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Operating Room Air Filtration-Sterilization and Surgical Infections: The ORACLE Randomized Trial in 110,538 Surgeries

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Abbreviations:

AM: After midnight

CDC: Center for Disease Control

DSMB: Data and safety monitoring board

FDA: Food and Drug Administration

GEE: Generalized estimating equation

GLMM: Generalized linear mixed effects logistic model

ICD: International classification of Disease

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Author contributions

Data curation and analysis: Edward J. Mascha PhD and Yanyan Han MS. Both had full access to all data.

Funding acquisition: Daniel I. Sessler

Conceptualization: Daniel I. Sessler, Alparslan Turan, and Edward J. Mascha

Supervision: Daniel. I. Sessler and Alparslan Turan

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Manuscript: Daniel I. Sessler and Edward J. Mascha drafted the manuscript.

Trial implementation and conduct: Elyad Ekrami, Mauro Bravo, Cataline Dussan, Federico Almonacid, Alparslan Turan, and all authors listed in **Appendix**.

Review and approve manuscript accept responsibility for this manuscript: All, including all authors listed in appendix.

Data sharing: Patient level data will be available collaboratively upon reasonable request.

Declarations of interests: Dr. Sessler serves on advisory boards and has equity interests in Calorint (Philadelphia, PA), TransQtronics (Philadelphia, PA, the Health Data Analytics Institute (Boston, Mass), Medasense (Tel Aviv, Israel), and Perceptive Medical (Newport Beach, CA). He consults for Forge Laboratories (Lubbock, TX). He occasionally consults for temperature-related companies, with all fees donated to charity. He is a Senior International Fellow at the Population Health Research Institute, McMaster University. *None of these ancillary interests is relevant to current trial*. None of the other authors declares any potential conflicts.

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Abstract

Background: Surgical infections are the most common nosocomial infections and cause substantial morbidity and mortality. Operating rooms are relatively clean, but far from sterile. An unknown fraction of infections result from wound contamination by air-borne bacteria. We therefore tested the hypothesis that supplemental air purification reduces wound infections and related complications.

Methods: Operating rooms, our clusters, were each randomized in each 4-week blocks to either active or identical-looking sham supplemental air sterilization. All investigators, clinicians, and patients were fully blinded to treatment. No other aspect of anesthetic or surgical management was proscribed. Intent-to-treat analysis was restricted to adults who had surgery lasting at least an hour without evidence of pre-existing wound infections. We tested the primary hypothesis that supplemental active purification reduces a collapsed (one or more) composite of surgical wound infections, infection-related complications, or death within 30 days after inpatient surgery. Secondarily, we tested the hypothesis that supplemental air purification reduces the same composite after combined inpatient and outpatient surgeries.

Results: A total of 110,538 combined inpatients and outpatients were enrolled across 68 operating rooms, with 107,334 qualifying for analysis. At the third interim analysis, the futility boundary on the composite outcome was crossed for inpatients and for all patients. Enrollment thus stopped with 58,938 randomized inpatients. The primary composite outcome occurred in 8.1% (n=2,389) of inpatients randomized to active purification versus 8.2% (n=2,405) with sham purification: odds ratio 0.98 (95%CI: 0.92 to 1.05), P=0.609. Across all patients, the secondary composite outcome occurred in 5.5% (n=2,959 / 53,730) of active purification cases versus 5.6%

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(n=2,981 / 53,604) sham cases: odds ratio 0.98 (95% CI: 0.93 to 1.05), P=0.669). Treatment effect did not vary over the weeks in the randomized periods.

Conclusion: Supplemental active purification did not reduce surgical wound infections or mortality in surgical patients. Infection-control efforts might better focus on limiting direct wound contamination.

Trial registration: *A priori* registration at ClinicTrials.gov: NCT04610294.

Funding: Supported by a grant from ActivePure (Bristol, VA) to the Cleveland Clinic. The funder approved the original protocol which was written by the lead author. The funder was not involved in data acquisition, analysis, or manuscript preparation. A draft of the manuscript was provided to the funder as a courtesy.

Keywords: Anesthesia, air filtration, purification, sterilization, surgery, surgical wound or site infection.

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Introduction

The world-wide incidence of surgical wound infection and complications related to wound healing is 1-3% in the general non-cardiac surgical population, and roughly 10-15% after colo-rectal surgery.[1] For serious infections, the incremental acute cost is probably about US $30,000,[2] rising to more than $50,000 over a year.[3] Patients who develop a wound infection require an extra week of hospitalization.[4] Complications related to surgical wound infections are thus a major source of morbidity. All surgical wounds become contaminated, but host defense, especially oxidative killing by neutrophils, usually prevents contamination from progressing to clinical infection.[5] While host defense is clearly an important determinant of infection risk, the degree and type of contamination also contributes, as does surgical site and presence of foreign bodies such as joint prostheses and hernia mesh. Contaminating bacteria can come from air, skin, or from within the body—especially during colon surgery.

All modern operating rooms have elaborate air cleaning and circulation systems, typically exchanging air at least 20 times each hour, and thus have many logs fewer circulating airborne bacteria than home or office environments. Nonetheless, modern operating rooms typical have 5-40 colony forming units per m^3.[6] However, estimates vary considerably and increase when more people are in a room. Furthermore, (sparse) available literature suggest that infection risk increases when bacterial load in ambient air increases, especially for prosthetic joint infections.[7] Strategies attempting to reduce airborne bacteria in operating rooms include limiting traffic,[8] far ultraviolet light,[9] special suits,[10] mobile screens,[11] and laminar flow.[12] Reducing airborne bacteria in operating rooms seems likely to reduce the fraction of surgical wound infections that result from airborne contamination. The ActivePure air filtration/sterilization system is FDA cleared and reduces airborne bacteria more than 99% within an hour under laboratory conditions.

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Over a month of continuous use, the system also more than halves surface contamination in critical care units via a photohydrolysis mechanism.[13]

Our primary objective was thus to determine whether supplemental operating room air purification and sterilization reduces perioperative infections and mortality. Specifically, we tested the primary hypothesis that supplemental air purification and sterilization reduces a composite of surgical wound infections, infection-related complications, or death within 30 days after inpatient surgery. Our focus was inpatients because they are more likely to have infections than outpatients, and typically have more serious infections. Secondarily, we tested the hypothesis that supplemental air purification reduces the same composite after inpatient and outpatient surgeries combined. On an exploratory basis, we tested the hypotheses that supplemental air treatment reduces composite complications in inpatients, and in combined inpatients and outpatients, who had at least one composite component present on admission (i.e., a pre-existing condition). Finally, we considered whether treatment effect varied as a function of purification period.

Methods

Our cluster-randomized multiple crossover trial was conducted with approval from the Cleveland Clinic Review Board and conducted at the Clinic's Main Campus. Individual consent was waived because risk was low and obtaining individual consent would have been impractical since surface decontamination requires days of continuous purification exposure. Our trial was registered at ClinicalTrials.gov (NCT04610294) October 26, 2020 and is reported per CONSORT guidance. The final protocol with change log is in **Supplement B (https://links.lww.com/ALN/E749)**. The primary analysis was restricted to inpatients and remained unchanged. Secondary outcomes were changed at the sponsor's request in October

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2023 from surgical wound infection and cost-of-care to the composite outcome in combined inpatients and outpatients. Changes were made without access to data or by-group analyses.

Procedures

Our trial was conducted in 68 adult operating rooms of the Cleveland Clinic Main Campus, two of which were equipped with laminar air flow air. Each operating room was considered a cluster and all adults who had surgery in qualifying operating rooms were included.

Nitrous oxide has not been found to increase wound infection risk,[14] and supplemental oxygen has not been found to reduce risk.[15] Restrictive fluid management slightly increases infection risk,[16] but is not commonly used at the Cleveland Clinic. There were thus no restrictions on anesthetic management and practitioners were free to use intravenous anesthetics and neuraxial analgesia per preference and manage fluid and oxygen as they saw fit. All surgical patients at the Cleveland Clinic are warmed intraoperatively. Prophylactic intravenous antibiotics, as indicated, were given intravenously within an hour before incision.

Individual operating rooms,each considered a cluster, were randomized before the study began with computer-generated code in 4-week periods to either ActivePure air sterilization ("Filter On") or conventional air handling with sham ActivePure filters ("Filter Off"). Since all operating rooms were exposed multiple times over the course of the trial in a randomized fashion to either active filtration and conventional air handling, this is a cluster-randomized multiple crossover trial. New randomized assignments were implemented the Sunday after the last weekday of each 4-week period; the designated active or sham filters thus operated through the weekend.

Allocation was concealed with a web-based system that was accessed one day before switch dates.

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The ActivePure system is 26 X 11 X 21" and weighs 48 pounds. It cleans 18,000 cubic feet of air per hour on its "high" setting, and generates 70 dB. The system cleans air with activated carbon, high-efficiency particulate filtration, and oxidative molecules generated with photohydrolysis (www.accessdata.fda.gov/cdrh_docs/pdf20/K201220.pdf). Non-cardiac adult operating rooms at the Cleveland Clinic are about 5,250 ft^3. Two units were positioned in adjacent unobstructed areas of each operating room and set to "high." Units used for the trial were modified internally by the manufacturer to be active or not, and then sealed to prevent operating room personnel from determining unit status. Units were inactivated by removing the activated carbon, high-efficiency particulate filter, and photohydrolysis chamber. However, the fan remained active as did indicator lights.

Randomization and masking

The manufacturer shared a list of active and inactive serial numbers with statisticians from the Department of Quantitative Health Sciences who instructed Department of Outcomes Research staff which units to position in each operating room for each 4-week period. Active and sham filters looked and sounded identical to investigators and clinicians; consequently, investigators and clinicians were fully blinded to supplemental purification. Investigators confirmed that supplemental filters were plugged in, switched on, and appropriately positioned.

Measurements

Demographic and morphometric characteristics, along with routine laboratory values and anesthetic variables were recorded electronically. Types of surgery were characterized from Current Procedural Terminology codes using Agency for Healthcare Research & Quality Clinical Classifications Software.

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Our primary outcome was a composite of 30-day surgical wound infections, healing-related wound complications, and mortality. Specifically, we included surgical wound infections, intra-abdominal abcess, sepsis, wound dehiscence, joint prothesis infections, and death. All outcomes were obtained from electronic records based on International Classification of Disease revision 9 and 10 (ICD 9 and ICD-10) diagnosis codes[17] as described in **Supplement A, Table 1 (https://links.lww.com/ALN/E748)**. Surgeons at the Cleveland Clinic generally consider wounds to be infected when they meet 1992 CDC criteria.[18] As a secondary outcome, we considered serious surgical wound infections alone.

Patient and Public Involvement

Patients were not involved in the design, interpretation, or reporting of this trial.

Statistical Methods

Statistical methods were finalized before data were accessed and are detailed in **Supplement A, Statistical Methods (https://links.lww.com/ALN/E748)**. Analysis was restricted to adults who had surgery lasting ≥1 hour, with an American Society of Anesthesiologists physical status 1-4. Reoperations within 30 days of an index surgery were excluded to prevent patients being randomized into both groups. Subsequent surgeries on the same patient during a different hospitalization were included. Operations starting between 8 AM and midnight on Sundays of the monthly treatment switch days were excluded. For the main analyses missing outcome and baseline data were assumed to be at random, and patients with missing outcomes were presumed uninfected. We assessed the veracity of this assumption using post-hoc sensitivity analyses, detailed below.

Baseline chronic diagnoses were measured by ICD-10 codes and U.S. Agency for Healthcare Research and Quality Clinical Classifications.[19] We assessed balance on baseline and operative

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characteristics (**Tables 1, 2**) using absolute standardized difference (ASD). Baseline variables with ASD >0.1 would be considered imbalanced.[20] However, none of the variables met the criteria for imbalance.

For our primary (inpatient only) and secondary (inpatient and outpatient) aims, we restricted analysis to patients without present-on-admission indicators for any component of the composite outcome. We assessed the effect of Filter On vs Filter Off on our collapsed composite (any versus none) outcome with a generalized linear mixed effects [GLMM] logistic model (logit link) with fixed effects for treatment and period and random intercepts for cluster (the operating room) and cluster-period. The cluster random effect accounts for correlation among observations from the same cluster across all study periods, whereas the cluster-period random effect accounts for additional correlation among observations within the same cluster and period. This specification accounts for the fact that subjects treated within the same cluster and period tend to be more highly correlated ("within-cluster within-period correlation") than subjects treated within the same cluster but in different periods ("within-cluster between-period correlation"). We estimated the odds ratio and confidence interval for the treatment effect assuming that with the <10% incidence we observed, reported odds ratios are good estimates of the relative risk.[21]
In the above model, since the dimensionality of the data was so extensive (50 periods by 68 clusters, with 58,000 cases), it was not technically possible to additionally fit a random effect for patient ID in order to directly account for within-subject correlation for those patients (~10% of the total) who had multiple surgeries during the study. To assess whether repeat surgeries across different operating rooms underestimated standard errors and thus inflated Type I error, we conducted a sensitivity analysis using logistic regression with Cameron-Gelbach-Miller multiway cluster-robust standard errors.[22] Standard errors were simultaneously clustered at both

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the operating room and patient levels to account for crossed, non-nested (e.g., same patient in different periods or operating rooms) correlation without making parametric assumptions about individual variance components. That is, no random effects were specified. These results were then compared to the GLMM primary results.The same sensitivity analysis was conducted for all models.

In sensitivity analyses on the primary outcome we assessed the treatment effect using 2 methods which use more information than a collapsed composite analysis. First, we used a multivariate (i.e., one record / component / case) GLMM logistic regression model to estimate a single "common effect" odds ratio across the six components while including random effects for cluster and cluster-period, as in the primary analysis.[23]

Second, we estimated the average relative effect using a generalized estimating equation (GEE) "distinct effects" logistic regression model in which we estimated the treatment effect (here, log odds ratio) for each component first, then averaged across components, with a standard error that incorporates the variance-covariance matrix across the components. This method avoids over-weighting high-frequency components, which by nature are often less important.[24,25] We also tested treatment-by-component interactions using the distinct effects model, significant if P< 0.029 (same interim-analysis criterion used for the main effects). A random effects model did not converge for the average relative effect model, likely due to the complexity of estimating effects for multiple components across so many periods and clusters, complicated further by the smaller incidences when assessing at the component level. Therefore, in the GEE model we adjusted for cluster and period as fixed effects to account for cluster and period differences when comparing groups, and adjusted for within-subject correlation across repeated surgeries assuming exchangeable correlation.

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Our random-effect and GEE models have different estimands and interpretations. The treatment effect for the random effects model is conditional, and represents the estimated effect given a particular cluster-period combination. In contrast, the GEE model estimates a marginal treatment effect, that is the average treatment effect across all clusters and periods after accounting for cluster and period differences. Primary and main sensitivity analyses, with planned and utilized methods, estimands and interpretations are summarized in **Supplement A, Table 11 (https://links.lww.com/ALN/E748).**

In post-hoc sensitivity analyses regarding missing data for the primary outcome we first assessed the association between missingness (missing any primary outcome component versus complete data) and baseline variables, for which some positive associations were found. We then imputed missing primary outcomes using multiple imputation with chained equations[26 27] to assess the robustness of the "missing at random" assumption for the primary analyses. Ten imputation datasets were created using all available baseline and outcome data, and results were statistically aggregated.

Pre-planned assessments for treatment effect heterogeneity on the primary collapsed composite outcome included inpatient versus outpatient surgery, various baseline conditions and demographic characteristics, surgical duration >2 hours (vs ≤ 2 hours), type of surgery, and whether operating rooms were equipped with laminar flow.[28] Heterogeneity was assessed with a treatment-by-covariate interaction for each factor (significant if P<0.10), in isolation and without multiplicity adjustment.

The trial was designed to have 90% power to detect a relative risk of 0.90 (5.8% versus 6.5% collapsed composite incidence) or stronger at alpha=0.05 for the combined inpatient and outpatient populations. Assuming a within-cluster within-period correlation of 0.01 and a within-

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cluster between-period correlation of 0.005, and assuming 40 periods, we estimated that a maximum of 86,299 *patients* (including inpatients and outpatients) would be required.[29] Because we used a group sequential design,[30] we report 97.1% confidence intervals throughout (corresponding to alpha of 0.029 at final analysis) and refer to them as 95% confidence intervals for simplicity and to indicate alpha was controlled at 5% throughout (see details in **Supplement A, Statistical Methods, https://links.lww.com/ALN/E748**).

At the 2nd Interim analysis, per protocol, we re-estimated within-cluster correlations and control group incidence using the observed data to date.[31] As national practice changes led to more outpatients than expected, the executive committee and DSMB requested re-estimation of sample-size for inpatients, using the observed incidence (7.7%), projecting a maximum N of 66,273 *inpatients* (details in **Supplement A, Statistical Methods, https://links.lww.com/ALN/E748**).

The sponsor was not involved in data collection, analysis, or interpretation. A copy of the manuscript was shared with the sponsor during preparation but the authors made all decisions about content, presentation, wording, conclusions, and manuscript submission.

Results

Our third interim analysis was conducted on the first 54,671 inpatient cases, representing 82.5% of the planned maximum, and the futility boundary was clearly crossed. Consequently, the DSMB recommended stopping the trial, **Supplement A, Figure 1 (https://links.lww.com/ALN/E748).** The final analysis included 4,267 additional operations that occurred while the interim analysis was being prepared, bringing the total to 58,938 qualifying inpatient cases, 29,507 with active purification and 29,431 without, representing 89% of the planned maximum.. A total of 110,538 inpatient and outpatient cases were enrolled between

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February 1, 2021 to December 15, 2024, with 55,357 assigned to active and 55,181 to inactive purification (**Figure 1)**. There were a median [quartiles] of 1661 [1427, 1860] operations in each of the 68 operating rooms across all patients. The median [interquartile] duration of surgery was 4.2 [2.8, 6.2] hours for inpatients and 2.2 [1.6, 3.1] for outpatients.

Our primary outcome was a composite of surgical wound infections, wound-related complications and death among inpatients without pre-existing composite components. At least one component occurred in 8.1% (n=2,389 of 29,507) patients with active purification and 8.2% (n=2,405 of 29,431) patients without: odds ratio 0.98 (95% CI: 0.92, 1.05), P=0.609 (**Figure 2, Supplement A, Table 2, https://links.lww.com/ALN/E748**). The overall incidence was fairly consistent over time (**Supplement A, Figure 2, https://links.lww.com/ALN/E748**). For inpatients there was no evidence of treatment effect heterogeneity across baseline variables (**Figure 3**, **Supplement A, Figure 3, https://links.lww.com/ALN/E748**). Details on the observed intracluster correlations are in **Supplement A, Intracluster Correlation Results (https://links.lww.com/ALN/E748).**

In our first sensitivity analysis the multivariate GLMM logistic regression model estimated the "common effect" odds ratio across the components of the composite outcome as 0.98 (95% CI: 0.92, 1.04), P=0.430. In our second sensitivity analysis we estimated the average odds ratio across the individual components as 1.00 (95% CI: 0.92, 1.09), P=0.916. There was some evidence that the treatment effect might vary by outcome component, with treatment-by-component interaction P=0.016 (significance criterion P<0.029). Among 15 comparisons across the 6 components, only SSI versus Intra-abdominal abscess (P=0.004) was significant (at criterion of P<0.029), and no individual component had a significant effect (**Figure 2, Supplement A, Table 2, https://links.lww.com/ALN/E748**). Serious surgical wound infection

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did not differ between Filter On versus Off, with estimated odds ratio of 1.13 (95% CI: 0.92, 1.39), P=0.187. A sensitivity analysis removing periods with non-functional devices (2% of total time in each group) had results similar to the primary analysis, with estimated odds ratio of 0.99 (95% CI: 0.92, 1.06) P=0.750 (**Supplement A, Table 2, https://links.lww.com/ALN/E748**). Our secondary analysis included 107,334 inpatients and outpatients without pre-existing composite components. At least one of the primary composite events occurred in 5.5% (n=2,959) of 53,730 active purification cases and 5.6% (n=2,981) of 53,604 of inactive: odds ratio 0.98 (95% CI: 0.93, 1.05), P=0.669). Removing periods with non-functional devices reached a similar conclusion, with estimated odds ratio of 0.98 (95% CI: 0.93, 1.04; P = 0.522). The common effect and average relative effect results were similarly non-significant. Treatment effect did not vary across components overall (interaction P=0.039; significance criterion P<0.029), but in exploratory analyses sepsis and infection of joint prostheses differed on the effect (P=0.015). No individual component treatment effects were found at P<0.029 **(Figure 2, Supplement A, Table 3, https://links.lww.com/ALN/E748**). Filter On versus Filter Off did not affect serious surgical wound infection, with estimated odds ratio of 1.11 (95% CI: 0.91, 1.34), P=0.249 (**Supplement A, Table 3, https://links.lww.com/ALN/E748**).

Results were similarly neutral when we included patients with at least one pre-existing primary outcome component either for inpatients alone (**Supplement A: Sensitivity Analysis and Tertiary Aim Results, https://links.lww.com/ALN/E748; Table 4**) or for combined inpatients and outpatients (**Supplement A, Table 5, https://links.lww.com/ALN/E748**). Treatment effect estimates from the cluster-robust sensitivity analyses which account for within-cluster and within-patient correlations without making distributinal assumptions were similar to those from the corresponding primary analyses (**Supplement A, Table 6,**

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https://links.lww.com/ALN/E748).Treatment effect did not differ between the weeks within 4-week treatment periods (**Supplement A, Table 7, https://links.lww.com/ALN/E748**) or between patterns of exposure (2 periods On versus 1 period On (**Supplement A, Table 8, https://links.lww.com/ALN/E748**). All results were similarly neutral in operating rooms with and without laminar flow.

In post-hoc sensitivity analyses using multiple imputation for patients with missing primary outcome data, association was found between some baseline variables and missingness status (any missing outcomes versus none), suggesting that some data may not have been missing at random **(Supplement A, Table 9, https://links.lww.com/ALN/E748).** However, primary results did not change noticeably after multiple imputation (**Supplement A, Table 10, https://links.lww.com/ALN/E748**) and no conclusions were different from the primary analysis results. In the process of conducting this sensitivity analysis we also obtained updated mortality details from the Ohio Death Index which reduced missing vital status data from 10% to 8% before conducting the imputation analyses.

Discussion

The fraction of surgical wound infections caused by airborne bacteria remains unknown, but some surely are[6] — despite substantial efforts to limit contamination. In 58,938 randomized inpatient cases, and 110,538 combined inpatient and outpatient cases, supplemental air purification did not reduce a composite of 30-day surgical wound infections, healing-related wound complications, or mortality. As might be expected, incidence of the composite outcome was higher among inpatients than in combined inpatients and outpatients, but supplemental air purification was ineffective in both populations. Our trial was extremely well powered,

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evidenced by very tight confidence intervals – e.g., odds ratio of 0.98 (95% CI 0.92, 1.05) for inpatient cases. The results are therefore truly neutral rather than being under-powered.

The risk of surgical wound infection is a strong function of surgical duration.[6] The median duration of surgery in our patients was 2.2 hours for outpatients and 4.2 hours for inpatients. Furthermore, a quarter of the inpatient operations lasted longer than 6.2 hours. Our patients were thus at high risk of infection. Furthermore, supplemental air purification was no more effective for longer than shorter operations. Our results therefore apply over a wide range of surgical durations.

When the trial started, we believed that maximal surface and air decontamination required 24 hours. Subsequent analyses in two critical care units suggest the surface disinfection accrues over 4 weeks and possibly persists for some weeks thereafter.[13] The treatment effect on our primary infection-related composite outcome was similar during the initial and subsequent days of each treatment period, during various treatment weeks, and with one versus two months of sequential active purification. Nonetheless, it remains possible that our 4-week cross-over periods were insufficient and that a wash-out period might have been helpful between treatments.

A limitation is that our trial was conducted in a single hospital and thus reflects local infection-control practices. The Joint Commission defers to the American Society of Heating, Refrigerating and Air-Conditioning Engineers and Facility Guidelines Institute standards for air exchanges in hospital environments. The current recommendation is at least 20 exchanges/hour, with at least 4 being from outside. Air exchange in Cleveland Clinic operating rooms is monitored and kept above that value. The Cleveland Clinic also limits operating room traffic and implements other procedures thought to reduce infection risk. It remains possible that supplemental air purification would be effective in less meticulous environments including

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hospital wards and critical care units. An additional limitation is that we did not directly assess airborne or surface bacterial loads in our operating rooms. We thus do not know how much baseline contamination there was, or the extent to which supplemental decontamination reduced air and surface bacterial load.

Composite outcomes necessarily group various outcomes that may respond differently to trial interventions. We thus tested the treatment-by-component interaction (for inpatients, our primary aim, significant at P=0.016), and evaluated components of the composite. Post-hoc pairwise tests comparing the 6 components on the treatment effect found only 1 of 15 pairs to differ (surgical site infection vs intra-abdominal abscess), but the study was not well powered for such exploratory comparisons. Furthermore, the one we identified would not be significant after controlling for multiple interaction comparisons. Finally, none of the components had a iindividually significant treatment effects.

In conclusion, among 58,938 inpatients and 110,538 combined inpatients and outpatients, supplemental intraoperative air purification did not reduce a composite of surgical wound infections, infection-related complications, or death within 30 days after inpatient surgery compared to controls (odds ratio: 0.98 [95%CI: 0.92 to 1.05]). Infection risk may better be reduced by efforts that focus on limiting direct contamination from surgeons to patients, strategies to limit wound contamination from patients' cutaneous and intestinal flora, and improved environmental disinfection during post-operative care.

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Figure Legends

Figure 1. CONSORT diagram.

Figure 2. Primary outcome. Forest plot of treatment effects for inpatients (primary aim), N = 58,938, and all patients (secondary aim), N=107,334 who did not have pre-existing components of the primary composite outcome. The squares represent the odds ratio comparing filter on to filter off. The horizontal bars show 97.1% confidence intervals for primary outcomes or Bonferroni-adjusted confidence intervals (99.52% CI for individual components of primary outcome). The treatment-by-component interaction P-value was 0.016 for the primary aim and 0.039 for the secondary aim.

Figure 3. Treatment effect heterogeneity tests for inpatients (primary aim), N = 58,938. The squares represent the odds ratio comparing filter on to filter off on the collapsed composite outcome, as estimated with the use of a generalized linear mixed effects model with logit link, adjusting for within-cluster within-period and within-cluster between-period correlatioins, estimated by including random intercepts for cluster and cluster-period. The horizontal bars show 95% confidence intervals. P-values test the treatment-by-baseline factor interaction.

Supplements

Supplement A: Statistical methods, results, **https://links.lww.com/ALN/E748**.

Supplement B: Protocol, **https://links.lww.com/ALN/E749**.

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Table 1. Baseline characteristics

	Inpatients (N = 58,938)			Inpatients + Outpatients (N=107,334)		
	Filter On (N=29,507)	**Filter Off (N=29,431)**	**ASD***	**Filter On (N=53,730)**	**Filter Off (N=53,604)**	**ASD***
Age, year	61 ± 15	61 ± 15	0.001	60 ± 16	60 ± 16	0.000
Female (%)	14319 (49) [a]	14337 (49) [a]	0.004	26972 (50) [a]	26935 (50) [a]	0.001
Height, cm	170 ± 11 [a]	170 ± 11 [a]	0.003	170 ± 11 [b]	170 ± 11 [b]	0.002
Weight, kg	86 ± 24 [b]	87 ± 24 [b]	0.010	86 ± 24 [b]	87 ± 24 [b]	0.006
BMI, kg/m^2	30 ± 7.8 [b]	30 ± 7.7 [b]	0.010	30 ± 7.5 [b]	30 ± 7.5 [b]	0.005
Race (%) [§]			0.026			0.008
- White/Caucasian	23707 (83) [d]	23410 (83) [d]		43097 (83) [e]	42923 (83) [e]	
- Black	3637 (13)	3876 (14)		6818 (13)	6952 (13)	
- Other	1092 (3.8)	1076 (3.8)		2067 (4.0)	2046 (3.9)	
Current smokers (%)	3183 (11) [c]	3099 (11) [c]	0.009	5640 (11) [c]	5585 (11) [c]	0.003
Preoperative albumin, g/dL	4.2 [3.8, 4.4] [f]	4.2 [3.8, 4.4] [f]	0.006	4.2 [3.9, 4.5] [g]	4.2 [3.9, 4.5] [g]	0.001
Primary diagnosis – **Cancer** (%)	2686 (9.1)	2673 (9.1)	0.001	5763 (11)	5685 (11)	0.004
Medical history (%)						
Congestive heart failure	6665 (23)	6726 (23) [a]	0.006	9955 (19)	9921 (19) [a]	0.000
Vascular disease	8853 (30)	8805 (30) [a]	0.002	12745 (24)	12662 (24) [a]	0.002
Pulmonary circulation disease	2860 (9.7)	2999 (10) [a]	0.017	4469 (8.3)	4641 (8.7) [a]	0.012
Peripheral vascular disease	6936 (24)	6878 (23) [a]	0.003	10442 (19)	10315 (19) [a]	0.005
Hypertension	21021 (71)	21032 (71) [a]	0.005	34875 (65)	34916 (65) [a]	0.005

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	Inpatients (N = 58,938)			Inpatients + Outpatients (N=107,334)		
	Filter On (N=29,507)	Filter Off (N=29,431)	ASD*	Filter On (N=53,730)	Filter Off (N=53,604)	ASD*
Paralysis	1279 (4.3)	1353 (4.6) [a]	0.013	1752 (3.3)	1830 (3.4) [a]	0.009
Other neurological disorders	5618 (19)	5597 (19) [a]	0.001	9046 (17)	9047 (17) [a]	0.001
Chronic pulmonary disease	8268 (28)	8149 (28) [a]	0.007	14336 (27)	14263 (27) [a]	0.002
Diabetes w/o chronic complications	8285 (28)	8400 (29) [a]	0.010	13479 (25)	13763 (26) [a]	0.014
Hypothyroidism	5580 (19)	5742 (20) [a]	0.015	9750 (18)	9919 (19) [a]	0.009
Renal failure	5766 (20)	5752 (20) [a]	0.000	9288 (17)	9278 (17) [a]	0.001
Liver disease	4574 (16)	4541 (15) [a]	0.002	7591 (14)	7676 (14) [a]	0.006
Peptic ulcer Disease (bleeding)	1364 (4.6)	1314 (4.5) [a]	0.008	2126 (4.0)	2105 (3.9) [a]	0.002
AIDS	96 (0.33)	105 (0.36) [a]	0.005	182 (0.34)	196 (0.37) [a]	0.005
Lymphoma	730 (2.5)	698 (2.4) [a]	0.007	1322 (2.5)	1289 (2.4) [a]	0.004
Metastatic cancer	3500 (12)	3456 (12) [a]	0.004	5839 (11)	5754 (11) [a]	0.004
Solid tumor w/out metastasis	5169 (18)	5223 (18) [a]	0.006	11031 (21)	11141 (21) [a]	0.006
Rheumatoid arthritis/collagen vas	3244 (11)	3250 (11) [a]	0.002	5910 (11)	6048 (11) [a]	0.009
Coagulopathy	8067 (27)	8138 (28) [a]	0.007	10120 (19)	10164 (19) [a]	0.003
Obesity	13735 (47)	13871 (47) [a]	0.012	23466 (44)	23598 (44) [a]	0.007
Weight loss	8955 (30)	8901 (30) [a]	0.002	11917 (22)	11920 (22) [a]	0.001
Fluid and electrolyte disorders	17262 (59)	17309 (59) [a]	0.006	22920 (43)	22898 (43) [a]	0.001

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	Inpatients (N = 58,938)			Inpatients + Outpatients (N=107,334)		
	Filter On (N=29,507)	Filter Off (N=29,431)	ASD*	Filter On (N=53,730)	Filter Off (N=53,604)	ASD*
Chronic blood loss anemia	1640 (5.6)	1599 (5.4) [a]	0.005	2786 (5.2)	2783 (5.2) [a]	0.000
Deficiency Anemias	11165 (38)	11131 (38) [a]	0.000	17907 (33)	17905 (33) [a]	0.002
Alcohol abuse	1488 (5.0)	1444 (4.9) [a]	0.006	2397 (4.5)	2265 (4.2) [a]	0.012
Drug abuse	2379 (8.1)	2443 (8.3) [a]	0.009	3976 (7.4)	3903 (7.3) [a]	0.005
Psychoses	2615 (8.9)	2630 (8.9) [a]	0.003	4721 (8.8)	4773 (8.9) [a]	0.004
Depression	7151 (24)	7064 (24) [a]	0.005	13165 (25)	13048 (24) [a]	0.004

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared);

Summary statistics are presented as N (%) for categorical variables, mean ± SD or median [Q1, Q3] for continuous variables.

***** ASD is the absolute standard difference of pairwise comparisons. Variables with ASD > 0.10 are considered imbalanced.

[§] Totals not 100% due to rounding error.

Missing data point: [a] 1~30, [b] 63~150, [c] 441~599, [d] 1069~1071, [e] 1683~1781, [f] 5377~5403, [g] 15844~15848,

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Table 2. Operative characteristics.

	Inpatients (N = 58,938)			Inpatients + Outpatients (N=107,334)		
	Filter On (N=29,507)	**Filter Off (N=29,431)**	**ASD***	**Filter On (N=53,730)**	**Filter Off (N=53,604)**	**ASD***
Surgery duration, hours	4.2 [2.8, 6.2]	4.2 [2.8, 6.2]	0.016	3.1 [2.0, 4.8]	3.1 [2.0, 4.9]	0.011
Anesthesiology type (%)			0.009			0.009
- General	26341 (89) [a]	26330 (89) [a]		47454 (88) [a]	47470 (89) [a]	
- Regional	539 (1.8)	522 (1.8)		1138 (2.1)	1148 (2.1)	
- General+ Regional	2064 (7.0)	2050 (7.0)		2942 (5.5)	2863 (5.3)	
- MAC	558 (1.9)	525 (1.8)		2187 (4.1)	2116 (3.9)	
ASA physical status			0.001			0.000
- 1 (Healthy)	146 (0.49)	141 (0.48)		785 (1.5)	769 (1.4)	
- 2 (Mild systemic illness)	2635 (8.9)	2603 (8.8)		8826 (16)	8677 (16)	
- 3 (Severe systemic illness)	15824 (54)	15811 (54)		30456 (57)	30652 (57)	
- 4 (Life-threatening)	10902 (37)	10876 (37)		13663 (25)	13506 (25)	
Type of surgery (%) [§]			0.010			0.008
- Cardiac	7307 (25) [a]	7303 (25) [a]		8864 (16) [a]	8808 (16) [a]	
- Colorectal	3785 (13)	3744 (13)		4873 (9.1)	4851 (9.1)	
- Orthopedic	4022 (14)	4104 (14)		7140 (13)	7271 (14)	
- Other	14392 (49)	14278 (49)		32846 (61)	32668 (61)	

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	Inpatients (N = 58,938)			Inpatients + Outpatients (N=107,334)		
	Filter On (N=29,507)	**Filter Off (N=29,431)**	**ASD***	**Filter On (N=53,730)**	**Filter Off (N=53,604)**	**ASD***
Intraoperative management						
Area MAP <65 mmHg, mmHg*min	37 [3.0, 124] [a]	39 [3.0, 126] [a]	0.016	15 [0.0, 76] [a]	16 [0.0, 78] [a]	0.011
TWA of heart rate, beats/min	73 [65, 81] [a]	72 [65, 81] [a]	0.007	72 [65, 80] [a]	72 [65, 80] [a]	0.002
Amount of anesthetic gas- MAC-hours	3.6 [2.4, 5.1] [b]	3.6 [2.5, 5.2] [b]	0.012	2.9 [1.8, 4.3] [c]	2.9 [1.8, 4.3] [c]	0.009
TWA of glucose, mg/dl	155 [132, 182] [d]	156 [132, 182] [d]	0.019	153 [129, 180] [e]	154 [129, 180] [e]	0.012
Colloid volume, L	0.0 [0.0, 0.25]	0.0 [0.0, 0.25]	0.004	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	0.001
Crystalloid volume, L	2.0 [1.3, 2.9]	2.0 [1.3, 2.9]	0.003	1.5 [1.0, 2.3]	1.5 [1.0, 2.3]	0.007
Estimated blood loss, ml	30 [0.0, 200]	30 [0.0, 200]	0.005	10 [0.0, 100]	10 [0.0, 100]	0.004
Blood transfusion (%)	8705 (30)	8706 (30)	0.002	8879 (17)	8861 (17)	0.000
Amount of blood transfusion, ml [†]	700 [362, 1461]	700 [365, 1535]	0.035	700 [360, 1445]	700 [364, 1511]	0.035

Abbreviations: ASA, American Society of Anesthesiologists; MAC, minimum alveolar concentration (a measure of volatile anesthetic potency with 1.0 being a typical dose); TWA, time-weighted average.

Summary statistics are presented as N (%) for categorical variables, median [Q1, Q3] for continuous variables.

***** ASD is the absolute standard difference of pairwise comparisons. Variables with ASD > 0.10 are considered imbalanced.

[§] Totals not 100% due to rounding error.

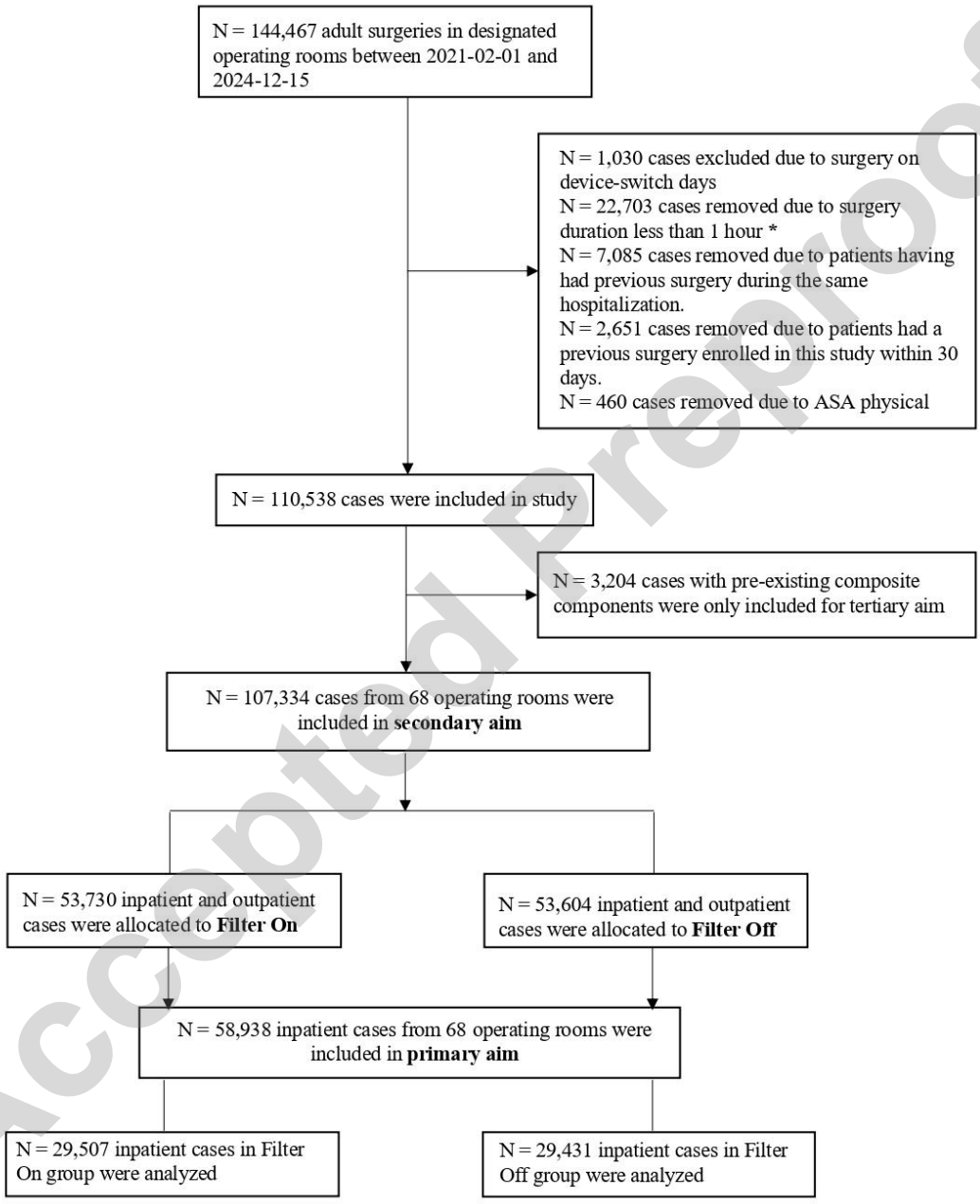
[†] Amount calculated for patients given blood transfusions.

Missing data point: [a] 1~30, [b] 1683~1781, [c] 4668~4824, [d] 13744~14017, [e] 36167~36214

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Figure 1

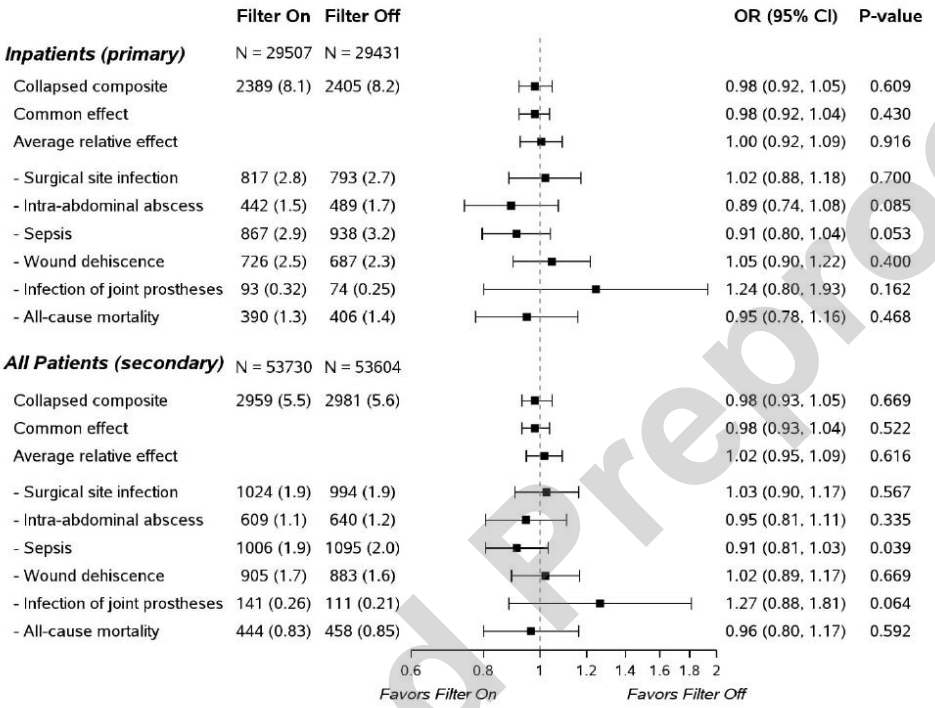


* Surgery duration: the time interval from induction to emergence from anesthesia.

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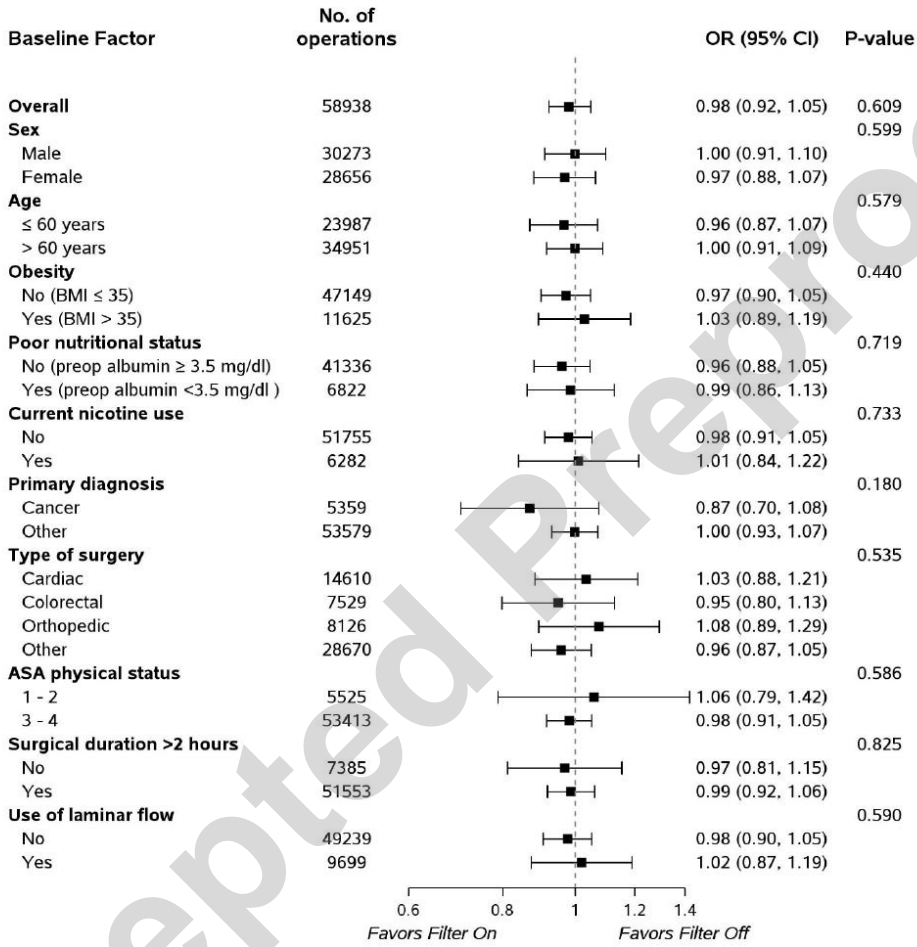
Figure 2



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