Microbiological Contamination of Drugs during Their Administration for Anesthesia in the Operating Room

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ABSTRACT

Background: The aseptic techniques of anesthesiologists in the preparation and administration of injected medications have not been extensively investigated, but emerging data demonstrate that inadvertent lapses in aseptic technique may be an important contributor to surgical site and other postoperative infections.

Methods: A prospective, open, microbiological audit of 303 cases in which anesthesiologists were asked to inject all bolus drugs, except propofol and antibiotics, through a 0.2-μm filter was performed. The authors cultured microorganisms, if present, from the 0.2-μm filter unit and from the residual contents of the syringes used for drawing up or administering drugs. Participating anesthesiologists rated ease of use of the filters after each case.

Results: Twenty-three anesthesiologists each anesthetized up to 25 adult patients. The authors isolated microorganisms from filter units in 19 (6.3%) of 300 cases (3 cases were excluded), including *Staphylococcus capitis*, *Staphylococcus warneri*, *Staphylococcus epidermidis*, *Staphylococcus haemolyticus*, *Micrococcus luteus/lylae*, *Corynebacterium*, and *Bacillus* species. The authors collected used syringes at the end of each case and grew microorganisms from residual drug in 55 of these 2,318 (2.4%) syringes including all the aforementioned microorganisms and also *Kocuria kristinae*, *Staphylococcus aureus*, and *Staphylococcus hominus*. Participants' average rating of ease of use of the filter units was 3.5 out of 10 (0 being very easy and 10 being very difficult).

Conclusions: Microorganisms with the potential to cause infection are being injected (presumably inadvertently) into some patients during the administration of intravenous drugs by bolus during anesthesia. The relevance of this finding to postoperative infections warrants further investigation. **(Anesthesiology 2016; 124:785-94)**

POSTOPERATIVE infections (*e.g.*, surgical site infections, blood stream infections, and pneumonia) form a substantial proportion of healthcare-associated infections.[1] The potential contribution of anesthesiologists to these infections has largely been overlooked, although it is clear that at least some of their practices could influence the rates at which they occur. For example, ensuring the completion of a bundle of care practices reduced the median rate of bloodstream infections associated with central line insertion from 2.7 per 1,000 catheter-days preintervention to 0 at 3 months,[2] albeit in the context of intensive care. This suggests that other aspects of anesthesiologists' practices could also (a) contribute to postoperative infections and (b) be amenable to improvement.

Anesthesiologists inject many intravenous drugs during every anesthetic—on average 10 bolus injections per patient and sometimes more than 100.[3,4] In a busy perioperative environment, where multiple drugs are drawn up and injected, sometimes with urgency, it is not surprising that aseptic technique may occasionally lapse. The aseptic techniques of anesthesiologists in the preparation and administration of injected medications have not been extensively investigated, but emerging data[5–11] demonstrate that inadequate aseptic technique may be an important, but previously overlooked, contributor to postoperative infections. In a recent study of 20 highly realistic simulated anesthetics using real drugs and standard practices, our group collected

What We Already Know about This Topic

- Postoperative infections represent a significant proportion of healthcare-associated infections
- Anesthesiologists' aseptic technique when making bolus injections of drugs may sometimes be deficient and could lead to postoperative infection
- Anesthesiologists make an average of 10 bolus injections per case

What This Article Tells Us That Is New

- Anesthesiologists were asked to make bolus injections of all drugs, except propofol and antibiotics, through a 0.2-μm filter in a prospective, open, microbiological audit of 300 cases
- Microorganisms with the potential to cause infections were isolated from the 0.2-μm filters of 19 (6.3%) of the 300 cases

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the injected drugs and associated intravenous fluid: we isolated Gram-positive staphylococci, Gram-negative bacilli, and other microorganisms from 5 of 38 bags (13%) of this collected injectate.[5]

The clinical relevance of this disconcerting finding is not clear. In particular, it is difficult to be certain that this result was not an artifact of simulation: perhaps, the same anesthesiologists would have paid more attention to aseptic technique in a clinical setting.

Therefore, we aimed to ascertain the extent to which microorganisms are injected by anesthesiologists in the process of drawing up and administering boluses of intravenous drugs in clinical practice.

Materials and Methods

The clinical study was conducted in adult patients undergoing surgery with anesthesia in 19 operating rooms (ORs) at Auckland City Hospital, Auckland, New Zealand, a tertiary teaching hospital. The laboratory work was carried out in the Department of Molecular Medicine and Pathology, University of Auckland, Auckland, New Zealand. The clinical study was approved by the Northern B Health and Disabilities Ethics Committee, Ministry of Health, Wellington, New Zealand (ref: 13/NTB/80) and registered with the Australian New Zealand Clinical Trials Registry (ref: ACTRN 12613000040763) (Alan F. Merry, Principle investigator; date registered: January 14, 2013). The ethics committee determined that this study was, in effect, a low-risk audit of the participating anesthesiologists' practice. Therefore, formal informed consent was not required from the patients. Instead, they were provided with an information sheet explaining the study, given the opportunity to discuss it with one of the research team, and given the opportunity to opt out of the study if they wished.

We tested the hypothesis that microbiological contamination of intravenous drugs administered during anesthesia occurs more often than 1 of 100 cases (a case being defined as one patient undergoing one anesthetic on one occasion[3]). To this end, we asked participating anesthesiologists to inject their intravenous bolus medications, except propofol (which could not be filtered because of its presentation in an emulsion), drugs given by infusion (because our primary interest was drugs given by intravenous bolus), and antibiotics (because they would inhibit the growth of contaminants) through a 0.2-μm filter unit (B. Braun Melsungen AG, Germany). We expected the filter membranes housed within the unit to trap any microorganisms inadvertently introduced during these injections. However, these units are sealed, which effectively prohibits extracting the membrane for culture without considerable risk of introducing contamination in the process. Therefore, we began by developing a method of quantifying the microorganisms trapped by the filter unit that we could apply to our clinical study.

A Method to Quantify Microorganisms Trapped on the Membrane of a Sealed Filter Unit

Informal experimentation demonstrated that flushing the B. Braun filter unit in the opposite direction to that used for injecting drugs ("backflushing") with 20 ml of a combination of sterile 3% tryptic soy broth, 1% Tween 80, and peptone water was effective in allowing us to release and culture *Staphylococcus epidermidis* previously inoculated onto the filter membrane in loads of approximately 10^5 colony-forming units (CFUs) per milliliter.

To obtain more precise quantification of the effectiveness of this backflushing method, we next prepared standard dilutions of four microorganisms: *S. epidermidis* ATCC 12228, *Escherichia coli* ATCC 25922, *Streptococcus pyogenes* ATCC 8668, and *Candida albicans* ATCC 1212. We cultured these microorganisms at 37°C on horse blood agar or in tryptic soy broth (both Fort Richard, New Zealand). Working with one organism at a time, we harvested an overnight culture by centrifugation at 4,000*g* at 22°C for 10 min and resuspended this in 0.9% sodium chloride (Demo S.A., Greece) at approximately 10^8 CFU/ ml. We made serial dilutions from this suspension under aseptic conditions producing four solutions with four levels of contamination and a control of sterile 0.9% sodium chloride. We injected 10 ml of each of these five solutions through a filter unit. The five filter units were kept under aseptic conditions at 22°C for 1 h to reflect the shortest time interval taken in the clinical study to retrieve filter units from the OR and return with them to the microbiology laboratory for further testing.

We then backflushed 20 ml of combined sterile 3% tryptic soy broth, 1% Tween 80, and peptone water through each of the five filter units using a pulsatile technique.[12] The backflushed fluid was collected in five separate, sterile 20-ml syringes (Becton, Dickinson and Company, USA), and then the content of each syringe was injected through another sterile but differently designed filter unit containing a 0.2-μm membrane. These secondary filter units are not approved for clinical use but are used in the laboratory where they are typically repeatedly resterilized and reused. They can be dismantled, which makes it possible to extract the membrane easily (both unit and membrane from Pall Corporation, USA). The five membranes from these units were retrieved and placed onto a separate blood agar plate. These were incubated at 37°C for 24 to 72 h, and the resulting CFU count was used as a measure of the microorganisms released by backflushing. We also collected the fluid passing through the secondary filter units during this second filtration and incubated it at 37°C for 24 h to establish whether all microorganisms had been captured by the membrane. We repeated this entire sequence five times with each of the five solutions for each of the four microorganisms.

The Clinical Investigation

We approached anesthesiologists at levels of seniority ranging from junior registrar to senior consultant working

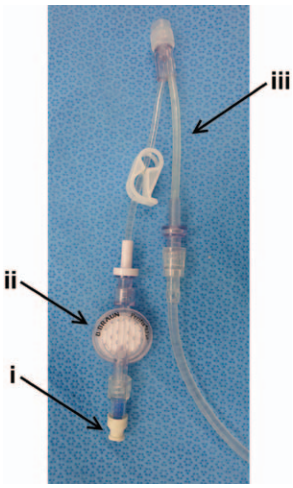

Fig. 1. Clinical setup for the injection port (i), filter unit (ii), and two-way extension line (iii).

Fig. 2. Label attached to the filter arm of the two-way extension line.

within the anesthesia service at Auckland City Hospital and obtained written informed consent from those who agreed to participate. Cases were eligible if scheduled for general anesthesia (with or without regional anesthesia) and cared for by participating anesthesiologists on days of the week when one of the investigators (Derryn Gargiulo) was available.

A filter unit and stopcock were incorporated into the drug administration line *via* a two-way extension set (both CareFusion, USA) by the participant or anesthetic technician after instruction by Derryn Gargiulo. The volume of dead space in the stopcock, filter unit, and filter arm of the two-way extension line (the filter unit "setup") was 1.16 ml (fig. 1). Therefore, the participating anesthesiologists were asked to flush the setup with 0.9% sodium chloride (Demo S.A.; drawn up by them) each time a drug was administered through the setup.

A label was attached to the filter arm of the two-way extension line indicating that it was for medications only, except propofol or antibiotics (fig. 2).

Intravenous fluids were administered *via* the nonfilter arm of the two-way extension. Propofol, drug infusions, and antibiotics were administered *via* a secondary stopcock available for this purpose on the fluid line, thus bypassing the filter unit. Participants were able to use one or more additional intravenous lines and cannulae for additional intravenous fluids or infusions at their discretion.

At the end of each case, the filter unit was removed, and its two ends were sealed with sterile caps (fig. 1). They were taken to the laboratory in zip-locked plastic bags for backflushing and subsequent analysis as described in A Method to Quantify Microorganisms Trapped on the Membrane of a Sealed Filter Unit section. Syringes used to prepare and administer medications during each case were sealed with sterile caps, taken to the laboratory and residual contents analyzed for contamination using quantitative methods described in our previous study.[5]

Care was taken to ensure that no microorganisms were introduced during the handling of the filter units and the syringes. In the laboratory, clean gowns and hats were worn, and sterile gloves were used. All work was undertaken in a validated laminar flow cabinet. Sterile 70% alcohol was used to decontaminate all work surfaces and the external surfaces of the filter units and syringes.[13,14] Senior microbiologists provided oversight of the processes of handling the filter units and syringes in the OR and the laboratory. Two independent senior anesthesiologists acted as monitors of our study method in the OR.

To evaluate the potential for false positives from contamination by the investigators during the testing of the filter units, the backflushing method and analysis were audited with 10 filter units analyzed on each of four separate occasions in conjunction with filter units collected from cases. We injected 10 ml of control solution through these audit filter units and then processed them in the same way as the patient's filter units.

If any microorganisms were grown from membranes or syringe contents, the agar plates were sent to the Clinical Microbiology Laboratory, LabPlus, Auckland City Hospital for identification of the organisms using the matrix-assisted laser desorption/ionization time of flight technique.[15]

At the end of each case, participating anesthesiologists were asked to complete a short form confirming that the study protocol had been followed or giving reasons if not (*i.e.*, if the filter unit setup had been bypassed). They were also asked to rate the ease of use of the setup using an unmarked 10-cm visual analog scale (created for this study) with anchors "very easy" (at 0 cm) and "very difficult" (at 10 cm) and to provide any comments if they so wished. The mean difficulty rating was calculated for each anesthesiologist, and then the mean of these means was calculated.

Sample Size

Our sample size estimate was pragmatic. In our previous simulation-based study,[5] contamination was identified in

13% of cases (5 of 38 bags of collected injectate and intravenous fluid grew microorganisms). We thought that a rate of at least one tenth of this would be very likely in the clinical setting—in other words, more than 1%. We thought, furthermore, that a rate of more than or equal to 1% would be clinically important, even allowing for the fact that only a proportion of injected bacteria are likely to cause harm. Taking these factors into account, we predicated our sample size on the potential interpretation of a negative result. In the event that no bacteria were cultured in any of our cases, it would require 300 cases to ensure that the upper 95% CI of the estimated point incidence of 0% was no higher than 1% and, therefore, allow us to reject our hypothesis with an α of 0.05.

Statistics

Data were entered into a spreadsheet (Microsoft Corporation, USA, 2010), and summary statistics were calculated.

Results

Laboratory Testing

Our method of diluting the broth for preloading the filters produced a range of concentrations of microorganisms in our inoculants. We were able to quantify microorganisms approximately, but reasonably consistently, from filter units loaded from these inoculants, even when the concentrations of microorganisms (estimated from plate counts) were less than 10 CFU. Below this value, the results were less reliable, but organisms could still be grown in most instances.

The fluid collected from the second filtration by the secondary filter unit produced no growth (as shown by clear solutions after incubation), indicating that all microorganisms present in the filtrate were captured by the membrane within the second filter unit.

The quality assurance testing of the "retrieval" method using 10 ml of control solution as inoculant was carried out on 38 of the 40 audit filter units because on two occasions, a sterile secondary filter unit was not available. No growth was obtained from any of these 38 units.

The Clinical Study

Patients, Cases, and Participants. Data were collected from 303 cases over 76 days between August 13, 2013, and June 16, 2014. Three cases were excluded because, respectively, one filter unit was lost in transit, one filter unit broke during testing in the laboratory, and there was a failure in timely supply of the testing supplies on one occasion; thus, the final analysis of filter units was undertaken on 300 cases from 298 patients (2 patients each had a second, different operation).

The cases were managed by 23 participating anesthesiologists (19 specialists, 2 registrars, and 2 fellows) of whom 11 were women and 20 were right handed. Participants managed a mean (range) of 13 (1 to 25) cases each. The distribution of cases with respect to order of the day, day of week, surgical specialty, and duration of anesthesia is presented in table 1.

Table 1. The Order in the Day, Day of Week, Surgical Specialty, and Duration of Anesthesia of the Cases in the Study

Variable	Category	n = 300, n (%)
Order of case in day	First	156 (52)
	Second	96 (32)
	Third	39 (13)
	Fourth	8 (2.7)
	Fifth	0 (0)
	Sixth	1 (0.3)
Day of week	Monday	39 (13)
	Tuesday	89 (30)
	Wednesday	67 (22)
	Thursday	85 (28)
	Friday	20 (7)
Surgical specialty	General surgery	100 (33.3)
	Otolaryngology	81 (27)
	Orthopedics	56 (18.7)
	Urology	25 (8.3)
	Cardiac	18 (6)
	Neurosurgery	9 (3)
	Dental	7 (2.4)
	Vascular	2 (0.7)
	Ophthalmology	1 (0.3)
	Thoracic	1 (0.3)
Duration of anesthesia (min)	0–30	21 (7)
	31–60	61 (20)
	61–90	55 (18)
	91–120	50 (17.7)
	121–480	110 (36.7)
	> 481	2 (0.6)

Microbiology. In total, 301 filter units from 300 cases were tested (two filter units were used on two different intravenous lines in one cardiac case at the request of the participant anesthesiologist). Microorganisms were grown from 19 (6.3%; 95% CI, 4.1% to 9.7%) of these filter units (table 2), collected from 19 cases. These cases were managed by 12 (50%) of the participants: 2 participants managed three cases, 3 more participants managed two cases, and a further 7 participants each managed one case (table 2).

In total, 2,318 syringes were collected from 295 of the cases, a mean (range) of 7 (0 to 16) syringes per case. The remaining five cases were excluded because there was a noted accident in maintaining the integrity of the aseptic collection of the syringes in two cases, one case was interrupted and then abandoned (but the filter unit still collected for analysis), and the syringes were accidently discarded by OR staff in two cases. In 48 (16%) cases managed by 18 (78%) participants, microorganisms were grown and identified from the contents of 55 syringes (tables 2 and 3).

Growth was obtained from both the filter units and (some of the) syringes used by 11 (48%) participants; from the syringes, but not the membranes used by 7 (30%) participants; and from neither the membranes nor the syringes

Table 2. Number of Cases Undertaken, Number of Syringes Collected from Each Participant, Number of Cases with Contaminated Filter Units, and Number of Syringe Contents Contaminated

Participant Number (n = 23)*	No. of Cases Undertaken (%), n = 300	No. of Cases with a Contaminated Filter Unit (%), n = 19	No. of Syringes Collected (%), n = 2,318	No. of Syringe Contents Contaminated (%), n = 55
1	25 (8.3)	2 (10.5)	216 (9.3)	8 (3.7)
2	23 (7.8)	3 (15.7)	145 (6.3)	4 (2.8)
3	23 (7.8)	3 (15.7)	182 (7.9)	0
4	22 (7.3)	2 (10.5)	169 (7.3)	2 (1.2)
5	22 (7.3)	1 (5.3)	186 (8)	3 (1.6)
6	20 (6.7)	1 (5.3)	133 (5.7)	6 (4.5)
7	20 (6.7)	1 (5.3)	181 (7.8)	2 (1.2)
8	17 (5.7)	2 (10.5)	130 (5.6)	4 (2.5)
9	14 (4.7)	1 (5.3)	124 (5.4)	2 (1.6)
10	10 (3.3)	1 (5.3)	73 (3.1)	5 (7.5)
11	9 (3)	1 (5.3)	58 (2.5)	3 (5.2)
12	6 (2)	1 (5.3)	59 (2.6)	5 (8.5)
13	21 (7)	0	129 (5.6)	2 (1.6)
14	17 (5.7)	0	134 (5.8)	1 (0.7)
15	15 (5)	0	98 (4.2)	2 (2)
16	15 (5)	0	124 (5.4)	3 (2.4)
17	5 (1.7)	0	57 (2.5)	2 (3.5)
18	5 (1.7)	0	54 (2.3)	1 (1.9)
19	2 (0.7)	0	22 (0.9)	1 (4.6)
20	6 (2)	0	42 (1.8)	0
21	1 (0.3)	0	12 (0.5)	0
22	1 (0.3)	0	7 (0.3)	0
23	1 (0.3)	0	5 (0.2)	0

*Participants have been numbered to show those with contaminated filters first (1–12) and then those without (13–23), in a descending order of number of cases in each category.

used by 4 (18%) participants. There was one participant from whom we obtained growth from each filter unit in three cases, but no growth in any of the syringes (table 3, participant 3). There was only one case in which the same organism was grown from a filter unit and a syringe (table 3, participant 1).

The cases were managed in 19 ORs. The mean (range) of cases per room was 16 (1 to 52). The cases in which growth was obtained from filters came from 12 ORs and those with growth from syringes came from 16 ORs; 11 ORs had cases where growth was obtained from both filter units and syringes.

Participants' Feedback. In five cases, the participant indicated that propofol was inadvertently injected through the filter unit, and that in two cases, an antibiotic was injected (no microorganisms were grown from the filter unit in any of these seven cases). In 96 cases, the filter unit was bypassed at least once (table 4).

The 23 participating anesthesiologists' mean ratings of ease of use of the filter units ranged from 0.1 to 7.2, with an overall mean of 3.5. In this analysis, 4 of the 300 cases were excluded because the responses were not clear, and 1 case was excluded because no response was given.

The participants' additional comments regarding the study included (among others) references to the extra pressure required to inject drugs though the filter units (11 cases); the consequent slowness of the injections (3 cases); and changes to normal behavior (10 cases).

Discussion

We trapped and grew potentially pathogenic microorganisms injected intravenously during the bolus administration of intraoperative drugs in 6.3% of 300 cases in which patients underwent general anesthesia. We have no reason to doubt the sterility of the drugs provided in ampules or vials and no reason to doubt that their subsequent contamination was other than inadvertent. In 16% of cases, we grew microorganisms from the residual contents of syringes that had been retained by the anesthesiologists, and which might potentially have been used again for further intravenous injections. Collectively, the varieties of microorganism grown from the filter units and syringes were similar, but we found little direct concordance in individual cases between microorganism isolates from the filter units through which drugs were injected and residual drug in retained syringes that had been used to inject these drugs (tables 2 and 3). Some of this species variation may be due to the matrix-assisted laser desorption/ionization time of flight identification: there may be less variation in deoxyribonucleic acid and/or bacterial resistance profile. The precise sources of contamination, and the aspects of practice that need to be addressed to prevent contamination, cannot be determined from this study. Nevertheless, these findings corroborate our previous data[5] and that of others,[6–11] which suggest that anesthesiologists' aseptic techniques, in relation to the injection of drugs by bolus, may sometimes be deficient.

Table 3. Microorganisms Recovered from Filter Membranes and Syringe Contents, by Participant and Case

Participant Number (n = 23)	Case	Microorganisms Recovered from Filter Units (n = 19)	Microorganisms Grown from Syringe Contents (n = 55)	Syringe Contents, as Labeled (n = 55)
1	A	*Staphylococcus capitis*	*S. capitis*	0.9% sodium chloride
	B	*Staphylococcus epidermidis*	No growth (NG)	NG
	C	NG	Mixed micrococcus	Midazolam
	D	NG	*S. epidermidis*	0.9% sodium chloride
	E	NG	*S. epidermidis*	0.9% sodium chloride
	F	NG	*S. capitis*	Metaraminol
	G	NG	*Staphylococcus* species*	0.9% sodium chloride
	H	NG	*S. capitis*	Metaraminol
			Staphylococcus hominis	Metaraminol
	Cases I–Y	NG		
2	A	*Corynebacterium* species	*Micrococcus luteus/lylae*	Fentanyl
	B	*S. epidermidis*	NG	NG
	C	*Staphylococcus haemolyticus*	NG	NG
	D	NG	*S. epidermidis*	0.9% sodium chloride
	E	NG	*S. hominis*	Propofol
	F	NG	*S. haemolyticus*	0.9% sodium chloride
	Cases G–W	NG		
3	A	*S. capitis*	NG	NG
	B	*M. luteus/lylae*	NG	NG
	C	*S. capitis*	NG	NG
	Cases D–W	NG		
4	A	*Bacillus* species	NG	NG
	B	*Staphylococcus warneri*	NG	NG
	C	NG	*M. luteus/lylae*	0.9% sodium chloride
	D	NG	*Cornybacterium* species	Propofol
	Cases E–V	NG		
5	A	*S. warneri*	NG	NG
	B	NG	*S. epidermidis*	0.9% sodium chloride
	C	NG	*Micrococcus* species	Unlabeled
	D	NG	*S. capitis*	Dexamethasone
	Cases E–V	NG		
6	A	*S. capitis*	*S. hominis*	Fentanyl
			S. hominis	Other
	B	NG	*Bacillus circulans*	0.9% sodium chloride
	C	NG	*S. epidermidis*	Fentanyl
			S. epidermidis	0.9% sodium chloride
			S. epidermidis	Other
	Cases D–T	NG		
7	A	*S. warneri*	*S. capitis*	Fentanyl
	B	NG	*S. warneri*	0.9% sodium chloride
	Cases C–T	NG		
8	A	*S. epidermidis*	NG	NG
	B	*S. capitis*	*S. epidermidis*	Propofol
	C	NG	*S. epidermidis*	Propofol
	D	NG	*S. haemolyticus*	Propofol + fentanyl
	Cases E–Q	NG		
9	A	*S. epidermidis*	NG	NG
	B	NG	*S. epidermidis*	Propofol
	C	NG	*S. epidermidis*	Propofol
	Cases E–N	NG		

(*Continued*)

Table 3. (Continued)

Participant Number (n = 23)	Case	Microorganisms Recovered from Filter Units (n = 19)	Microorganisms Grown from Syringe Contents (n = 55)	Syringe Contents, as Labeled (n = 55)
10	A	*S. capitis*	*Staphylococcus caprae*	Fentanyl
			Staphylococcus species*	Unlabeled
	B	NG	*S. epidermidis*	Unlabeled
	C	NG	*S. epidermidis*	Propofol
	D	NG	*S. capitis*	0.9% sodium chloride
	Cases E–J	NG		
11	A	*S. warneri*	*Bacillus* species	0.9% sodium chloride
	B	NG	*S. hominis*	Fentanyl
	C	NG	*Staphylococcus aureus*	Propofol
	Cases D–I	NG		
12	A	*S. warneri*	*Kocuria kristinae*	Fentanyl
	B	NG	*K. kristinae*	Fentanyl
			K. kristinae	Metaraminol
	C	NG	*K. kristinae*	0.9% sodium chloride
	D	NG	*S. capitis*	Unlabeled
	Cases E and F	NG		
13	A	NG	*S. epidermidis*	Unlabeled
	B	NG	*S. capitis*	Propofol
	Cases C–U	NG		
14	A	NG	*Bacillus* species	Magnesium sulphate
	Cases B–Q	NG		
15	A	NG	*S. epidermidis*	Propofol
	B	NG	*S. capitis*	Ondansetron + dexamethasone
	Cases C–O	NG		
16	A	NG	*K. kristinae*	Dexamethasone
	B	NG	*M. luteus/lylae*	Fentanyl
	C	NG	*S. warneri*	0.9% sodium chloride
	Cases D–O	NG		
17	A	NG	*S. epidermidis*	Fentanyl
	B	NG	*S. epidermidis*	Propofol
	Cases C–E	NG		
18	A	NG	*S. epidermidis*	Unlabeled†
	Cases B–E	NG		
19	A	NG	*S. haemolyticus*	Propofol + lidocaine
	Case B	NG		
20	Cases A–F	NG		
21	A	NG		
22	A	NG		
23	A	NG		

*Not *S. aureus.* †Syringe was unlabelled, but contents were visually identified as propofol.

To what extent were the isolates retrieved from the filter units a true reflection of our patients' actual exposure to microorganisms injected inadvertently with intravenous bolus drugs during anesthesia? It is difficult to completely rule out the possibility that at least some of the cultured microorganisms could have been introduced during the collection and flushing of the filter units. However, we took considerable care to avoid introducing microorganisms in our handling of the filters and syringes. Furthermore, the data from the testing of the 38 sterile filter units included to audit this aspect of the study are reassuring.

One related limitation in our development of the backflush technique is that only four microorganisms were tested. These were chosen to align with previous research,[5] to include common environmental[16] and population-based microorganisms[17] likely to be associated with postoperative infections, and to include an example of a coccus, a bacillus, and a yeast. Other microorganisms, *e.g.*, endospore-forming bacteria may behave differently. Similarly, only one type of commercial filter unit was studied; alternative brands with different filter materials may show different characteristics when backflushed.

Table 4. Reasons for Bypassing Filter Unit (More than One Reason Could Be Given for Each Case)

Reason	Cases (n = 96)
Inadvertence	36
Emergency	13
No reason given	15
Before or after setup connected	14
Other*	18

*Drug given by nonconsented, secondary anesthesiologist unfamiliar with the study (four cases); drugs given directly into bypass circuit (two cases); to check line patency (four cases); difficulty of initial line patency so drugs not given *via* setup (four cases); premedication drugs given quickly as patient anxious (two cases); reversal of muscle relaxant given directly into stopcock to ensure patient received dose (one case); and unable to decipher answer (one case).

Weaknesses of this study include the use of a sample of convenience and the fact that the study was conducted in one center only; these results might not apply to other anesthesiologists or other centers. On the other hand, there is no particular reason to assume that that the practices evaluated here would be in any way unusual. We acknowledge that relieving anesthesiologists, who were not participants, managed the participants' cases for periods of time, but we do not believe that this changes the clinical relevance of our finding—our study was not directed at individual practitioners, but rather at the overall process by which intravenous drugs are administered to patients during anesthesia. Our rating scale for ease of use of the filters was not formally validated, but it was similar to visual analog scales used in many previous studies (*e.g.*, in the study by Merry *et al.*[3]). We assumed that the 0.2-μm filter units performed to specifications, but we did not verify this; the filter unit was bypassed at least once in almost a third of our cases for various reasons (table 4): these points also have implications for the potential utility of such filters in addressing the problem of inadvertently injected microorganisms.

The potential confounding of our data by failure of the filter units to trap all organisms, or failure of the backflush method to retrieve all trapped microorganisms, could have resulted in our underestimating the exposure of patients to microorganisms by the intravenous route. In addition, although anesthesiologists were encouraged to behave "normally" in respect of their aseptic practice, the open-label nature of the study may have influenced them to be more fastidious. Given propofol's known ability to promote the growth of microorganisms,[18] its exclusion from injection through the filter units is also relevant. Thus, there were several potential confounders that could have resulted in our underestimating of the rate of intravenous injection of microorganisms. However, the use of the filter unit on a Y-connector and the associated need to flush boluses of drug into the intravenous line using sodium chloride involved more opportunities for contamination. Any failures in our own handling of filter units and syringes might also have inflated our results. Therefore, it is possible that our data could either overestimate or underestimate the true incidence of intravenous injection of microorganisms. Ultimately, it is the order of magnitude of our result that matters, more than the exact rate. We selected 1% as the threshold for *clinical* concern in our hypothesis; this was a subjective judgment, which took into account factors discussed in the following paragraph, but, arguably, the injection of intravenous drugs should be accomplished in a sterile fashion, and in the context of processes control, it would be reasonable to expect a failure rate very close to 0 and certainly less than 1%.

The extent to which microorganisms from the bolus injection of intravenous drugs might contribute to postoperative infections is not clear. Microorganisms may be present in the blood stream without causing harm, after brushing one's teeth for example.[19] In at least some patients, any injected microorganisms may be adequately dealt with by the immune system and through the use of prophylactic antibiotics (which are given routinely for many surgical procedures). However, the operative wound is an ideal environment for microorganisms, seeded through the bloodstream, to establish infection, particularly given that many patients undergoing surgery and anesthesia are debilitated or ill or may have reduced immune responses.[20–22] It seems at least plausible that injecting microorganisms in this way could contribute to some postoperative infections in at least some patients. Recent research has found 18.6% of injection ports (on stopcocks) in intravenous lines used for drugs other than propofol and 17.3% of those used for propofol to be contaminated with microorganisms at 6 h after first use.[23] This potential source of contamination may be *additional* to that demonstrated by our results or may explain some or all of our results. A filter strategy would likely be an effective way to reduce blood stream contamination in either case, at least for drugs other than propofol, because the injection port on the filter unit is proximal to the filter membrane. In the end, the clinical relevance of these potential sources of infection will need to be evaluated through a randomized controlled trial of an intervention to prevent or at least reduce them.

The question arises, then, of how one might reduce the frequency with which anesthesiologists inadvertently inject microorganisms while injecting intravenous drugs through injection ports, given that it is difficult to change embedded clinical practices (this can be seen, *e.g.*, in the difficulty improving practice in relation to hand hygiene[24–26]). Our ease-of-use ratings confirm that it would be practical for anesthesiologists to routinely include 0.2-μm filter units into their cases. It would not be possible to inject propofol through the filter units, and, as discussed earlier, some microorganisms might pass through the filters, but the majority of bolus injections could be filtered, and the load of injected microorganisms could be substantially reduced. Therefore, we plan a study in which we will test the hypothesis that using filter units of this type will reduce subsequent postoperative infections. Our results

reinforce the importance of meticulous aseptic technique in administering intravenous injections, particularly when using high stakes access points, such as central venous catheters and peripherally inserted central catheters (where the opportunity for catheter-related blood stream infection is ever present). The routine use of an alcohol wipe of the septum before accessing drug vials may also warrant emphasis (data from the study by Hilliard *et al.*[27] and from our previous simulation-based study[5] suggest that the value of this may not be fully appreciated in New Zealand and elsewhere).

In the meantime, we conclude that microorganisms with the potential to cause infection are being injected into at least some patients during the administration of intravenous bolus drugs during anesthesia. Clearly this could include any pathogen present in the OR environment.[28] Strategies to reduce this potential source of infection should be developed.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available from Dr. Merry: a.merry@auckland.ac.nz. Raw data available from Dr. Merry: a.merry@auckland.ac.nz.

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