinding, and they discontinued randomization after the first two weeks of the study.**			X
Aside from the experimental intervention, were the groups treated equally?	X		
Have the authors taken account of the potential confounding factors in the design and/or in their analysis? **They did not account for the use of positive end expiratory pressure (PEEP) by the anesthesia provider, also they allowed the 30% O_2 group to receive more then 30% O_2 when a patients O_2 saturation fell below 95%.**			X
How large was the treatment effect?		X	
How precise was the estimate of the treatment effect?		X	
Do you believe the results? **The lack of randomization and evaluation of SSI via chart review by staff does not give me confidence that I can trust these findings.**		X	
Can the results be applied to the local population?		X	
Do the results of this study fit with other available evidence? **No, this is in opposition to most other studies. A study by this same group done a couple of years earlier resulted in contradicting findings**			X

Appendix D

Table D-1. *Cross Study Analysis*

Study	Treatment	SSI rates	Morality
Greif et al. (2000)	250 patients received 80% O_2 intraoperative; 250 patients received 30% O_2 intraoperative	13 (5.2%) in the 80% O_2 group developed SSI; 28 (11.2%) in the 30% O_2 group developed SSI.	1 patient (0.4%) died within the 15 days after surgery in the 80% O_2; 6 patients (2.4%) died within the 15 days after surgery in the 30 % O_2.
Pryor et al. (2004)	80 patients received 80% O_2 intraoperative; 80 patients received 35% O_2 intraoperative	20 (25%) in the 80% O_2 group developed SSI; 9 (11.3%) in the 35% O_2 group developed SSI.	Mortality was not measured.
Belda et al. (2005)	148 patients received 80% O_2 intraoperative; 143 patients received 30% O_2 intraoperative.	22 (14.9%) in the 80% O_2 group developed SSI; 35 (24.4%) in the 30% O_2 group developed SSI.	0 patients in the 80% O_2 group died; 2 patients in the 35% O_2 group died.
Meyhoff et al. (2009)	685 patients received 80% O_2 intraoperative; 701 patients received 30% O_2 intraoperative	131 (19.1%) in the 80% O_2 group developed SSI; 141 (20.1%) in the 30% O_2 group developed SSI.	30 (4.4%) in the 80% O_2 group died before the 30-day follow up period; 20 patients (2.9%) in the 30% O_2 group died before the 30-day follow up period.
Bickel et al. (2011)	107 patients received 80% O_2 intraoperative; 103 patients received 30% O_2 intraoperative .	6 (5.6%) in the 80% O_2 group developed SSI; 14 (13.6%) in the 30% O_2 group developed SSI	Mortality was not measured.

Kurz et al. (2018)	2896 patients received 80% O_2 intraoperative; 2853 patients received 30% O_2 intraoperative.	118 (4.1%) patients in the 80% O_2 group developed SSI; 112 (3.9%) patients of the 30% O_2 group developed SSI.	20 patients (0.7%) died within the 30 days after surgery in the 80% O_2; 10 patients (0.4%) died within the 30 days after surgery in the 30% O_2

Note: All data tables discussed in the cross-study analysis are included under Appendices A, B, and C.