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Prävention einer beatmungsassoziierten Pneumonie bei Langzeitbeatmung am Universitätsklinikum der Ludwig-Maximilian-Universität München: Effekte der selektiven oralen Dekontamination auf mikrobielle Resistenzlage und klinisches Outcome

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Inhaltsverzeichnis

Abkürzungsverzeichnis

SOD = Selective oral decontamination

SDD = Selective digestive decontamination

ETL = Extract, Transform, Load

MDRB = Multidrug-resistant bacteria

MRSA = Methicillin-resistant Staphylococcus aureus

VRE = Vancomycin-resistant Enterococcus faecium

ESBL = Extended-spectrum beta-lactamase

Publikationsliste

Publikationen

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Vorträge

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Ihr Beitrag zu den Veröffentlichungen

Beitrag zu Paper I

Design, Datenerfassung, Analyse, Interpretation, Entwurf und Überarbeitung des Manuskripts

Beitrag zu Paper II

Datenerfassung, Analyse, Interpretation

Beitrag zu Paper III

Datenerfassung, Analyse, Interpretation

Beitrag zu Paper IV

Datenerfassung, Analyse, Interpretation

Einleitung

Die beatmungsassoziierte Pneumonie ist die führende krankenhauserworbene Infektion auf Intensivstationen, vor allem bei kritisch kranken Patienten, die sich einer Langzeitbeatmung (künstliche Beatmung > 48 Stunden) unterziehen. Sie erhöht die Mortalität und Behandlungsdauer der betroffenen Patienten erheblich und ist die nosokomiale Infektion, die weltweit zu einen der häufigsten Todesursachen bei hospitalisierten Patienten zählt.

Selektive orale Dekontamination (SOD) und selektive Darmdekontamination (SDD)

SOD/SDD ist eine prophylaktische Strategie zur Verhinderung oder Minimierung nosokomialer Infektionen bei kritisch kranken Patienten, die sich einer Langzeitbeatmung unterziehen. Sie verwendet nicht resorbierbare orale und enterische Antibiotika sowie parenterale Antibiotika. Auf diese Weise eliminiert SOD/SDD potenziell pathogene Mikroorganismen aus dem Oropharynx und dem oberen Verdauungstrakt von Patienten und reduziert Infektionen. Durch Studien ist belegt, dass eine SDD/SOD auf allgemeinen Intensivstationen vorteilhafte Effekte auf die Überlebensrate kritisch kranker Patient ausübt, in erster Linie durch Senkung der Rate beatmungsassoziierter Pneumonien [1, 2].

Im Jahr 2011 führte die Krankenhausapotheke am LMU Klinikum eine einheitliche SOD-Lösung ein, die Colistin und Gentamicin in Kombination mit Nystatin oder Amphotericin B enthält, für die routinemäßige topische antimikrobielle Anwendung im Oropharynx und Magen. Diese soll alle sechs Stunden verabreicht werden. Auf vielen, aber nicht allen Intensivstationen des LMU Klinikums ist SOD ein Routineverfahren zur Prävention von beatmungsassoziierter Pneumonie geworden. Dennoch bleibt der Nutzen einer SOD bzw. SDD trotz der überzeugenden Datenlage in der Literatur nach wie vor umstritten [2–6]. Das Hauptargument gegen den Einsatz topischer Antibiotika ist die Gefahr zunehmender Antibiotikaresistenzen auf den Stationen. Dies hat wiederum erhebliche Konsequenzen auf die insgesamte Resistenzsituation bakterieller Erreger im Krankenhaus und kann eine erfolgreiche Therapie von Infektionen mit nosokomialen Erregern erschweren.

Studienziele

Die vorliegende Dissertation befasst sich mit den Effekten der selektiven oralen Dekontamination auf mikrobieller Resistenzlage und dem klinischen Outcome. Ziel dieser Ar-

beit war es, auf den Intensivstationen für Erwachsene am Klinikum der Ludwig-Maximilians-Universität München (KUM) die Langzeitentwicklung von MDRB (multidrug-resistant bacteria) über einen Zeitraum von 5 Jahren im Zusammenhang mit der Anwendung der selektiven oropharyngealen Dekontamination (SOD) zu untersuchen.

Sowohl die auf der Intensivstation erworbene MDRB als auch die auf die Intensivstation mitgebrachte MDRB wurden erfasst. Nach den Definitionen im deutsche Krankenhaus-Infektions-Surveillance-System für Intensivstation (ITS-KISS) wurde ein Erreger als mitgebracht angenommen, wenn der Erreger bereits vor der Aufnahme auf die Station nachgewiesen wurde, oder das Material, in dem der Erreger nachgewiesen wurde, an Aufenthaltstag 1 oder 2 abgenommen wurde. Wurde das Untersuchungsmaterial, in dem der MRE erstmalig nachgewiesen wurde, ab Aufenthaltstag 3 oder später abgenommen, wird der Erreger als auf der Station erworben angenommen [7, 8]. Die Unterschiede in den Raten und Inzidenzdichten (ID, Fälle pro 1000 Patiententage) von MDRB wie methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecium* (VRE), extended-spectrum beta-lactamase (ESBL) produzierende *Escherichia coli* und *Klebsiella pneumoniae,* fluoroquinolone-resistant *Escherichia coli, carbapenem-resistant Klebsiella pneumoniae, Enterobacter cloacae, Serratia marcescens, Pseudomonas aeruginosa, Stenotrophomonas maltophilia* und *Acinetobacter baumannii* wurden im Zusammenhang mit der Verwendung von SOD bei allen Patienten analysiert. Zusätzlich wurde die Inzidenz nosokomialer Infektionen sowie die Sterblichkeit auf der Intensivstation untersucht.

<table>
<tr><td>Aufnahme auf die Station</td><td></td><td></td><td></td><td></td><td></td><td>Entlassung/Verlegung von der Station</td></tr>
<tr><td>Tag 1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>…</td></tr>
<tr><td colspan="2">Abnahme des Materials, aus dem der MDRB-Nachweis erfolgt, bereits vor Aufnahme oder an Tagen 1-2</td><td colspan="5">Abnahme des Materials, aus dem der MDRB-Nachweis erfolgt, ab Tag 3</td></tr>
<tr><td colspan="2">MDRB mitgebracht</td><td colspan="5">MDRB erworben</td></tr>
</table>

Abbildung 1: Klassifikation in „mitgebrachte“ und „auf Intensivstation erworbene“ MDRB

Studiendesign

Diese Studie stellt eine retrospektive Observationsstudie ohne studienbedingte Intervention dar (Kohortenvergleich: SOD vs. Standard). Inzidenzraten wurden zwischen

den Intensivstationen mit und ohne SOD vergleichen. Um Effekte der SOD auf nosokomiale Infektionen und Sterblichkeit auf der Intensivstation zu ermitteln, wurde mittels Propensity-Score-Analyse eine Fallkontroll-Studie durchgeführt.

Die Extraktion aller Datensätzen verschiedener Datenbanken des LMU Klinikums erfolgte datentechnisch unter Verwendung der Fallnummer bzw. der Patientennummer, was einer Pseudonymisierung der verwendeten Daten entspricht. Nach Erfassung der Daten wurden diese den beiden Gruppen zugeordnet und anschließend anonymisiert.

Verfahren zur Prävention einer beatmungsassoziierten Pneumonie während des Studienzeitraums (Januar 2011 bis Dezember 2016) wurden in einem strukturierten Interview mit Ärzten und Pflegenden vor Ort erfasst. Dabei wurden die Empfehlungen der KRINKO des Robert-Koch-Instituts von 2013 zu Grunde gelegt und die Adhärenz der vorgeschlagenen Maßnahmen zur Prävention einer beatmungsassoziierten Pneumonie untersucht [9, 10]. Auf Basis dieser Befragung erfolgte die Bildung von Gruppen in Einheiten mit und ohne SOD zur Prävention einer Pneumonie bei einer Langzeitbeatmung.

Die administrativen Daten aus dem Krankenhaus Arbeitsplatzsystems (KAS), die Daten zu mikrobiellen Erregern und Resistenzprofilen aus der Mikrobiologie und die Daten zu Operationen aus der Narkodata Datenbank wurden erfasst. Außerdem wurden den einzelnen Antiinfektivagruppen (Penicilline, Cephalosporine, Carbapeneme, Chinolone, Lincosamide etc.) definierte Tagesdosen (Defined Daily Dose, DDD) als Messgröße für den Antibiotika-Verbrauch über den Zeitraum der Untersuchung zugeordnet.

ETL-Prozess

Da die Daten aus unterschiedlichen Anwendungen stammen und unterschiedliche Formate besaßen, kam ein ETL-Prozess (Extract, Transform, Load), der aktuell häufig zur Verarbeitung großer Datenmengen im Big-Data- und Business-Intelligente-Umfeld verwendet wird, zum Einsatz. Im Rahmen des ETL-Prozesses wurden die Daten aus den verschiedenen Datenquellen extrahiert (csv-Dateien, Textdateien und SQL-Datenbanksystemen), mit Tools und selbst implementierten Skripte umgewandelt und in das Format der Zieldatenbank transformiert. Als letzten Schritt wurden die Daten in der Zieldatenbank gespeichert. Vor der Datenanalyse wurde die Datenqualität geprüft und die unvollständigen oder duplizierten Datensätze wurden entfernt.

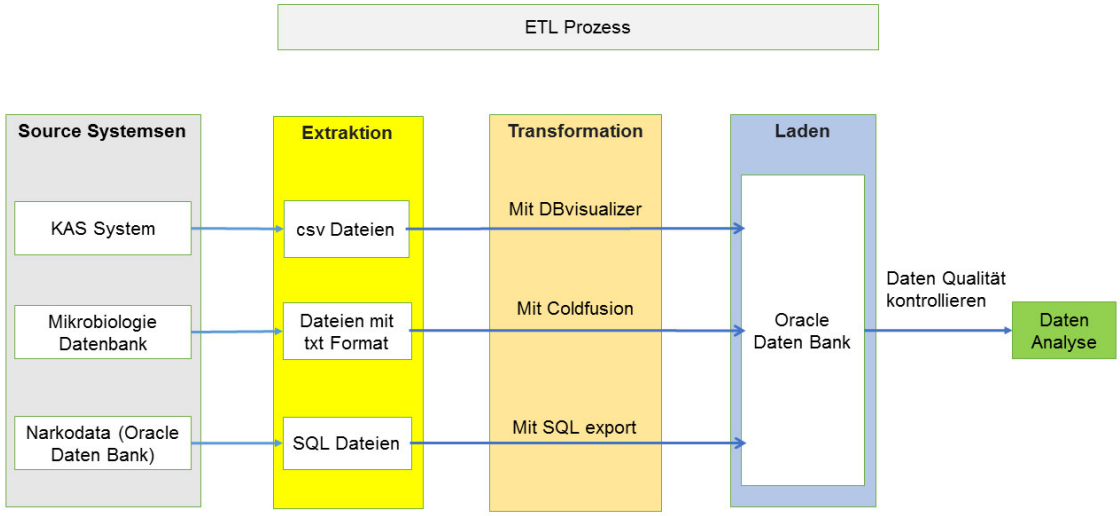

Abbildung 2: ETL-Prozess

Die Notwendigkeit einer Risikoadjustierung ist gegeben, wenn heterogene Patientenkohorten verglichen werden. Das Tool von Ford et al [11] erfasst und bewertet die administrativen Daten (2 demographische Kriterien, 5 intensivmedizinische Akutmaßnahmen und 20 Komorbiditäten), um damit einen Score, den sogenannten *sepsis severity score* für die Schwere der Krankheit zu berechnen.

Propensity Score Matching

Um eine möglichst gute Vergleichbarkeit von Gruppen herzustellen, wurde eine „propensity score“ Methodik gewählt. Das „propensity score matching“ ist eine statistische Technik, die zunehmend verwendet wird, um eine Randomisierung nachzuahmen, damit die Kausaleffekte in medizinischen und epidemiologischen Beobachtungsstudien abgeschätzt werden können [12, 13]. Eine Kohortenanalyse mit dem Propensity-Score kann ziemlich effektiv auf die Einheitlichkeit der Patientenpopulation, Faktoren und wichtige Variablen kontrolliert werden [14]. Hierbei werden prognostisch relevante Kovariablen wie Krankheitsschwere (sepsis severity score) [11], Alter, Geschlecht, Beatmungsdauer, dem ersten SAPS-II-Score [15] und die Aufenthaltsdauer auf der Intensivstation, sowie die Art der Aufnahme erfasst und bewertet, um auf diese Weise eine möglichst balancierte Verteilung dieser Einflussgrößen auf die Vergleichsgruppen zu erzielen. Nach diesem „propensity score matching“ der Vergleichsgruppen wurden Variablen des „Patienten-Outcome“ wie die Inzidenz von nosokomialer Pneumonie, die auf der Intensivstation erworbene Bakteriämie und Harnwegsinfektion und die ICU-Sterblichkeit in den gebildeten Gruppen verglichen.

Ergebnisse

Insgesamt wurden 11 Intensivstationen für Erwachsene am LMU Klinikum analysiert. Davon verwendeten 7 Intensivstationen routinemäßig SOD bei mechanisch beatmeten Patienten und 3 Intensivstationen verwendeten keine SOD. Eine Intensivstation verwendete SOD nur bei ausgewählten Patienten mit hohem VAP-Risiko. Diese Intensivstation wurde von der Analyse ausgeschlossen.

Im Zeitraum von 01.10.2011 bis 30.09.2016 wurden 12.172 konsekutive erwachsene (≥ 18 Jahre) kritisch kranke Patienten ausgewählt, die sich einer mechanischen Beatmung (MV) unterzogen haben. Für die Analyse wurden nur Patienten eingeschlossen, die für einen Zeitraum > 48 Stunden künstlich beatmet wurden. 5034 Patienten erfüllten dieses Kriterium. 3340 Patienten davon erhielten eine topische SOD und 1694 Patienten keine SOD.

Über den Studienzeitraum von 5 Jahren wurden insgesamt 143.842 mikrobiologische Befunde elektronisch extrahiert. Dabei wurden 26.957 Untersuchungen von gewonnenen Materialien aus dem Respirationstrakt berücksichtigt, 20.719 Blutkulturen, 19.655 Urinkulturen sowie 4605 Rektalabstriche. 71.906 Untersuchungsmaterialien stammten von verschiedenen Körperregionen der Intensivpatienten (Wundabstriche etc.).

Während des 5-jährigen Studienzeitraums gab es keine Unterschiede in der Inzidenzdichte der auf der Intensivstation erworbenen multiresistenten Erreger aller eingeschlossenen Patienten zwischen den beiden Gruppen. Allerdings war die Inzidenzdichte von Vancomycin-resistentem *E. faecium* häufiger und *Klebsiella pneumoniae* mit erweitertem Beta-Lactamase-Spektrum seltener zu beobachten, wenn die SOD angewendet wurde.

Nach dem „propensity score matching“ konnte die SOD mit einer geringeren Rate an beatmungsassoziierter Pneumonie und einer geringeren Sterblichkeit auf der Intensivstation, aber nicht mit der auf der Intensivstation erworbenen Bakteriämie oder Harnwegsinfektionen in Verbindung gebracht werden. Die Sterblichkeitsrate auf der Intensivstation war in der SOD-Gruppe signifikant niedriger.

Zusammenfassung

Die beatmungsassoziierte Pneumonie ist eine nosokomiale Infektion, die die Mortalität und Behandlungsdauer der kritisch kranken Patienten, die sich einer Langzeitbeatmung unterziehen erhöht. SOD/SDD kann potenziell pathogene Mikroorganismen aus dem Oropharynx und dem obereren Verdauungstrakt von Patienten eliminieren, wodurch sie nosokomiale Infektionen verhindert oder minimiert. Trotzdem bleibt die Nutzung der SOD/SDD wegen der Gefahr zunehmender Antibiotikaresistenzen umstritten.

Die vorliegende Dissertation befasst sich mit den Effekten der selektiven oralen Dekontamination auf mikrobielle Resistenzlage und klinisches Outcome. Ziel dieser Arbeit war es auf den Intensivstationen für Erwachsene die Unterschiede in den Raten und Inzidenzdichten (ID, Fälle pro 1000 Patiententage) von MDRB wie methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecium* (VRE), extended-spectrum beta-lactamase (ESBL) produzierende *Escherichia coli* and *Klebsiella pneumoniae*, fluoroquinolone-resistant *Escherichia coli*, carbapenem-resistant *Klebsiella pneumoniae*, *Enterobacter cloacae, Serratia marcescens, Pseudomonas aeruginosa, Stenotrophomonas maltophilia* und *Acinetobacter baumannii* über einen Zeitraum von fünf Jahren im Zusammenhang mit der Verwendung der SOD zu analysieren und die Effekte auf nosokomiale Infektionen sowie die Sterblichkeit auf der Intensivstation zu untersuchen. Die administrativen Daten aus KAS, die Daten aus der Mikrobiologie und die Daten zu Operationen aus der Narkodata Datenbank wurden durch ETL-Prozesse erfasst. Ein „propensity score matching“ wurde verwendet, um vergleichbare Gruppen zu bilden.

Zusammengefasst wurde festgestellt, dass es keine signifikanten Unterschiede in der Inzidenzdichte multiresistenter Bakterien gibt, mit der Ausnahme einer geringeren Rate an *Klebsiella pneumoniae* mit erweiterter Beta-Laktamase und einer höheren Rate an Vancomycin-resistentem *Enterococcus faecium* bei selektiver oraler Dekontamination. Dem „propensity score matching“ nach nahm bei selektiver oraler Dekontamination die Sterblichkeitsrate auf den Intensivstationen und die Rate beatmungsassoziierter Pneumonien ab.

Abstract (English):

Ventilator-associated pneumonia (VAP) is a nosocomial infection that increases the mortality and duration of treatment of critically ill patients undergoing long-term ventilation. SOD/SDD can eliminate potentially pathogenic microorganisms from the oropharynx and upper digestive tract of patients. Thus, it prevents or reduces nosocomial infections. The use of SOD/SDD remains controversial because of the risk of increasing antibiotic resistance.

The present thesis deals with the effects of selective oral decontamination on multidrug-resistance bacteria (MDRB) and clinical outcome. The aim of this work was to investigate the differences in rates and incidence densities (ID, cases per 1000 patient days) of MDRB such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecium* (VRE), extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae*, fluoroquinolone-resistant *Escherichia coli* in adult intensive care units, carbapenem-resistant *Klebsiella pneumoniae, Enterobacter cloacae, Serratia marcescens, Pseudomonas aeruginosa, Stenotrophomonas maltophilia* and *Acinetobacter baumannii* over five years in the context of the use of SOD and to analyze its effects on nosocomial infections and the mortality in ICUs. Administrative, microbiological and operative data were extracted from the KAS, the microbiology laboratory database and the Narkodata database using ETL process (Extract, Transform, Load). Using propensity score matching two comparable groups were established.

In conclusion, it was found that there were no significant differences in the incidence density of MDRB when SOD was used, except for more vancomycin-resistant Enterococcus faecium, and fewer ESBL-producing Klebsiella pneumoniae. According to propensity score matching, ventilator-associated pneumonia and ICU deaths were less common with SOD.

Paper I

Ecological effects of selective oral decontamination on multidrug-resistance bacteria acquired in the intensive care unit: A case-control study over 5 years

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ORIGINAL

Ecological effects of selective oral decontamination on multidrug-resistance bacteria acquired in the intensive care unit: a case–control study over 5 years

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Abstract

Purpose: This case–control study investigated the long-term evolution of multidrug-resistant bacteria (MDRB) over a 5-year period associated with the use of selective oropharyngeal decontamination (SOD) in the intensive care unit (ICU). In addition, effects on health care-associated infections and ICU mortality were analysed.

Methods: We investigated patients undergoing mechanical ventilation > 48 h in 11 adult ICUs located at 3 campuses of a university hospital. Administrative, clinical, and microbiological data which were routinely recorded electronically served as the basis. We analysed differences in the rates and incidence densities (ID, cases per 1000 patient-days) of MDRB associated with SOD use in all patients and stratified by patient origin (outpatient or inpatient). After propensity score matching, health-care infections and ICU mortality were compared.

Results: 5034 patients were eligible for the study. 1694 patients were not given SOD. There were no differences in the incidence density of MDRB when SOD was used, except for more vancomycin-resistant *Enterococcus faecium* (0.72/1000 days vs. 0.31/1000 days, $p < 0.01$), and fewer ESBL-producing *Klebsiella pneumoniae* (0.22/1000 days vs. 0.56/1000 days, $p < 0.01$). After propensity score matching, SOD was associated with lower incidence rates of ventilator-associated pneumonia and death in the ICU but not with ICU-acquired bacteremia or urinary tract infection.

Conclusions: Comparisons of the ICU-acquired MDRB over a 5-year period revealed no differences in incidence density, except for lower rate of ESBL-producing *Klebsiella pneumoniae* and higher rate of vancomycin-resistant *Enterococcus faecium* with SOD. Incidence rates of ventilator-associated pneumonia and death in the ICU were lower in patients receiving SOD.

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Springer

Keywords: Selective oral decontamination, selective digestive decontamination, antimicrobial resistance, intensive care units/statistics and numerical data, Methicillin-resistant *Staphylococcus aureus*/drug effects, *Klebsiella pneumoniae*/drug effects, Polymyxins/drug effects, *Pseudomonas aeruginosa*/drug effects, Vancomycin/drug effects

Introduction

In critically ill patients undergoing mechanical ventilation, the use of selective decontamination of the oropharynx (SOD) and the digestive tract without or with systemic antibiotics (SDD) still remains controversial [1–5]. The main argument against its use is the possible ecological impact on antibiotic resistance. Although recent publications in intensive care units (ICUs) with low and highly resistant microorganisms show that prolonged use of SOD or SDD has no overall ecological impact, both regimens are not widely used in ICUs in Europe [6–11].

In Germany, a country with medium rates of multidrug-resistant bacteria (MDRB), SOD is used in 24.1% of all adult ICUs (unpublished data from the ONTAI study) [12]. Even in large hospitals, ICU directors disagree on its use resulting in different preventive strategies. At Munich University Hospital (LMU Klinikum), a large-scale hospital at two campuses and an affiliated cardiac clinic, SOD without systemic antibiotics is in clinical use in some multidisciplinary ICUs for more than 3 decades [13, 14]. Close surveillance and strict infection control have not shown any differences in the resistance rates of bacterial pathogens over the years. However, the increasing prevalence of MDRB in German ICUs carries the risk of higher selection under SOD in mechanically ventilated critically ill patients and thus poses a threat [15].

The aim of this study was to analyse the emergence of MDRB associated with SOD over a period of 5 years in mechanically ventilated patients. In particular, it should be determined which MDRB emerged during and after the use of SOD in the ICU with focus on extended-spectrum beta-lactamases (ESBL) expressing Enterobacterales and carbapenemase-producing Gram-negative bacteria (GNB) [5]. Possible interactions through the administration of systemic antibiotics were also analysed.

Methods

This is a case–control study of the long-term effects of SOD on ecological safety in 11 adult intensive care units of a 2000-bed hospital of the Ludwig-Maximilians-University of Munich (LMU Klinikum). The intensive care units at LMU Hospital are spread across three locations within the city limits, on two campuses and in a cooperating cardiac clinic. The study protocol was approved by the Ethical Committee (EC) of the LMU in December 2016 (Projekt Nr: 733-16). The EC waived the requirement for informed patient consent because of anonymous data processing after completion of data sampling and eligibility.

Take-home message

In this case–control study in mechanically ventilated patients (>48 h), no differences in the incidence density of multidrug-resistant bacteria were observed, except for a lower rate of *Klebsiella pneumoniae* with extended beta-lactamase and a higher rate of vancomycin-resistant *Enterococcus faecium* with selective oral decontamination. According to propensity score matching, ventilator-associated pneumonia and ICU deaths occurred less frequently with selective oral decontamination

The study protocol was prepared and discussed with an interdisciplinary group of infectiologists, microbiologists, pharmacists, and intensive care physicians (iKUM Group, Infektiologie am Klinikum der Universität München). Data were collected and analysed by a computer scientist trained in health informatics and qualified in medicine. The adherence to preventive measures and procedures to control ventilator-associated pneumonia were investigated in all participating ICUs according to the recommendations given by a national group of experts of the Robert-Koch-Institute in Berlin, Germany [16].

Since 1987, SOD has been a routine procedure for prevention of ventilator-associated pneumonia in some ICUs of the LMU hospital based on a previous study of our institution [13]. Over the decades, only SOD (without IV antibiotics) was performed in routine clinical practice, except during the period of participation in a prospective randomized controlled trial (RCT), where intravenous ciprofloxacin was additionally administered [14]. From 2011, a hospital-wide written SOP was introduced and SOD, when performed, was done in a standardised manner by nursing staff. Compliance with the SOP was part of a quality assurance measure conducted in parallel with this analysis. The SOD solution was prepared by the pharmacy department. Each 80 ml bottle contained 9.5 mg per ml colistin sulphate and 13.6 mg per ml gentamicin sulphate in a sodium hydrogen sulphate solution. A single dose consisted of 10 ml, of which 5 ml was administered into the oral cavity and 5 ml into the gastric tube, which was clamped for 30 min. The SOD was administered every 6 h. Commercially available solutions of nystatin or amphotericin B (in transplanted or immunosuppressed patients) were administered every 6 h in

between. Prior to administration, either oral hygiene was performed or at least the oral cavity and nasopharynx was suctioned. SOD was administered until the tracheal tube was removed. In patients with a tracheal cannula via a tracheostoma, in transplanted patients and in immunosuppressed patients, SOD was administered until discharge from the ICU.

For the objective of this analysis, all directors of the 11 ICUs of the hospital were contacted and informed about the purpose of the study. They provided detailed information on preventive measures and procedures to control ventilator-associated pneumonia and on the routine use or non-use of SOD in mechanically ventilated patients during the study period (January 2011 to December 2016). Intensive care units that did not use SOD served as control.

The primary objective of this exploratory analysis was to detect differences in the evolution of multidrug-resistant bacteria (MDRB) associated with the use of selective oropharyngeal decontamination in critically ill patients undergoing mechanical ventilation > 48 h. We analysed all patients admitted to the ICU and used all routine surveillance samples taken in the patients under study at admission and during the stay in the ICU.

MDRBs that developed during the stay in the ICU were considered, and the respective incidence density and resistance rate of MDRBs were calculated. We used the definition of the German Hospital Infection Surveillance for Intensive Care Units (ITS-KISS) to distinguish MDRBs that were already present on admission to the ICU or acquired during the ICU stay [17]. From day 3 onward in the ICU, if emerging MDRBs were cultured in any sample taken, they were considered acquired during the ICU stay. MDRBs isolated within the first two days in the ICU or up to 14 days prior to ICU admission have been documented but were not considered associated with the use of SOD. In addition, we carried out subgroup analyses in patients who were admitted directly to the ICU from the community and in patients who had already been hospitalised outside the ICU for > 48 h. Secondary endpoints were rates of MDRB in all cultures taken at ICU admission (in the first 2 days) and incidence density of MDRB in total (MDRB at admission and ICU-acquired).

Overall, the ecological impact on resistance was assessed in the participating ICUs, including surveillance and clinical samples. Surveillance endpoints were the rates and incidence densities of MDRB such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus faecium* (VRE), extended-spectrum beta-lactamase (ESBL) producing *Escherichia coli and Klebsiella pneumoniae,* fluoroquinolone-resistant *Escherichia coli,* carbapenem-resistant *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia* and *Acinetobacter baumannii.* Resistance were analysed in total, in all cultures taken at admission to the ICU (on day 1 or 2 of stay on the ICU) and during the stay in the ICU (on day 3 or later of stay on the ICU) according to the criteria of the German Nosocomial Infection Surveillance System (KISS) [18].

The results of all microbiological examinations carried out during the study period were taken from an electronic database of the Department of Medical Microbiology and Hospital Hygiene (Max von Pettenkofer Institute, LMU Munich) and combined with electronic clinical data of the study patients. After data processing, the data were irreversibly anonymised. The incidence density (ID) under SOD was calculated by dividing the number of first incident isolation of multidrug-resistant pathogens by the cumulative sum of days of length of stay in the ICU related to 1,000 patient-days. Repeat cultures confirming a previous finding of MDRB with the same resistance profile during the ICU stay were not counted for the analysis.

In addition, in order to detect a possible selection pressure under SOD, the development of the incidence density of MDRB, which differed between the groups, was analysed and compared over the 5 years of the study period. The overall antimicrobial use was assessed by recording all administered antibiotics (except from SOD) by the defined daily doses (DDD) for each participating ICU. The antibiotic use density was calculated as follows: (antibiotic use in g/DDD in g) × 100 patient-days.

The secondary objective of this study was to analyse health care-associated infections (HAI) such as ventilator-associated pneumonia, nosocomial blood stream infection and nosocomial urinary tract infections during the intervention with SOD [19]. For the diagnosis of ventilator-associated pneumonia (VAP), any documented pneumonia that occurred during the period under mechanical ventilation was used [20]. For the diagnosis of bacteremia, every blood culture in which a pathological pathogen could be cultivated was counted. In case of *Staphylococcus epidermidis*, at least two blood cultures taken from different puncture sites had to be positive to be counted. For urinary tract infections, we counted any catheter-associated urinary tract infection in which > 10^5 CFU per millilitre were detected in the urine collected from the urinary catheter.

For the propensity score analysis, the variables were matched for age, gender, duration of mechanical ventilation, sepsis severity score [21], first SAPS II score [22], length of stay (LOS) in the ICU and for type of admission. Finally, we assessed observed incidence death rates before and after propensity score matching.

Statistical analysis

We used MedCalc® Statistical Software version 20 (MedCalc Software Ltd, Ostend, Belgium) and the open source statistical software R (version 3.6.0, Vienna, Austria) for statistical analysis. The incidence rate was compared between the groups as the ratio of MDRB first isolates and the total number of days in the ICU. Repeated comparisons of each MDRB over the years were corrected according to Bonferroni–Holms. To obtain two highly similar groups for comparison of health-care infections and death in the ICU, propensity score matching was performed considering 7 variables such as age, sex, duration of mechanical ventilation, sepsis severity, Simplified Acute Physiology Score (SAPS) II at ICU admission, length of ICU stay and type of ICU admission (surgical or non-surgical). Propensity scores were matched using nearest-neighbour matching to achieve lowest standardised mean differences of the seven variables. After matching, scores were tested for normality. Incidence rates were compared as the ratio between the number of events observed and the total number of days at risk. Trends over years between the groups were tested with repeated measures analysis of variance. p values < 0.05 were considered significant.

Results

Of the 11 ICUs participating in this analysis, 7 ICUs used SOD routinely in mechanically ventilated patients and 3 ICUs did not use any SOD. One ICU used SOD only in selected patients at high risk for VAP. Due to this inconsistent use of SOD, 478 ventilated patients in this ICU were excluded from case–control study (Fig. 1). Additional preventive measures and procedures to control ventilator-associated pneumonia were followed in the

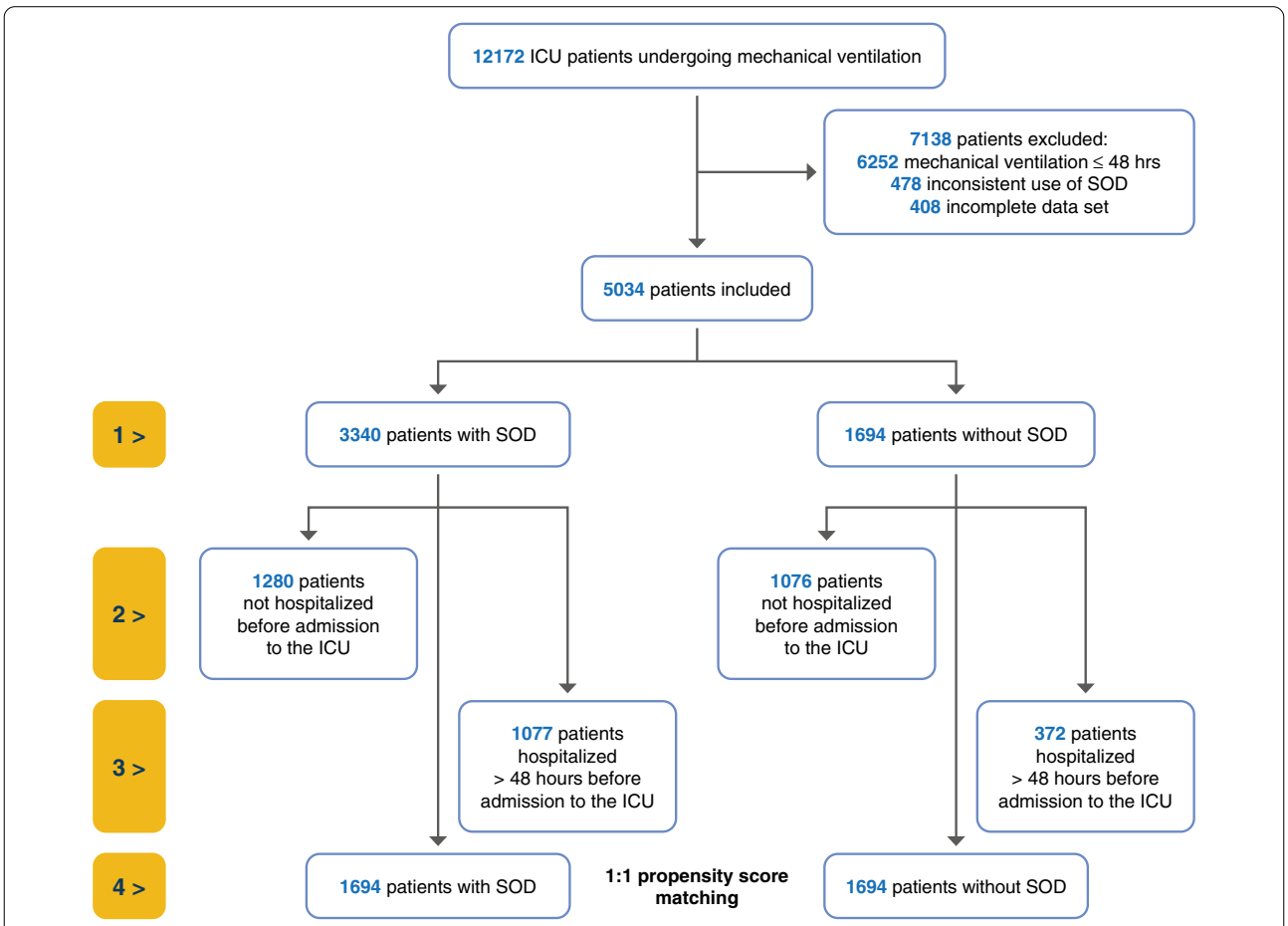

Fig. 1 Flow chart of the patients in this study. Incidence density was assessed in 3340 patients with SOD and in 1694 patients without SOD (1 >), in 1280 patients with SOD and 1076 patients without SOD admitted to the ICU from the community (2 >), and in 1077 patients with SOD and 372 patients without SOD who were already in hospital but not in the ICU 48 h before admission to the ICU (3 >). For comparison of health care-associated infections and mortality in the ICU, 1694 patients without SOD were compared with corresponding patients with SOD according to a 1:1 propensity score matching (4 >)

ten remaining ICUs in the same way as documented in a separate quality control analysis.

Between January 2012 and December 2016, 12,172 consecutive adult (≥ 18 years) critically ill patients undergoing mechanical ventilation (MV) were identified from the hospital electronic databases. 7138 patients were excluded because of MV ≤ 48 h (6252 patients), use of SOD only in selected patients in 1 ICU (478 patients) and additional 408 patients because of incomplete electronic datasets (see Fig. 1).

During the study period of 5 years, 5034 patients were eligible for the study from whom a total of 143.842 microbiological test results were available (respiratory samples $n = 26.957$, blood cultures $n = 20.719$, urine sample $n = 19.655$; rectal swabs $n = 4.605$, other samples $n = 71.906$). 1694 patients did not receive topical SOD and 3340 patients did (Fig. 1, 1>). Out of these patients, 1280 patients with SOD and 1076 patients without SOD were admitted from the community to the ICUs (Fig. 1, 2>), whereas 1077 and 372 patients were already in the hospital but outside the ICU > 48 h prior to admission (Fig. 1, 3 >).

Characteristics of all included patients with mechanical ventilation (> 48 h) are given in Table 1. Large standardised mean differences (SMD) between the two groups (SMD > ± 0.3) were found for the type of ICU admission, with more surgical and transplant patients in the SOD group and more medical patients in the non-SOD group. Length of stay in the ICU was also longer in the SOD group. Other differences were small (SMD ≤ ± 0.3). After propensity score matching two comparable groups of 1694 patients were generated with high agreement in age, gender, duration of mechanical ventilation, sepsis severity score, SAPS II score, LOS in the ICU, and type of admission (SMD < ± 0.03, see Table 2).

Ecological effects on MDRB

During the 5-year study period, the rates and incidence densities of all ICU-acquired MDRB such as methicillin-resistant *Staphylococcus aureus* (MRSA),

Table 1 Characteristics of included patients with mechanical ventilation (> 48 h)

1 > all included patients	3340 patients with SOD	1694 patients without SOD	SMD
Age [years]	61 (16)	66 (15)	− 0.30
Female [no]	1265 (38)	564 (33)	0.10
Sepsis severity score [points]	50 (14)	49 (12)	0.01
SAPS II at ICU admission [points]	40 (14)	43(13)	− 0.21
Duration of mechanical ventilation [hours]	351 (412)	304 (304)	0.15
Length of stay in the ICU [days]	26 (28)	19 (17)	0.41
Medical admission [no]*	1322 (40)	1305 (77)	− 0.89
Surgical admission [no]	2018 (60)	389 (23)	0.89
Post solid organ transplantation [no]	316 (9)	19 (1)	0.93

Results are expressed as mean with standard deviation (SD) in parentheses or number of cases with percentage in parentheses

*Without previous surgery at admission to hospital or ICU, respectively

ICU, intensive care unit; *SAPS II*, Simplified Acute Phisiology Score II; *SMD*, standardised mean differences; *SOD*, selective oropharynx decontamination

Table 2 Characteristics of patients before and after propensity score matching

	Before propensity score matching			After propensity score matching		
	With SOD ($n = 3340$)	Without SOD ($n = 1694$)	SMD	With SOD ($n = 1694$)	Without SOD ($n = 1694$)	SMD
Age [years]	61.23	65.72	− 0.30	61.89	65.72	− 0.25
Female [percent]	37.87	33.29	0.10	35.71	33.29	0.05
Duration of mechanical ventilation [hours]	350.81	304.14	0.15	338.26	304.14	0.11
Sepsis severity score [points]	49.58	49.48	0.01	48.81	49.48	− 0.06
SAPS II at ICU admission [points]	39.99	42.67	− 0.21	41.09	42.67	− 0.12
Length of stay in the ICU [days]	25.83	18.99	0.41	21.35	18.99	0.14
Surgical admission [percent]	60.42	22.96	0.89	26.21	22.96	0.08

ICU, intensive care unit; *SAPS II*, Simplified Acute Phisiology Score II; *SMD*, standardised mean differences; *SOD*, selective oropharynx decontamination

vancomycin-resistant *Enterococcus faecium* (VRE), extended-spectrum beta-lactamase (ESBL) producing *Escherichia coli* and *Klebsiella pneumoniae,* fluoroquinolone-resistant *Escherichia coli,* carbapenem-resistant *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia* and *Acinetobacter baumannii* of all included patients did not differ between the two groups with the exception of vancomycin-resistant *Enterococcus faecium* (VRE) being significantly increased, and *Klebsiella pneumonia* ESBL being significantly decreased in the group undergoing SOD (Table 3). Incidence densities were about twice as high in the SOD group for VRE (0.72/1000 days vs. 0.31/1000 days, $p<0.01$), and about half as high for ESBL-producing *Klebsiella pneumoniae* (0.22/1000 days vs. 0.56/1000 days, $p<0.01$). MRSA rates tended to be lower in the SOD group (0.19/1000 days vs. 0.37/1000 days, $p=0.06$). Analysis of patients admitted to the ICU directly from the community also found that VRE rates develop more frequently in patients with SOD (Table 4). In patients who were treated in the hospital for more than 48 h prior to admission to the ICU, we found a lower incidence rate of *Klebsiella pneumoniae* ESBL in the group treated with SOD (Table 5). The evolution of the ICU-acquired MDRB over the 5 years revealed no trend of MDRB selection found to be different between

Table 3 ICU-acquired MDRB over a 5-year period in all patients under study

1 > all included patients	86,281 days with SOD ($n=3340$)		32,177 days without SOD ($n=1694$)		Comparison of two rates
	No	Incidence densities/1000 days	No	Incidence densities /1000 days	*p* value
Methicillin-resistant *S. aureus*	16	0.19	12	0.37	0.06
Vancomycin-resistant *E. faecium*	62	0.72	10	0.31	< 0.01
ESBL-producing *E. coli*	58	0.67	15	0.47	0.20
Fluoroquinolone-resistant *E. coli*	57	0.66	25	0.78	0.50
ESBL-producing *K. pneumoniae*	19	0.22	18	0.56	< 0.01
Carbapenem-resistant *K. pneumoniae*	3	0.03	4	0.12	0.07
Enterobacter cloacae	36	0.42	13	0.40	0.92
Serratia marcescens	10	0.12	4	0.12	0.91
Stenotrophomonas maltophilia	80	0.93	33	1.03	0.63
Pseudomonas aeruginosa	58	0.67	25	0.78	0.54
Acinetobacter baumannii	16	0.19	3	0.09	0.26

ICU, intensive care unit; *SOD*, selective oropharynx decontamination; *MDRB*, multidrug-resistant bacteria; *ESBL*, extended-spectrum beta-lactamases

Table 4 ICU-acquired MDRB over a 5-year period in patients admitted from the community

2 > patients not hospitalised before admission to the ICU	30,768 days with SOD ($n=1280$)		18,433 days without SOD ($n=1076$)		Comparison of two rates
	No	Incidence densities/1000 days	No	Incidence densities /1000 days	*p* value
Methicillin-resistant *S. aureus*	3	0.10	6	0.33	0.07
Vancomycin-Resistant *E. faecium*	18	0.59	3	0.16	0.03
ESBL-producing *E. coli*	18	0.59	11	0.60	0.96
Fluoroquinolone-resistant *E. coli*	18	0.59	13	0.71	0.61
ESBL-producing *K. pneumoniae*	7	0.23	10	0.54	0.07
Carbapenem-resistant *K. pneumoniae*	1	0.03	3	0.16	0.12
Enterobacter cloacae	12	0.40	8	0.43	0.81
Serratia marcescens	4	0.13	3	0.16	0.77
Stenotrophomonas maltophilia	32	1.04	15	0.81	0.43
Pseudomonas aeruginosa	26	0.85	10	0.54	0.23
Acinetobacter baumannii	8	0.26	1	0.05	0.10

ICU, intensive care unit; *SOD*, selective oropharynx decontamination; *MDRB*, multidrug-resistant bacteria; *ESBL*, extended-spectrum beta-lactamases

Table 5 ICU-acquired MDRB over a 5-year period in patients hospitalised > 48 h before admission to the ICU

3 > included patients hospitalised > 48 h	29,019 days with SOD ($n = 1077$)		8234 days without SOD ($n = 372$)		Comparison of two rates
	No	Incidence densities/1000 days	No	Incidence densities/1000 days	*p* value
Methicillin-resistant *S. aureus*	6	0.21	5	0.61	0.06
Vancomycin-resistant *E. faecium*	39	1.34	5	0.61	0.09
ESBL-producing *E. coli*	22	0.76	2	0.24	0.10
Fluoroquinolone-resistant *E. coli*	22	0.76	5	0.61	0.65
ESBL-producing *K. pneumoniae*	6	0.21	7	0.85	< 0.01
Carbapenem-resistant *K. pneumoniae*	1	0.03	0	0.00	0.60
Enterobacter cloacae	14	0.46	2	0.24	0.35
Serratia marcescens	4	0.14	0	0.00	0.29
Stenotrophomonas maltophilia	28	0.96	13	1.58	0.14
Pseudomonas aeruginosa	19	0.65	7	0.85	0.55
Acinetobacter baumannii	5	0.17	1	0.12	0.74

ICU, intensive care unit; *SOD*, selective oropharynx decontamination; *MDRB*, multidrug-resistant bacteria; *ESBL*, extended-spectrum beta-lactamases

the groups in the analysis (Fig. 2). The incidence rate of all MDRB in samples taken at admission and during the stay in the ICU differed for MRSA, VRE, and ESBL-producing *Klebsiella pneumoniae* between the groups (Tab. S1). On admission, patients in the SOD group had a higher rate of *Pseudomonas aeruginosa*.

Consumption of antibacterial drugs in all patients ($n = 12,172$) treated in intensive care units during the entire study period is shown in the supplement (including patients treated for less than 48 h or excluded for other reasons, Fig. S1). Overall, there was a significantly higher consumption of antibiotics administered intravenously in the ICUs with SOD. The cumulative DDD per 100 patient-days were 147 (95% CI 138-155) in the SOD group vs. 125 (95% CI 115-135) the group without SOD. ICUs with SOD used more carbapenems, 2nd-generation cephalosporins, glycopeptides, and other antibiotics, whereas ICUs without SOD used more 3rd-generation cephalosporins, penicillins with beta-lactamase inhibitors, and fluoroquinolones.

Effect of SOD on health care-associated infections

Propensity analysis of nosocomial infections (HAI) revealed lower incidence rates and densities of ventilator-associated pneumonia but not bacteremia or urinary tract infections in the group receiving SOD (Table 6). The number needed to prevent a VAP was 29. The incidence densities found in the studied patients were higher than reported by national surveillance.

Effect of SOD on death in the ICU

The incidence rate of death in the ICU was significantly lower in the SOD group. After 1:1 propensity score matching for demographic characteristics, sepsis severity, severity of illness, length of mechanical ventilation, LOS in the ICU and type of admission, mortality in the ICU was 28% in the group receiving SOD and 30% in the group not receiving SOD (Table 7).

Discussion

This case–control study of 5034 mechanically ventilated critically ill patients over a 5-year period found an incidence density of all MRDB equal to or lower than that reported for German ICUs in 2015 [15]. With SOD, there were no statistically significant differences in the incidence densities of ICU-acquired MDRB under study, with the exception of vancomycin-resistant *Enterococcus faecium* (VRE), which was more common with SOD, and extended beta-lactamase *Klebsiella pneumoniae*, which was less common with SOD. There was no trend towards an increased selection of these MDRBs over the years observed. The propensity score analysis of health care-associated infections found that SOD was associated with less ventilation-associated pneumonia, but not with bacteremia or urinary tract infections acquired in the intensive care unit. Incidence rate of death in the ICU was lower in the SOD group.

Three limitations of this case–control study should be noted. First, there was already a difference in the rates of MDRB isolates at admission to the ICU, which can be attributed to the specifics of patients under study. Although we excluded MDRB isolates found in the first 48 h after ICU admission, this could influence the analysis. Second, many characteristics and disease severity were similar in the two groups, but there were more surgical patients in the SOD group and more medical

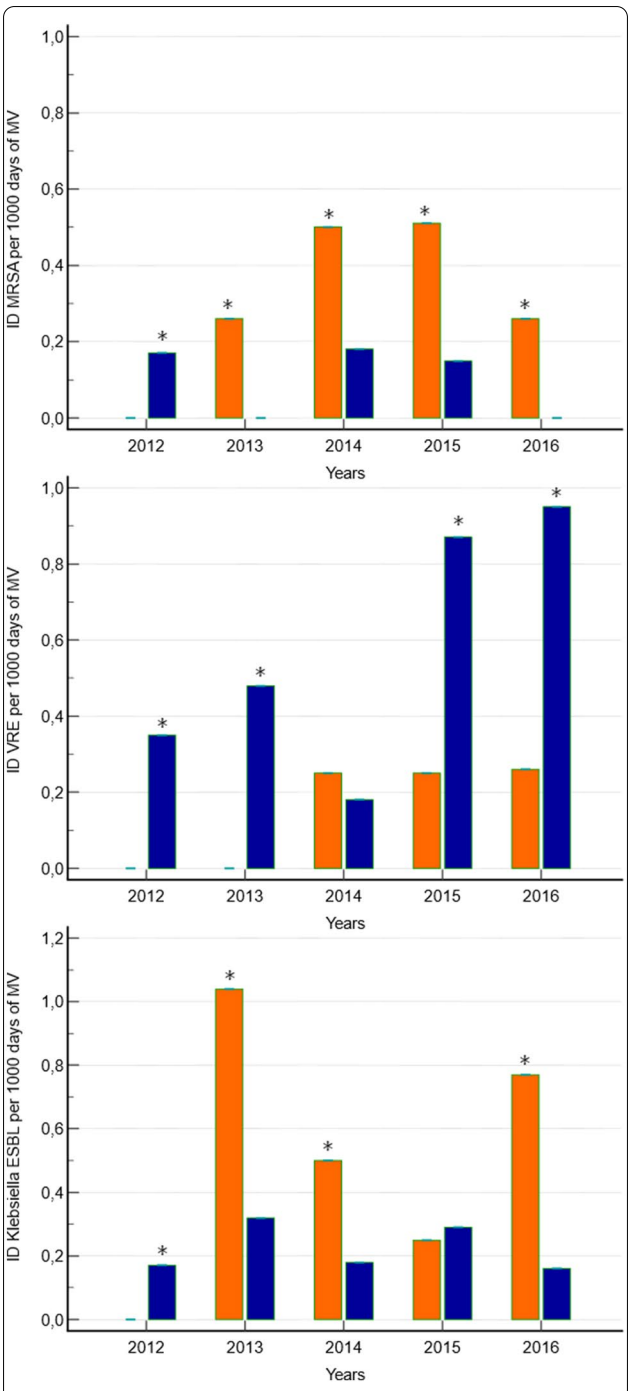

Fig. 2 Incidence densities of MDRB acquired in the ICU in patients with SOD (blue bars) and patients without SOD (orange bars). Significant differences in the annual incidence rates between the groups are marked with an asterisk. There was no significant trend for emergence of MDRB over time in each group

patients in the non-SOD group (Table 1). The surgical patients included also patients after solid organ transplantation such as heart, lung, and liver transplantation. In this group of patients, the rates of *Pseudomonas aeruginosa* were found more frequently already at admission to the ICU (see Table S2 in the supplement). The increased rate of *Pseudomonas aeruginosa* on admission may be related to patients with cystic fibrosis admitted prior and after lung transplantation. Although this particular patient cohort was more common in the SOD group, no higher rate of ICU-acquired Pseudomonas could be observed. Third, it was not possible to stratify the included patients according to the systemic antibiotics they received, since only the total antibiotic consumption of all patients treated in the intensive care units during the study period was available.

The increased occurrence of VRE under SOD may be related to the fact that there were more surgical patients in the SOD group. Many isolates with *E. faecium* in this study were found in swabs from rectum, wounds and abscesses. This may have led to the fact that *E. faecium* and thus VRE were found more frequently in the group with SOD during the stay in the ICU. In the analysis of antibiotic selection pressure over the study period of 5 years, our results did not support the assumption that selection pressure increased under SOD. It is noteworthy, that during the study period, the prevalence of VRE increased in German hospitals, particularly in southern regions of Germany accounting for 11 to 26% of all isolates [15, 23]. This was attributed, in part, to an extensive use of fluoroquinolones in outpatients in the corresponding areas of Germany [15, 23]. Both the trend over the years and the distribution of isolates at the end of this study suggest against an association with the use of SOD.

An new finding from this study is that ESBL-producing *Klebsiella pneumoniae* was more common in ICU patients not treated with SOD. When comparing the antibiotics used systemically during ICU stay, there was no difference in the indication for antibiotic therapy, that could explain this finding. SOD may be specifically successful in preventing colonisation and subsequent infection with ESBL-producing *Klebsiella pneumoniae*.

We found an increased total consumption of antibacterial drugs in intensive care units with SOD. This can be attributed, among other things, to the large number of postoperative surgical patients who spent only a day or two in the ICU and were not included in this study. A large proportion of these patients received antibiotics as perioperative antibiotic prophylaxis.

The propensity score analysis of health care-associated infections showed that ventilator-associated pneumonia occurred less frequently with SOD than in patients without SOD. This is consistent with the results of controlled studies on this prophylactic measure [14, 24, 25]. The extent to which the additional systemic administration of cefotaxime for 4 days would have further reduced this

Table 6 Health-care-associated infections in both groups after propensity score matching

ICU-acquired infections during prevention*	with SOD ($n=1694$)			Without SOD ($n=1694$)			*p* value
	Number of cases	%	Incidence density/1000 days	Number of cases	%	Incidence density/1000 days	
Ventilator-associated pneumonia	243	14	10.2	302	18	14.1	< 0.01
Bacteremia	218	13	8.92	182	11	8.48	0.61
Urinary tract infections	162	10	6.79	138	8	6.43	0.64

*Days at risk with mechanical ventilation: 23,876 days with SOD, 21,467 days without SOD

ICU, intensive care unit; *SOD*, selective oropharynx decontamination

Table 7 Incidence rate of death in the ICU in both groups

Death in the ICU*	With SOD			Without SOD			*p* value
	No	%	Incidence density/1000 days	No	%	Incidence density/1000 days	
Before propensity score matching	759/3340	23	8.8	509/1694	30	15.8	< 0.01
After propensity score matching	478/1694	28	13.2	509/1694	30	15.8	< 0.01

*Days at risk in the ICU: 86,281 and 36,167 days with SOD, respectively; 32,177 days without SOD

ICU, intensive care unit; *SOD*, selective oropharynx decontamination

incidence, as recently described [25], cannot be assessed on the basis of our data. Blood stream infections did not differ between the groups, which is consistent with findings of a large European trial [26].

The propensity score analysis also showed lower death rate in the SOD group. Both groups were equally severely ill and also well matched for LOS in the ICU and type of admission. Therefore, the observed lower ICU mortality in surgical patients compared to non-surgical patients can, therefore, be ruled out as a cause [2, 27].

Conclusion

In this case–control study of mechanically ventilated adult patients (> 48 h), we found that the use of SOD was not associated with the development of antibiotic resistance in a set of ICUs with medium rates of MDR bacteria. According to propensity score matching, a recognised approach for causal inference in observational data, the use of SOD was associated with a lower incidence rate of ventilator-associated pneumonia and death in the ICU. Even though encouraging, these findings could not be extrapolated to intensive care units with high rates of MDR bacteria. Future studies are still required for these settings.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s00134-022-06826-7.

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Author contributions

Design, data acquisition, analysis, interpretation, drafting and revising the manuscript, and final approval: JB, BW, JJ, AW, RD, JB, LH, and BG; data acquisition, analysis, interpretation, drafting the manuscript, and final approval: WK, UL, SN, MZ, and SN; interpretation, drafting and revising the manuscript, and final approval: SF, MI, LN, TW, EK, and PM. BW and JB contributed equally to this work.

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Declarations

Conflicts of interest
The authors declare no conflict of interest.

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Paper II

Association between post-operative delirium and use of volatile anesthetics in the elderly: A real-world big data approach

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Original Contribution

Association between post-operative delirium and use of volatile anesthetics in the elderly: A real-world big data approach

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ABSTRACT

Study objective: Early post-operative delirium is a common perioperative complication in the post anesthesia care unit. To date it is unknown if a specific anesthetic regime can affect the incidence of delirium after surgery. Our objective was to examine the effect of volatile anesthetics on post-operative delirium.
Design: Single Center Observational Study.
Setting: Post Anesthesia Care Units at a German tertiary medical center.
Patients: 30,075 patients receiving general anesthesia for surgery.
Measurements: Delirium was assessed with the Nursing Delirium Screening Scale at the end of the recovery period. Subgroup-specific effects of volatile anesthetics on post-operative delirium were estimated using generalized-linear-model trees with inverse probability of treatment weighting. We further assessed the age-specific effect of volatiles using logistic regression models.
Main results: Out of 30,075 records, 956 patients (3.2%) developed delirium in the post anesthesia care unit. On average, patients who developed delirium were older than patients without delirium. We found volatile anesthetics to increase the risk (Odds exp. (B) for delirium in the elderly 1.8-fold compared to total intravenous anesthesia. Odds increases with unplanned surgery 3.0-fold. In the very old (87 years or older), the increase in delirium is 6.2-fold. This result was confirmed with internal validation and in a logistic regression model.
Conclusions: Our exploratory study indicates that early postoperative delirium is associated with the use of volatile anesthetics especially in the sub-cohort of patients aged 75 years and above. Further studies should include both volatile and intravenous anesthetics to find the ideal anesthetic in elderly patients.

List of abbreviations

AIC	Akaike-Information-Criterion
ASA	Anesthesiologists physical status
CI	Confidence Interval
DAG	Directed Acyclic Graph
GAM	Generalized Additive Model

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IPTW	Inverse Probability of Treatment Weighting
NCD	neuro-cognitive dysfunction
Nu-DESC	Nurse Delirium Screening Scale
OR	Odds Ratio
SD	Standard Deviation
SE	Standard Error
SMD	Standardized Mean Difference

1. Introduction

1.1. Background

Postoperative delirium (POD) in the in the post anesthesia care unit is a frequent neuropsychiatric syndrome following general anesthesia with incidence rates around 10% and a range between 3 and 54% [1] depending on the diagnostic tool used, the specific cohort of patients, and the period of the assessment [1–4]. Delirium itself may lead to post-operative neuro-cognitive dysfunction (NCD), a long-time decline in cognitive performance that occurs after surgery [5]. As delirium in the post anesthesia care unit predicts later postoperative delirium [6], guidelines state to diagnose delirium at this early stage [7].

Besides many known risk factors for delirium, there is limited data on the ideal anesthetic for elderly patients. For hip fracture repair, there might be an increased risk for postoperative delirium with general in contrast to regional anesthesia [8], while the recently published REGAIN trial found similar incidences of postoperative delirium irrespective of spinal or general anesthesia being performed [9]. A recent Cochrane review [10] describes volatile anesthetics as common - but not evidence based - "gold standard" for surgical general anesthesia. There are ecological considerations because of the significant contribution of anesthetic gases to the carbon-dioxide burden [11]. However, there is increasing evidence of a causal relationship between sevoflurane and NCD, and sevoflurane induced NCD may be associated with neuro-inflammation [10,12,13]. Studies seeking strategies to reduce post-operative cognitive deficits suggest preferring intravenous maintenance of anesthesia [14], a strategy current guidelines adhere to [15]. Age-dependent end-tidal concentration measurement enables adequate dosing in elderly people, still doses used are often higher than required [16]. As an alternative to volatile anesthesia, propofol-based total intravenous anesthesia offers a comparable rapid recovery and reduced postoperative nausea and vomiting. However, in terms of postoperative cognitive outcomes, the optimal therapeutic regimen is unknown [10]. A reduction of NCD was observed for total intravenous anesthesia (OR 0.52, 95% CI 0.31 to 0.87; 869 participants) [10], but it was not superior to volatiles in terms of delirium incidence. A recent analysis found differences between several volatile anesthetics, but the study did not compare volatile versus intravenous anesthesia [17]. Generally, volatile anesthetics are associated with increased emergence delirium, a status presenting subsequent to regaining consciousness after anesthesia [18]. Emergence delirium itself often converts into postoperative delirium at the time of discharge onto the ward [19].

Studies comparing volatile anesthesia versus intravenous anesthesia often evaluate induction time, time to recovery or hemodynamic stability [20,21]. Little is known about the effect of drug choice on the incidence of postoperative delirium [22]. Neurocognitive recovery seems to be compromised by using sevoflurane in contrast to intravenous anesthesia [13,23]. Increased sensitivity to volatile anesthetics even at lower sedation levels might contribute to this fact [24].

These studies show that the question about the ideal anesthetic is not easy to answer. In addition, delirium is likely not attributable to a single cause, and the effect of different pathological conditions is difficult to discern from individual risks for delirium.

1.2. Aim of the study

In this single-center study, we hypothesized an effect of volatile anesthetics on delirium and sought to identify subgroup-specific effects of developing delirium at the time of discharge from the post anesthesia care unit.

2. Material and methods

The institutional review board of the Ethics Committee of the Faculty of Medicine, Ludwig-Maximilians University (LMU), Munich, Germany, approved the study (279–15) and informed consent was waived for a retrospective analysis of anonymized data. The study was performed at a German tertiary single center providing >2000 hospital beds between January 2015 and February 2017.

Patients of all ages who received a surgical procedure under general and/or regional anesthesia and were monitored postoperatively in one of the eight post-operative care units at the University Hospital, LMU Munich were included in the study (Fig. 1). We excluded patients without any measurement of a Nurse Delirium Screening Scale (Nu-DESC) score in the postoperative care unit. This was for example due to prolonged ventilation before their transfer to an intensive care unit and monitored anesthesia care.

Regular screening for delirium before discharge was implemented in 2015 using the Nu-DESC. Nurses and anesthesiologists received theoretical and practical training and refresher training. The Nu-DESC is an observational instrument judging delirium by the five items of disorientation, inappropriate behavior, inappropriate communication, illusions or hallucinations, and psychomotor retardation. Each item is scored based on its severity (0 = item absent, 1 = mild changes, 2 = severe disturbance), and a score of 2 or more is suggestive of delirium

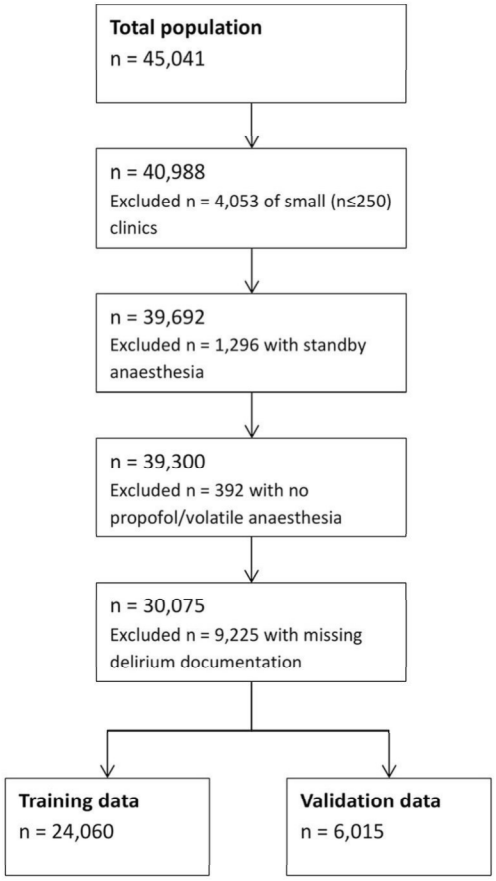

Fig. 1. Flow chart of patient selection.

[25].

Premedication (usually with midazolam) was prescribed at the disposition of the individual anesthetist. Patients older than 70 years received a lower dose of 3.75 mg of oral midazolam in contrast to a standard dose of 7.5 mg for younger patients. The anesthetic regime was not standardized but determined by the individual anesthetist (total intravenous or volatile based anesthesia with sevoflurane). Following surgery, patients not scheduled for intensive care were monitored. When the decision to discharge the patient to the ward was made, the electronic chart prompted the Nu-DESC instrument, which then had to be completed by a trained nurse. If the patient was conspicuous for delirium during the postoperative monitored stay, nurses were encouraged to fill out the score once or several times before discharge. Additionally, doctors added their comments regarding delirium to the chart. Anesthesia and the immediate postoperative period were documented in an electronic data base (Narko Data 4.8.3., IMESO IT GmbH, Giessen, Germany). In addition to the Nu-DESC, a clinical diagnosis of delirium, documented in the record, contributed to a diagnosis of delirium.

2.1. Statistical analysis

2.1.1. Sample description

Patient characteristics were described using descriptive statistics (categorical: count, percentages; continuous: mean, standard deviation [SD]) stratified by patients receiving volatile anesthetics.

Differences in delirium between dosing of anesthetics (propofol, sevoflurane, desflurane), adjusted for weight, were explored by calculating mean, SD and standardized mean differences (SMD).

2.1.2. Model

To estimate the effect of volatile anesthetics, the dataset was split randomly into a training set (80%) and validation set (20%). All models were estimated on the training set, and the validation set was only used to assess model performance on new data.

To avoid bias in the selection of covariates, we constructed a directed acyclic graph (DAG, see Fig. 2) [26]. Covariates and their relationships were entered into the DAG based on their reported association with the exposure or the outcome in the literature and expert opinion. The minimal adjustment set for estimating the total effect of volatile anesthetics was identified as age, American Society of Anesthesiologists physical status (ASA) score, type of anesthesia (general or/and regional), and whether the intervention was scheduled or not.

As treatment was not randomized for this study, we aimed to adjust for differences in the likelihood of receiving volatile anesthetics using Inverse Probability of Treatment Weighting (IPTW) [27]. Propensity scores for volatile anesthetics used in IPTW were estimated using a logistic regression model including age, ASA score, type of anesthesia, and whether the intervention was scheduled or not as independent variables and volatile anesthetics as dependent variable. Estimated propensity scores were truncated at the 0.01 and 0.99 percentiles to eliminate extreme propensity scores [28]. There was no evidence that the overlap assumption was violated, i.e., all subjects had a positive probability to receive each treatment level. All further analyses were weighted using the obtained IPTWs.

In the primary analysis, we estimated the effect of volatile anesthetics on delirium in different subgroups using Generalized Linear Model (GLM) trees [29,30]. The aim of GLM trees for subgroup analyses is to detect patient characteristics which (1) interact with the treatment (i.e., volatile treatment effect differs for different values of the patient characteristic), (2) directly affect the outcome (i.e., probability of delirium differs for different values of the patient characteristic), or (3) affect both outcome and treatment effect. The data is partitioned into relevant subgroups based on the selected patient characteristics, and a separate model is estimated for each subgroup. GLM trees allow for exploratory analyses and are aimed at hypothesis generation.

The GLM tree was validated on the internal validation dataset by calculating the c-statistic for benefit [31]. This measure illustrates the model's ability to predict treatment effects by computing the difference of observed outcomes of treated and control subjects in the identified subgroups (see Supplementary Material 1).

As the GLM tree identified age as an important predictive factor, we further explored the interaction effect of age and volatile anesthetics using logistic regression models. First, we fitted a model using the age-specific subgroups identified by the model. As a next step, we fitted a Generalized Additive Model (GAM) using a smooth term for age to describe a possible smooth effect (instead of a step function as in the first model). The methodological difference between a stepwise versus a smooth effect is impressively depicted in Fig. 4.

Dose response analyses for propofol and sevoflurane were performed post hoc. Analyses were performed using R 3.5.3 (2019, Foundation for Statistical Computing, Vienna, Austria). The GLM tree was computed using the partykit package [32], the mgcv package was used for computing the GAM [33]. The analysis script is provided in the Supplementary Material 2 together with the analysis of missing data.

3. Results

In total, 45,041 eligible patient records were evaluated, of which 30,075 had a complete Nu-DESC assessment (Fig. 1). The complete records were split into training and validation data, leaving 24,060

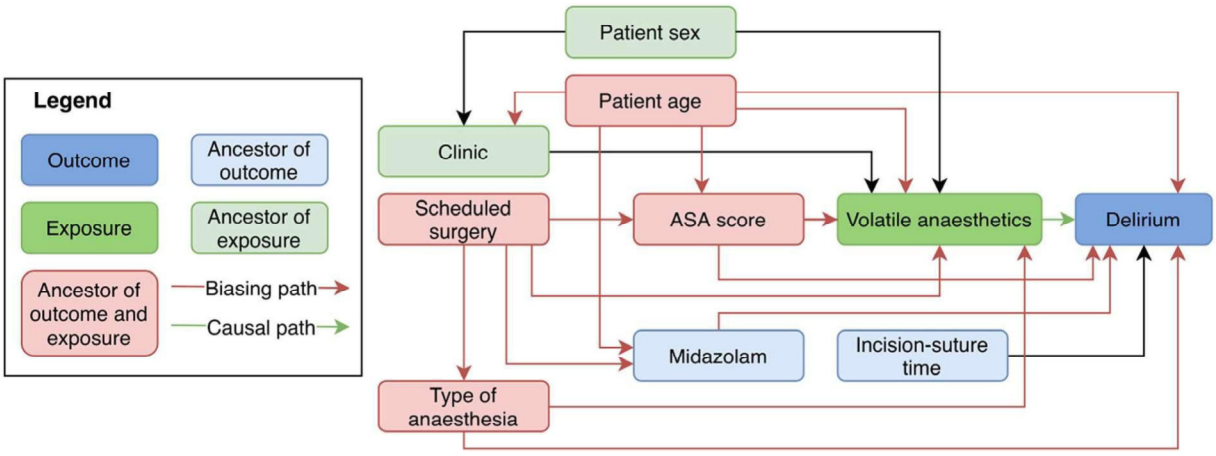

Fig. 2. Directed acyclic graph with volatile anesthetics as exposure variable and delirium as outcome variable. Green nodes are ancestors of the exposure and blue nodes of the outcome. Red nodes are ancestors of both the exposure and the outcome. The Green arrow shows the causal paths and red arrows biasing paths. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

patients for model building and 6015 patients for model validation.

Table 1 presents patients' demographic and clinical characteristics of the total cohort stratified by volatile and intravenous anesthetics. For the intravenous group, the mean age (SD) was 51.1 (20.3) years and 51.8% were female. Patients who had received volatile anesthetics were a mean age (SD) of 50.7 (24.2) years and 39.2% female. Overall, 956 patients (3.2%) developed delirium in the immediate postoperative period as diagnosed with the Nu-DESC, of which 496 (2.4%) had received intravenous anesthesia and 460 (5.1%) volatile anesthesia. Delirious patients were older and stayed longer in the hospital than patients without delirium (see Table 1). Missing data analysis did not overt outlier in the data.

Supplementary Table 2 shows the mean concentrations of the anesthetics used according to the state of delirium in the post-operative care unit, adjusted for patient weight. Patients with delirium had received slightly lower dose of propofol as the predominant intravenous anesthetic. Contrary, patients with delirium had received more than double the dose of sevoflurane compared to patients without delirium (a medium standardized mean difference (SMD), see Supplementary Table 2). For sevoflurane, we showed a dose dependent increasing risk of delirium, especially for patients older than 85 years (see supplement 2, 7.1. and 7.2.).

Fig. 3 displays the resulting GLM tree showing the subgroup-specific treatment effects of volatile anesthetics on post-operative delirium. The data are first split at an age of 75 years. For all subgroups with patients older than 75 years, the tree indicates that volatile anesthetics affect the likelihood of having delirium. The tree divides these older patients in two subgroups: age > 87 years and patients between 75 and 87 years, and if the intervention was planned or unplanned. The results suggest that the risk for postoperative delirium is increased for older patients with volatile anesthetics (exp (B) in the multinominal model 6.2-fold for patients older than 87 [node 12]; odds 1.8 for patients between 75 and 87 years and planned surgery [node 11]; odds 3.0 for patients older than 75 and unplanned surgery [node 13]).

The result of the c-for-benefit validation indicate that the model performed well on this dataset. For details, we refer to Supplementary Material 2.

We used the age-based subgroups identified by the GLM tree as covariate with treatment interaction in a logistic regression model. This simplifies interpretation and shows the main results of the GLM tree in a single model. The results (see Table 2 and Fig. 4) confirm the findings: The probability of delirium and the effect of volatile anesthetics increases with increasing age. The odds for delirium in young patients (below 75 years) is 1.4 times as high if they receive volatile anesthetics. Patients between 75 and 87 years had odds of 2.2 to develop delirium and an odd of 1.4 if they received volatile anesthetics. The odds for delirium in very old patients (>87 years) was 2.9, and 3.6 if they received volatile anesthetics. Please note that confidence intervals shown in Table 2 are to be interpreted with care as this is an exploratory study.

The GLM tree aims to identify discrete subgroups, i.e., age groups with incrementing risks. However, it is safe to assume that the risk increases smoothly with increasing age. To describe a smooth effect of age and its interaction with volatile anesthetics we fitted a GAM. Estimates of the GAM are presented in Supplementary Table 2 and Fig. 4 and show similar effect as the first logistic regression model. The smooth term of the GAM improved the model slightly (AIC = 13,898) compared to the regression with step-function (AIC = 14,026).

All models suggest that patients older than 75 have a high risk of delirium, especially when exposed to volatile anesthetics.

Table 1
Patients' demographic and clinical Characteristics (total data set).

Characteristics		Type of anesthesia	
		Intravenous (n = 20,989)	Volatile (n = 9086)
Delirium, n (%)		496 (2.4)	460 (5.1)
Age, mean (SD)		51.1 (20.3)	50.7 (24.2)
Age ≥ 75 years, n (%)		2723 (13.0)	1612 (17.7)
Age > 4 and < 75 year, n (%)		18,030 (85.9)	6873 (75.6)
Female sex, n (%)		10,874 (51.8)	3561 (39.2)
ASA score, n (%)	1	4377 (20.9)	1507 (16.6)
	2	9643 (45.9)	3491 (38.4)
	3	6740 (32.1)	3851 (42.4)
	4 and 5	229 (1.1)	237 (2.7)
Anesthesia type, n (%)	General	17,048 (81.2)	7816 (86.0)
	General and regional	2509 (12.0)	1196 (13.2)
Emergency surgery, n (%)		1495 (7.1)	1010 (11.1)
Duration of surgery (minutes), mean (SD)		68.9 (63)	94.0 (76.5)
Length of stay, mean days (SD)		9.6 (16.4)	11.5 (17.4)
Oral premedication with midazolam, n (%)		9014 (42.9)	3436 (37.8)
Other pharmaceutical for premedication, n (%)		1892 (9.0)	2246 (24.7)
Surgical specialty, n (%)	Surgery, department 1	4289 (20.4)	1585 (17.4)
	Surgery, department 2	2312 (11.0)	1704 (18.8)
	Gynecology, department 1	2077 (9.9)	302 (3.3)
	Gynecology, department 2	1719 (0.4)	158 (1.7)
	Cardiac surgery	79 (0.4)	99 (1.1)
	Ear Nose Throat	1859 (8.9)	2551 (28.1)
	Oral/maxillofacial surgery	690 (3.3)	593 (6.5)
	Neurosurgery	1406 (6.6)	215 (2.4)
	Orthopaedics	2175 (10.4)	742 (8.2)
	Urology	4383 (20.9)	1137 (12.5)

Peri-operative characteristics of the study population receiving volatile or other types of anesthesia. Values are mean (SD) or number (proportion). ASA, American Society of Anesthesiologists.

Table 2
Logistic regression (step-function) of volatile anesthetic and age on delirium.

Variable		OR	95% CI
Volatile anesthetic	No	–	–
	Yes	1.43	1.27, 1.61
Age	≤75 years	–	–
	>75 & ≤87 years	2.23	1.81, 2.73
	>87 years	2.92	1.41, 5.34
Age & volatile anesthetic	≤75 years	–	–
	>75 & ≤87 years	1.44	1.12, 1.85
	>87 years	3.60	1.89, 7.68

The table shows the odds ratio (OR) and 95% Confidence Interval (CI) for age and volatile anesthetic and their interaction effect in the logistic regression.

4. Discussion

This single-center study aimed to evaluate the effect of volatile anesthetics on postoperative delirium in patients with different characteristics. We found an increased risk for delirium in patients over 75 years, which is enhanced by volatile anesthetics. To the best of our knowledge, this is the largest cohort so far examining the effects of volatile anesthetics on postoperative delirium in the immediate perioperative period.

There is little data on the ideal anesthetic for maintaining general anesthesia in older adults. Preclinical studies, predominantly in animal models, described a cardioprotective effect of volatiles. However, in a recent study total intravenous anesthesia was found to be comparable to volatile anesthesia in isolated coronary artery bypass surgery [34]. In a small study with 40 male patients with carotid endarterectomy, volatile anesthesia improved early postoperative cognition compared to propofol anesthesia [35], while in one study, total intravenous anesthesia was the preferred anesthetic regime for transcatheter aortic valve replacement [36]. This study suggested total intravenous anesthesia to be a

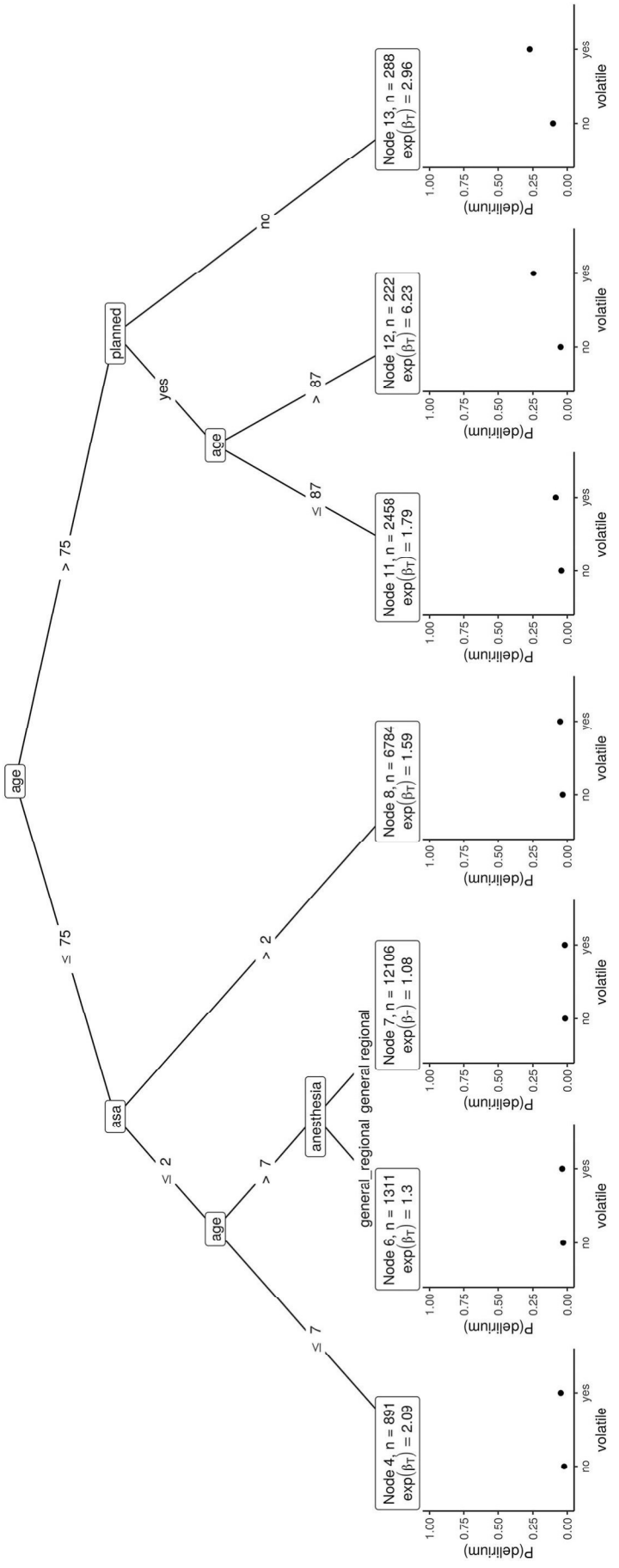

Fig. 3. Generalized Linear Model (GLM) tree for volatile anesthetics on post-operative delirium.

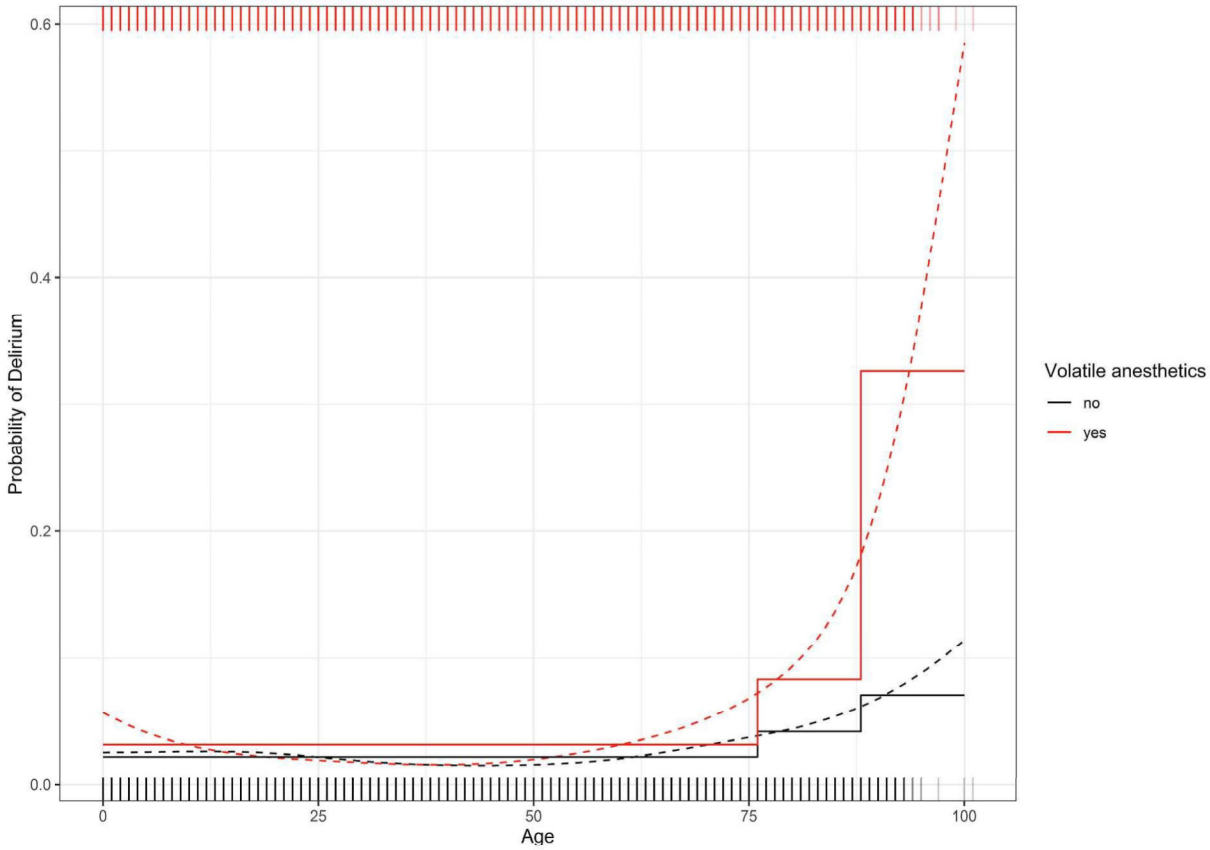

Fig. 4. Probability of delirium after receiving volatile anesthetics (red, solid line) in contrast to non-volatiles (black, dashed line). Step-regression on top and additive model with smooth term at the bottom. Both results suggest an increase in delirium probability with increasing age. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

favorable alternative in patients requiring general anesthesia [36]. These patients reflect a small group with older age and distinct multimorbidity for aortic valve repair. Our study implies, that there may be comparable patients also in non-cardiac surgery that might benefit from an individual anesthetic approach. To date, there is no scientific answer on the important question if a specific anesthetic can influence the risk of delirium or even prevent the evolvement of delirium or neurocognitive decline. Our results suggest a possible, age- and dose-dependent effect of the volatile agent sevoflurane on the evolvement of delirium following general anesthesia. This age-dependent effect implies the need for future prospective trials on the ideal anesthetic for older patients.

There are additional possible influences on postoperative outcome than the type of anesthesia used. Features of cerebral autoregulation and cerebral malperfusion lead to postoperative cognitive decline. Several volatile anesthetics have neurotoxic features that may increase the likelihood of delirium and neurocognitive decline as much as they improve hemodynamic stability [37]. With an analysis of data lacking delirium screening, (supplementary material 3), we could rule out selection bias.

Strengths of our study include the large sample size and the standardized screening for delirium in the postoperative care unit. In contrast to previous studies, we evaluated a total of 22 months to outweigh fluctuations of delirium incidence or specific diseases throughout a year [38]. To minimize bias, we applied IPTW to adjust for differences in treatment assignment. The GLM tree specifically aims to identify subgroup of patients with differing risks based solely on the data structure. The internal validation of the model on new data showed that the model was able to predict delirium adequately.

Delirium was assessed using the Nu-DESC, which is a well-validated and adequately sensitive score for the diagnosis of postoperative delirium. All personnel were trained and periodically refreshed on administering the Nu-DESC, and they were familiar with the categories tested and their relevance for delirium detection. However, some cases of delirium may have been missed, for example because patients with dementia may have been misclassified as delirious, even though dementia may not affect validity of delirium tests. The focus of the delirium assessment at our site was to identify all delirious patients, therefore we used a Nu-DESC threshold for delirium with a lower risk of missing delirium patients (high specificity) and as such accepted a decreased sensitivity.

We used a conservative Nu-DESC threshold of 2 as a cut-off to decrease specificity, even if studies showed an improved sensitivity with a threshold of 1 [39].

One might point out that with 3.2% cases of delirium the incidence at the end of the recovery period in our study is surprisingly low. However, it lies within the range of a Swiss study (4.4%) [40], a recent study at our center (4.1%) [41] and specific work assessing agitated delirium at discharge (4%) [19]. We excluded patients scheduled for intensive care medicine or solely sedated anesthetic care, who are prone to an increased risk for delirium. As the prevalence of neuro-cognitive disorders increases with age, this confounder is partially included.

Patients with delirium had high amounts of sevoflurane. As we were unable to diligently collect data of anesthetic depth, further studies

should investigate anesthetic depth with its detrimental consequences like delirium in both volatile and intravenous anesthesia.

Given the exploratory study design and its limitation, our results should be validated in future studies, optimally in a randomized controlled trial. According to the current clinical evidence, there is currently no reason to change well working anesthetic regimes, avoid volatile agents and prefer total intravenous anesthesia.

5. Conclusions

We showed an association of postoperative delirium with use of volatile anesthetics measured as early as at the end of the postoperative care period. Especially patients aged over 75 years seemed to be at risk for delirium with general anesthesia under volatile anesthetics.

We found a low incidence of delirium in a mixed cohort at an academic center. The incidence was comparable with similar studies.

Further studies should include both volatile and intravenous anesthetics in order to find the ideal anesthetic regime for older patients.

Disclosures

The authors declare that they have no competing interests.

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Authors' contributions

TS, LH, HS and VvD designed the study, ZS, BG, PG and VvD performed the preparation and collection of the data, LH and HS analyzed the data, TS and LH wrote the draft of the manuscript. TS, LH, HS, ZS, PG, RP and LC discussed the data, VvD, HS and LC proofread and rewrote the manuscript. All authors have read and approved the final manuscript.

Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinane.2022.110957.

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Anhang A: Paper III

Decontamination regimens: do not forget half of the protocol. Author's reply

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CORRESPONDENCE

Decontamination regimens: do not forget half of the protocol. Author's reply

Josef Briegel[1*], Wolfgang A. Krueger[2], Baocheng Wang[1], Ludwig Christian Hinske[1] and Beatrice Grabein[3]

We thank our colleagues for their critical comments, which give us the opportunity to point out the study methods in some more details [1, 2]. First, it is correct that the resistance rates of some multi-drug resistant bacteria (MDRB) differed between groups with and without selective oral decontamination (SOD) already at admission (first 48 h). Importantly, these findings were excluded from the analysis. The objective of the study was to specifically investigate the emergence of MDRB due to selection pressure of SOD in the intensive care unit (ICU). Second, the incidence densities in MDRB are reported as we found them. Clinically important differences in patient characteristics (medical or surgical admission, transplantation, Table 1 in [1]) are not taken into account since the effectiveness of SOD is not modified by the type of ICU admission [3]. Third, the outcome analysis on health care infections and in-hospital death, however, was done after propensity score analysis which was based on seven clinically important variables (Table 2 in [1]). This gave us the opportunity to compare two well balanced groups, especially with respect to type of admission, severity of illness, duration of ventilation and length of stay in the ICU. The effect of propensity score matching on hospital death rate is illustrated in Table 7 of our publication [1]. Of note, the death rates found in the groups after propensity score matching were very similar to those in recent clinical trials [1, 4, 5]. Fourth, we believe that the inclusion of length of stay in the propensity score analysis is a strength of our study, as it generates two homogeneous groups with respect to length of exposure at risk between these groups. From this point of view, it is also justified to compare incidence rates of these two groups. Fifth, as detailed in the methods the protocols for infection control were investigated in all participating ICUs according to guidelines given by a national group of experts of the Robert-Koch-Institut in Berlin, Germany. Quality assurance measures showed strict adherence to recommendations in all ICUs included in our analysis.

The strength of our observational study is the analysis of real-world data over a long period of time without changing the SOD intervention. This differs from recent clinical trials that used cross-over designs [4, 5]. In particular, the 143.842 microbiological tests we evaluated represent a large dataset. We acknowledge that meta-analyses suggest that the full selective digestive decontamination (SDD) regimen including a 4-days course of prophylactic systemic antibiotics may be slightly more effective than SOD alone [3, 6]. In our original controlled trial, we also administered prophylactic intravenous antibiotics [7]. However, in terms of antibiotic stewardship, we find it problematic to argue against overuse of antibiotics as prolonged prophylaxis after complex surgical procedures, and then to implement routine 4-days antibiotic prophylaxis for ventilated patients. So we have not forgotten half of the protocol. Rather, we try to find an appropriate balance between the benefits and risks of antibiotic prophylaxis and feel reassured by the data we have presented in our publication [1].

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Availability of data
Data may be made available in coordination with the authors and LMU University Hospital Munich, Germany.

Declarations

Conflict of interest
The authors declare no conflict of interest.

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