

associated with death are inconsistent, because cost can be high, for example with death after many days in the ICU, or low with sudden postoperative death.

How can we reconcile Pearse and colleagues' study with that by Wunsch and colleagues,² who looked at variation in critical care services across the USA, Canada, and western Europe? Wunsch identified a substantial difference in ICU admissions, for example a ten-times difference between the USA and Germany, and a seven-times difference between the UK and Germany. The Netherlands, with one of the lowest mortality rates in Pearse and colleagues' study, was in the lowest rank in terms of availability of ICU beds of the eight countries assessed by Wunsch and colleagues. Such data suggest that quality assurance in surgery relies on several factors, of which the availability of ICU beds is only one. In future studies, we need to learn more about the relevant issues and optimum processes to secure quality. Targets could include the type of intensive care beds needed, volume, university versus community hospitals, and surgeons' qualifications. Costs for the overall postoperative course would also be key, to allow us to propose cost-effective and relevant corrective measures.

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We declare that we have no conflicts of interest.

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Should intravenous catheters be replaced routinely?

Currently the US Centers for Disease Control and Prevention (CDC) state that peripheral catheters do **not need to be replaced more frequently than every 72–96 h** to reduce the risk of infection and phlebitis in adults.¹ Although results from some observational studies have shown that the risk of phlebitis rises with increasing catheter dwell time,^{2–4} other studies have **not** confirmed this finding.^{5–8} Catheter replacement trials are frequently limited by study design and small sample size.^{6,8} Therefore, the study in *The Lancet* by Claire Rickard and colleagues,⁹ which compares intravenous catheter replacement in adults every **3 days** with replacement when clinically **indicated**, is a major contribution to this debate. It is a large (3283 patients), multisite,

randomised trial with high quality methods, excellent enrolment (97%) and follow-up (100%), and broad inclusion criteria.

The investigators postulated that occurrence of phlebitis and other complications would be equivalent when intravenous catheters were replaced when clinically indicated compared with routine changes every third day. Indeed, the occurrence of the primary outcome of phlebitis was 7% in both groups (absolute risk difference 0.41%, 95% CI –1.33 to 2.15). Rickard and colleagues acknowledge that the non-masking of research nurses was a limitation that could have biased the recording of phlebitis. However, the high quality of this study provides a strong basis for their



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conclusion that a fifth of patients will avoid unnecessary procedures when catheters are changed as clinically indicated. Indicative of the realities of a busy acute care setting, 30% of catheters in the routine change group were not changed as frequently as required. Although this nonadherence decreased the difference between groups in catheter dwell times, in view of the costs associated with routine catheter changes, the potential benefits of clinically indicated catheter changes are still very large indeed.^{3,6,10}

Occurrence of phlebitis in this study was low compared with other reports^{3,6,7} but within the 1–7% occurrence reported with polyurethane intravenous catheters.^{3,4,11} Use of polyurethane catheters, insertion of 40% of catheters by an intravenous insertion team, and daily presence of research nurses at study sites might have contributed to this low level of phlebitis. Factors such as catheter material, insertion procedures, and personnel^{6,11–13} are associated with an increase in the rates of phlebitis and catheter-related infection. Therefore, the findings of this study might not be generalisable to settings in which different types of intravenous catheters and insertion and maintenance procedures are used.

Because the median catheter dwell time of 84 h (IQR 64–118) in the clinically indicated group is within the CDC guidelines of up to 96 h, some clinicians might argue that these findings are not enough to support a policy of clinically indicated catheter changes for intravenous therapy of more than 96 h. However, there was nothing to suggest an increase in the risk of phlebitis when catheters were used for longer periods. Additionally, no data suggested that patients who required catheters for longer periods were more prone to catheter-related bloodstream infection. A quarter had catheters in situ for more than 5 days with no evidence of infection, and only one person (who was in the routine change group) had a catheter-related bloodstream infection. Although catheter colonisation was 5%, this finding was not associated with bloodstream infection, confirming previous reports that catheter contamination is a poor predictor of infection.¹⁴ To prevent complications, Rickard and colleagues emphasise that a policy of resiting of intravenous catheters as indicated must be accompanied by close monitoring and prompt removal of catheters at the completion of treatment and when complications occur.

A major finding of this study was the high proportion of catheter failures, at nearly 30%. The failure of catheters due to infiltration, occlusion, or accidental removal was far more frequent than phlebitis and infection. Therefore, future studies that identify means of prevention of such catheter failures might have even greater implications for cost, reduction of unnecessary invasive procedures, and staff workloads than the present findings.

This is a worthy paper describing a large scale, pragmatic, real-world trial that shows the potentially very large benefits in questioning of accepted practices. Clinically relevant studies such as this one are very important to improve evidence for clinical practice. Discontinuation of unnecessary practices is ever more important when clinical demands and health budgets continue to increase. Since routine replacement of intravenous catheters does not seem to decrease phlebitis and infection, future clinical practice should focus less on routine catheter changes and more on the resources, training, and education needed to ensure the highest level of care in the insertion, maintenance, and assessment of intravenous catheters.

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Perioperative mortality in developed and developing countries



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For the **Anesthesia Patient Safety Foundation** see <http://www.apsf.org>

For the **Australian Incident Monitoring System** see <http://www.apsf.net.au/history.php>

For the **Safety Committee of the Association of Anaesthetists of Great Britain and Ireland** see <http://www.aagbi.org/safety/safety-and-standards-committee/committees/safety-committee/>

Ether-based anaesthesia was introduced by William Morton in 1846. General anaesthesia has since been regarded as one of the most important medical advances; it has facilitated life-saving and enhancing surgical procedures and has protected patients from suffering and physiological duress. However, this advance came with a high toll. Until recent decades, there was a substantial risk of adverse events with general anaesthesia, and many patients died.¹ Anaesthetists, recognising the need to prevent devastating complications, established patient safety initiatives and foundations. Examples include the Anesthesia Patient Safety Foundation in the USA, the Australian Incident Monitoring System, and the Safety Committee of the Association of Anaesthetists of Great Britain and Ireland. Safer anaesthetic drugs were introduced, new surgical and anaesthetic techniques were pursued, pulse oximetry and capnography were incorporated into anaesthetic practice, simulation was included in training, and process improvement checklists were implemented.²

Daniel Bainbridge and colleagues,³ using a meta-regression technique, took on the daunting task of reviewing the published medical work on anaesthesia-related mortality, cardiac arrest, and overall perioperative mortality over six decades in countries around the world, and report their provocative findings in *The Lancet*. They confirm the impression that perioperative mortality, defined as death from any cause within 48 h of surgery, has been steadily declining from an estimated 1.06% (95% CI 1.04–1.08) before the 1970s to 0.12% (0.11–0.12) in the 1990s–2000s. This improvement was noted despite data showing that patients with more severe and uncontrolled morbidities are undergoing surgery today than in the past. Encouragingly, this declining pattern was evident both in developed and in developing countries. Nevertheless, a discomfiting finding is that, over the past six decades,

perioperative mortality has consistently been much higher in developing than in developed countries. Furthermore, the decrease in mortality and cardiac arrests has been more extensive in developed than developing countries.

Bainbridge and colleagues’ findings³ are of considerable interest, and we agree with the investigators that evidence-based interventions should be implemented to mitigate some of the disparities between developed and developing countries. Fortunately, many of the recent gains in patient safety in developed countries are based on process improvement, not expensive technologies. For example, the Safe Surgery Saves Lives Study,⁴ undertaken under the banner of WHO, showed that a structured checklist, with simple interventions spanning the perioperative period, could markedly affect mortality and improve surgical outcomes: 30-day mortality among patients undergoing non-cardiac surgery was decreased from 1.5% to 0.8% after introduction of the checklist. This effect was noted across the entire gamut of developed and developing countries.

However, Bainbridge and colleagues’ findings³ must be placed into a broader context to avoid a sense of complacency in developed countries. All but four of the included studies described deaths that occurred intraoperatively or within the first 48 h postoperatively. This procedure-centric definition belies the reality of perioperative patient outcomes. We know from large epidemiological studies that 30-day all-cause perioperative mortality for patients undergoing a broad range of in-patient surgeries remains between 1% and 2%.^{5,6} There is less information on intermediate-term mortality, but from studies including both high-risk and broad surgical patient populations we can estimate that 1-year mortality is alarmingly high—between 5% and 10%.^{7,8} The logistical and cost challenges of tracking patient outcomes far beyond

Routine versus clinically indicated replacement of peripheral intravenous catheters: a randomised controlled equivalence trial

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Summary

Background The millions of peripheral intravenous catheters used each year are recommended for 72–96 h replacement in adults. This routine replacement increases health-care costs and staff workload and requires patients to undergo repeated invasive procedures. The effectiveness of the practice is not well established. Our hypothesis was that clinically indicated catheter replacement is of equal benefit to routine replacement.

Methods This multicentre, randomised, non-blinded equivalence trial recruited adults (≥ 18 years) with an intravenous catheter of expected use longer than 4 days from three hospitals in Queensland, Australia, between May 20, 2008, and Sept 9, 2009. Computer-generated random assignment (1:1 ratio, no blocking, stratified by hospital, concealed before allocation) was to clinically indicated replacement, or third daily routine replacement. Patients, clinical staff, and research nurses could not be masked after treatment allocation because of the nature of the intervention. The primary outcome was phlebitis during catheterisation or within 48 h after removal. The equivalence margin was set at 3%. Primary analysis was by intention to treat. Secondary endpoints were catheter-related bloodstream and local infections, all bloodstream infections, catheter tip colonisation, infusion failure, catheter numbers used, therapy duration, mortality, and costs. This trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12608000445370.

Findings All 3283 patients randomised (5907 catheters) were included in our analysis (1593 clinically indicated; 1690 routine replacement). Mean dwell time for catheters in situ on day 3 was 99 h (SD 54) when replaced as clinically indicated and 70 h (13) when routinely replaced. Phlebitis occurred in 114 of 1593 (7%) patients in the clinically indicated group and in 114 of 1690 (7%) patients in the routine replacement group, an absolute risk difference of 0.41% (95% CI -1.33 to 2.15%), which was within the prespecified 3% equivalence margin. No serious adverse events related to study interventions occurred.

Interpretation Peripheral intravenous catheters can be removed as clinically indicated; this policy will avoid millions of catheter insertions, associated discomfort, and substantial costs in both equipment and staff workload. Ongoing close monitoring should continue with timely treatment cessation and prompt removal for complications.

Funding Australian National Health and Medical Research Council.

Introduction

Up to 70% of patients in acute care hospitals need a short peripheral intravenous catheter; about 200 million are used each year in the USA alone.^{1,2} Intravenous catheters frequently fail before the end of treatment because of irritation of the vein (phlebitis) with symptoms including pain, swelling, redness, occlusion, and a palpable venous cord. Phlebitis necessitates catheter removal and replacement. Peripheral intravenous catheter-related bloodstream infection is a less frequent but serious complication, occurring in about 0.1% of intravenous catheters or 0.5 per 1000 catheter days.³

Intravenous catheters are often needed for a week or more, but have been recommended for regular removal and replacement with a new catheter in an attempt to decrease both phlebitis and infection. Replacement requires additional needlesticks for patients, increases work for clinical staff, and contributes to insertion of

intravenous catheters being the most common invasive medical procedure and therefore a substantial contributor to health-care costs.² Routine intravenous catheter replacement no more frequently than every 72–96 hours is currently recommended for adults by the US Centers for Disease Control and Prevention (CDC).⁴ By contrast, the CDC recommends not to routinely replace intravenous catheters in children, or in high-risk catheters, such as arterial, haemodialysis, and central venous catheters, for which research has shown routine replacement does not prevent infection.^{4,5}

Modern intravenous catheters are made of low-irritant materials and might not need routine replacement. Results of well-designed observational studies have shown that longer dwell time increases daily phlebitis risk in a linear rather than exponential manner (ie, more intravenous catheter days overall increases risk, but later days of cannulation are not higher risk than

Lancet 2012; 380: 1066–74

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earlier days).^{6–8} Thus, routine replacement of intravenous catheters might not benefit patients overall, since the same number of complications might be spread between larger numbers of devices. In 2007–10, results of four randomised controlled trials (n=200–755) supported clinically indicated removal of intravenous catheters as a safe alternative to routine replacement.^{9–12} Despite this evidence, concerns have remained about whether abandoning this established practice would increase bloodstream infections.¹ The 2011 CDC guidelines designate clinically indicated replacement of intravenous catheters as an unresolved issue, indicating that more research is needed.⁴

We aimed to understand the effect of extension of intravenous catheter dwell-time beyond 3 days with replacement of catheters only for clinical reasons. We postulated that patients who had intravenous catheters replaced when clinically indicated would have equivalent rates of phlebitis, and no difference in other complications, but reduced costs and number of catheter insertions, compared with patients with catheters removed every third day.

Methods

Study design and participants

We did this multicentre, non-blinded, randomised controlled equivalence trial in three university-affiliated, government hospitals in Queensland, Australia (Royal Brisbane and Women's Hospital, Herston; Princess Alexandra Hospital, Woolloongabba; and Gold Coast Hospital, Southport). Recruitment was from May 20, 2008, until the target sample size was achieved on Sept 9, 2009.

Research nurses screened medical and surgical units daily for participants. Patients aged at least 18 years with an intravenous catheter in place and expected treatment of longer than 4 days were eligible. Exclusion criteria were bloodstream infection, planned removal of intravenous catheter within 24 h, or intravenous catheter already in situ for more than 72 h. We permitted intravenous catheters inserted in any clinical area, including the emergency department and operating room. Intravenous catheters inserted in an emergency were not eligible (hospital policies required that these be replaced within 24 h). Intravenous catheters could be inserted by any nurse or doctor or by intravenous insertion teams (with no post-insertion care) in two of the hospitals. The ethics committee at each hospital and at Griffith University approved the protocol. We obtained written, informed consent from all participants before enrolment.

Randomisation and masking

Patients were randomly assigned to one of two treatment groups (simple randomisation with 1:1 ratio, no blocking, stratified by hospital). Random allocations were computer-generated on a hand-held device, at the point of each patient's study entry, and thus were

concealed to patients, clinical staff, and research staff until this time. Patients and clinical staff could not be masked after allocation because of the nature of the intervention. Research nurses were similarly not masked because they had to allocate patients to the treatment group and monitor the integrity of the intervention. However, laboratory staff were masked for rating of all microbiological endpoints, and a masked, independent medical rater diagnosed catheter-related infections and all bloodstream infections. We did blinded inter-rater reliability checks on a subset of phlebitis assessments.

Procedures

Patients in the clinically indicated group had their intravenous catheters removed only for completion of therapy, phlebitis, infiltration, occlusion, accidental removal, or suspected infection. Patients in the routine replacement group had their intravenous catheters replaced every third calendar day, unless clinical reasons made this impossible (eg, intravenous catheters failed before day 3, or patient unable to be recannulated). The day 3 resite occurred at about 72 h (48–96 h depending on insertion and removal times). Investigators and research nurses had no involvement in the decision to remove intravenous catheters, or to order cultures, and did not resite the catheters. Preinsertion skin disinfection was with 2% chlorhexidine in 70% ethanol. Insyte Autoguard 30 mm intravenous catheters (BD Medical, Franklin Lakes, NJ, USA) and Tegaderm 1624W transparent dressings (3M, St Paul, MN, USA) were used, with dressings replaced weekly and when soiled or loose. Chlorhexidine-impregnated sponges were not used. We placed no restriction on products administered through the intravenous catheters. Patients generally entered the study with their first intravenous catheter,

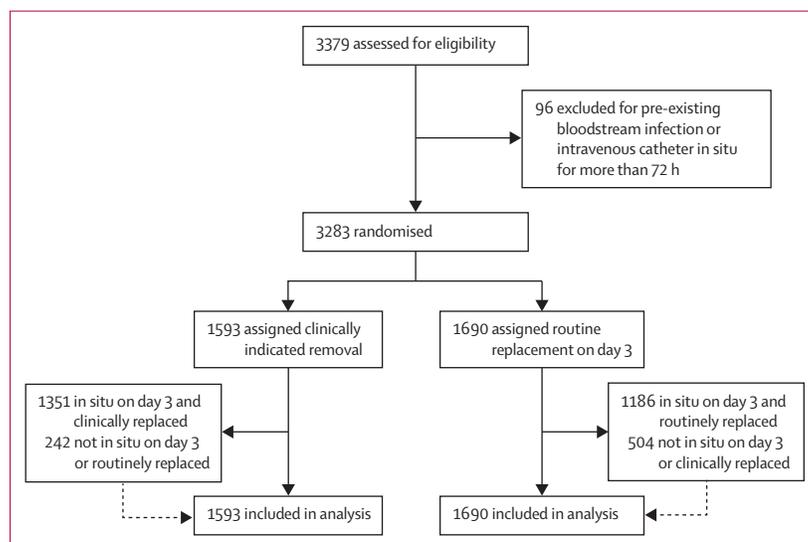


Figure 1: Study profile of patient flow

and all subsequent intravenous catheters (maximum five) for a course of treatment were included. An independent data and safety monitoring committee reviewed blinded data at two a-priori defined intervals (n=1000 and n=2000), and recommended that the trial continue. Stopping rules were a greater than 2:1 ratio in either group for phlebitis or catheter-related bloodstream infection.

The primary outcome was phlebitis during catheterisation or within 48 h after removal.^{8,13} Phlebitis was two or more of the following, present simultaneously: (1) patient-reported pain or tenderness (on questioning, then palpation by the research nurse) with a severity of two or more on a ten-point scale; (2) erythema, extending at least 1 cm from the insertion site; (3) swelling, extending at least 1 cm from the insertion site; (4) purulent discharge; or (5) palpable venous cord beyond the intravenous catheter tip. All items apart from patient-reported pain or tenderness were rated by the research nurse after direct assessment of the patient, and review of clinical data. Phlebitis measures were repeated daily, and at 48 h after removal (by telephone if the patient had been discharged). A structured outcome assessment form was used and inter-rater reliability testing was done. A study manager visited each site at least monthly and was available to the research nurses at any time over the telephone. She audited study data for completeness and accuracy against hospital records and supervised the research nurses for compliance with study procedures. Monthly meetings were held by the investigators, research nurses, and the study manager to review progress and ensure consistency between sites.

	Clinically indicated (n=1593)	Routine replacement (n=1690)
Intravenous catheter dwell time (h)*		
Mean (SD)	99 (54)	70 (13)
Median (IQR)	84 (64–118)	70 (57–77)
Age (years)	55.1 (18.6)	55.0 (18.4)
Men	1022 (64%)	1034 (61%)
Type of admission		
Medical	292 (18%)	331 (20%)
Surgical	1301 (82%)	1359 (80%)
Comorbidities		
None	387 (24%)	411 (24%)
One	350 (22%)	372 (22%)
Two or more	856 (54%)	907 (54%)
Present wound infection	256 (16%)	244 (14%)
Wound drain	95 (6%)	116 (7%)
Stoma	27 (2%)	37 (2%)

Data are mean (SD) or n (%). *Per protocol, N=1351 clinically indicated; N=1186 routine replacement.

Table 1: Baseline demographics and clinical characteristics of patients

Secondary endpoints were: (1) catheter-related bloodstream infection, defined as positive blood culture from a peripheral vein; clinical signs of infection (ie, fever, chills, or hypotension); no other apparent source for the bloodstream infection except the intravenous catheter (in situ within 48 h of the bloodstream infection); and a colonised intravenous catheter tip culture with the same organism as identified in the blood;¹⁴ (2) all-cause bloodstream infections, defined as any positive blood culture drawn from a peripheral vein while intravenous catheter in situ or for 48 h after removal; (3) local venous infection, defined as organisms grown from purulent discharge or vein segment with no evidence of associated bloodstream infection;¹⁴ (4) colonisation of intravenous catheter tip, with more than 15 colony-forming units¹⁵ (substudy of a convenience sample of 5% of patients, ie, catheters that were removed on days and times that the research nurses were available to take cultures); (5) infusion failure, defined as any premature removal of intravenous catheter before end of treatment, other than for routine replacement—includes phlebitis, infiltration, occlusion, accidental removal, and catheter-related bloodstream infections; (6) number of intravenous catheters needed per patient for course of treatment; (7) overall duration of intravenous therapy (cumulative of all intravenous catheters) per patient (h); (8) costs per patient for the course of intravenous therapy, based on equipment required for insertion and removal of intravenous catheters¹² with prices from negotiated hospital supply contract rate; and (9) mortality with intravenous catheter in situ or within 48 h of removal, collected from hospital records. Hospital costs were set at AU\$25.13 for intravenous catheter plus administration set, burette, and fluid bag; \$21.83 for intravenous catheter plus administration set and fluid bag; \$12.73 for intravenous catheter plus end cap; and \$0.37 gauze and tape for removal; and staff time (observed rates of 14.5 min per insertion and 4.5 min per removal at fixed industrial award wages for registered nurses of \$32.93/h, junior [\$45.96/h] and senior [\$67.16/h] medical staff). Catheters inserted by intravenous insertion teams were costed at registered nurse rates; intravenous catheters inserted in an operating theatre or radiology suite were costed at senior medical officer rates, and other insertions were costed at junior medical officer to registered nurse rates in a 3:1 ratio (on the basis of internal observations). We did not include the cost of treating complications associated with intravenous catheters (since treatment typically consisted only of removal and replacement of the affected intravenous catheter, which was already accounted for in the cost calculations).

Statistical analysis

We used a two-sided design to test equivalence between groups. The sample size was calculated to detect equivalence at 4% phlebitis¹¹ (equivalence margin 3%) with 5% significance and more than 95% power. This

determined a total sample of 3000 patients, plus 300 to allow for attrition. Data were entered directly into a purpose-built Microsoft Access (version 97) database. We used SPSS (version 18) and StataSE (version 10) for analyses.

Baseline characteristics of patients and catheters were described by group. The primary analysis was by intention to treat, including all patients (and all catheters) in their randomised group. First, we calculated relative incidence rates of phlebitis and absolute rate differences per 100 catheters and per 100 patients, and we then used two-sided Fisher's exact test to assess equivalence in risk between groups. Second, we calculated hazard rates per 1000 catheter hours, with 95% CI, with a Cox proportional hazards model (assumptions were checked) to summarise the effect of intervention per patient (including all catheters per patient). Finally, we used Kaplan-Meier survival curves to compare rates of time until first phlebitis per patient between groups.

We also did a per-protocol analysis. Specifically, we analysed the first intravenous catheter per patient remaining in situ on day 3 that was treated as per the random allocation. Rates per 1000 days for this analysis consisted of aggregated rate comparisons (incident rate ratios) instead of hazard ratios (HR), we did not compare groups for survival from phlebitis beyond day 3, since in this analysis all intravenous catheters in the routine resite group were removed on day 3. We calculated intravenous catheter dwell times from this analysis since only first catheters were assessed prospectively as required for 4 days or more, and to estimate the difference in catheterisation that clinically indicated removal would achieve. We retrospectively assessed power to detect equivalence with the per-protocol analysis.

We compared patient-level costs and the number of peripheral intravenous catheters used per patient with arithmetic means and the independent sample *t* test; we used bootstrapping with 1000 replications to calculate 95% CI for costs.¹⁶ We collected resource-use data as how many catheters a patient had fitted and removed, and the costs associated with the insertion setting (eg, by staff in the operating theatre vs the medical and surgical wards). We compared overall treatment time (all intravenous catheters) between groups with the median, quartile, range, and Mann-Whitney test. We deemed *p* values less than 0.05 to be significant.

This trial is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12608000445370.

Role of the funding source

The sponsor had no involvement in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the report. The corresponding author had full access to study data and final responsibility in submitting the report for publication.

Results

Of 3379 eligible patients, 3283 were enrolled, and no patient withdrew consent (figure 1). In total, we studied 5907 intravenous catheters and 17412 catheter days (clinically indicated 8693 days; routine replacement 8719 days). Tables 1 and 2 show patient and catheter characteristics. Protocol adherence was 85% in the

	Clinically indicated* (n=2692)	Routine replacement† (n=3215)
Inserted by		
General clinical staff	1656 (62%)	1856 (58%)
Intravenous insertion service	1002 (38%)	1320 (42%)
Catheter gauge		
≤18	430 (16%)	481 (15%)
20	1517 (57%)	1746 (54%)
≥22	736 (27%)	984 (31%)
Insertion in		
Ward	2002 (74%)	2467 (77%)
Emergency	276 (10%)	305 (9%)
Operating theatre or radiology	361 (13%)	386 (12%)
Other	53 (2%)	57 (2%)
Skin integrity		
Poor	116 (4%)	153 (5%)
Fair	767 (29%)	849 (26%)
Good	1809 (67%)	2213 (69%)
Vein quality		
Poor	381 (14%)	499 (16%)
Fair	928 (35%)	1154 (36%)
Good	1383 (51%)	1562 (49%)
Insertion side		
Left side	1390 (52%)	1616 (50%)
Right side	1301 (48%)	1599 (50%)
Insertion site		
Cubital fossa	347 (13%)	394 (12%)
Hand	577 (21%)	726 (23%)
Inner forearm	277 (10%)	346 (11%)
Lower forearm	561 (21%)	662 (21%)
Mid forearm	442 (16%)	532 (17%)
Outer forearm	182 (7%)	164 (5%)
Wrist	69 (3%)	81 (3%)
Upper arm	201 (8%)	248 (8%)
Other	36 (1%)	62 (2%)
Prescribed treatment		
Oral antibiotic	84 (3%)	88 (3%)
Intravenous antibiotic	1835 (68%)	2235 (70%)
Intravenous crystalloid	2668 (99%)	3180 (99%)
Intravenous potassium	222 (8%)	247 (8%)
Intravenous antipyretic	160 (6%)	158 (5%)
Intravenous cortisone	92 (3%)	73 (2%)
Other intravenous drugs	1158 (43%)	1327 (41%)

In some instances, total numbers are not 2692 or 3215 per group because of missing data. Some totals do not add to 100% because of rounding. *In 1593 patients. †In 1690 patients.

Table 2: Characteristics of peripheral intravenous catheters (per intravenous catheter analysis)

	Clinically indicated (n=1593)	Routine replacement (n=1690)	Risk (95%CI)	p value
Primary outcome, intention-to-treat analysis				
Phlebitis per patient, n (%)	114 (7%)	114 (7%)	RR 1.06 (0.83 to 1.36); ARD 0.41% (-1.33 to 2.15)	0.64
Phlebitis/1000 intravenous catheter days (95% CI)	13.08 (10.68-15.48)	13.11 (10.71-15.52)	HR 0.94 (0.73 to 1.23)	0.67
Primary outcome, per-protocol analysis*				
Phlebitis per patient	63/1351 (5%)	47/1186 (4%)	RR 1.18 (0.81 to 1.70); ARD 0.70% (-0.88 to 2.28)	0.39
Phlebitis/1000 intravenous catheter days (95% CI)	11.4 (8.6-14.2)	13.8 (9.9-17.8)	IRR 0.83 (0.56 to 1.23)	0.32
Secondary outcomes, n (n per 1000 intravenous catheter days)				
Any infusion failure†	670 (76.9)	636 (73.2)	HR 0.99 (0.89 to 1.11)	0.87
Infiltration	279 (32.0)	235 (27.0)	HR 1.06 (0.89 to 1.27)	0.51
Occlusion	344 (39.5)	344 (39.6)	HR 0.92 (0.79 to 1.07)	0.92
Accidental removal	166 (19.0)	159 (18.3)	HR 0.98 (0.79 to 1.23)	0.88
CRBSI‡	0 (0)	1 (0.11)
All BSI	4 (0.46)	9 (1.03)	HR 0.46 (0.14 to 1.48)	0.19
Venous (local) infection‡	0	0
Mortality, n (%)§	4 (<1%)	4 (<1%)	RR 1.06 (0.27 to 4.23)	0.93

ARD=absolute risk difference. BSI=bloodstream infection. CRBSI=catheter-related bloodstream infection. HR=hazard ratio. IRR=incident rate ratio. RR=relative risk. *First catheter per patient only. †Combined endpoint of phlebitis, infiltration, occlusion, accidental removal, and CRBSI. ‡Risk and p value inestimable because of 0 incidence in one or both groups. §In all cases, mortality was unrelated to intravenous catheter treatment.

Table 3: Study outcomes by treatment group (per-patient analysis)

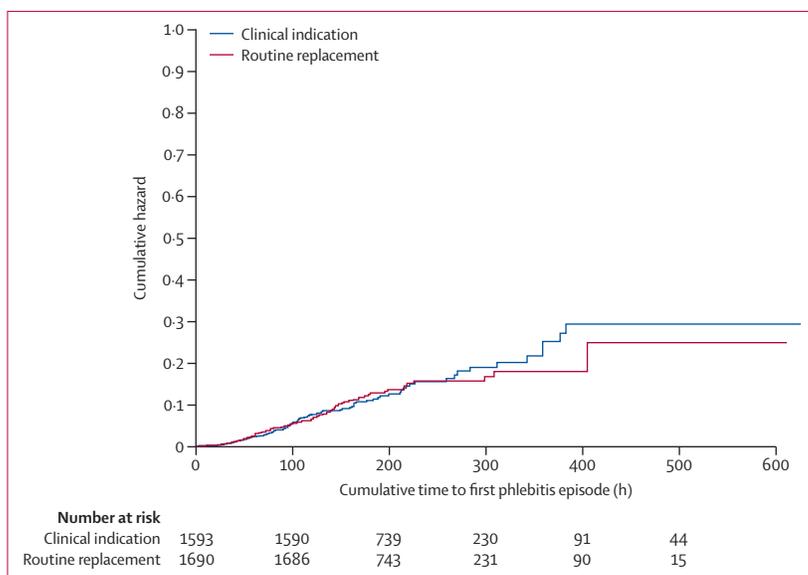


Figure 2: Kaplan-Meier analysis of survival from phlebitis per patient
Includes all catheters per patient, log-rank p=0.96.

clinically indicated group and 70% in the routine replacement group (figure 1). Of 1593 patients in the clinically indicated group, 1351 had 1844 intravenous catheters in place on day 3, and removed for clinical reasons; of 1690 patients randomised to routine replacement, 1186 had 1744 intravenous catheters removed on day 3. Intravenous catheter dwell times (per protocol) were 48–561 h in the clinically indicated group and 48–96 h in the routine replacement group.

Phlebitis inter-rater reliability testing across the three hospitals (248 blinded paired observations) showed 98% agreement, with a Cohen’s κ of 0.33. In the primary analysis, in both groups 7% of patients had phlebitis (table 3), with an absolute risk difference (ARD) of 0.41% (95% CI -1.33 to 2.15), which was within the predefined equivalence margin of 3%. Therefore we accepted the equivalence hypothesis. All comparisons of phlebitis occurrence between study groups were equivalent including per patient (p=0.64, table 3) and per 1000 catheter days (p=0.67, table 3), and on survival analysis (p=0.96, figure 2). The per-protocol analysis (n=2537) had consistent results with the primary analysis with ARD 0.70% (95% CI -0.88 to 2.28, table 3); this comparison had 90% power (p=0.05) to detect equivalence (margin 3%) at the recorded occurrence of phlebitis of 5.5%.

No patient had a venous (local) infection and groups were equivalent for all-cause bloodstream infections, and catheter colonisation. Only one patient had a catheter-related bloodstream infection and this patient was in the routine replacement group. Overall, we identified 15 positive blood cultures from 13 patients (four patients in the clinically indicated group; nine patients in the routine replacement group [two patients had two separate bloodstream infections]). All bloodstream infections in the clinically indicated group were Gram positive organisms, whereas Gram positive and negative organisms were similarly represented within the routine replacement group (table 4). In the substudy (n=298), intravenous catheter colonisation rates did not differ between groups (clinically indicated 13.0/1000 catheter days

	Study group	Clinical signs of sepsis	Antimicrobial treatment started	Matched positive intravenous catheter tip culture	Other matched positive culture
<i>Staphylococcus aureus</i>	Clinically indicated	Yes	Yes	No	No
<i>S aureus</i>	Clinically indicated	Yes	Yes	No	No
Coagulase negative staphylococci	Clinically indicated	No	No	No	No
<i>S epidermidis</i>	Clinically indicated	No	No	No	No
<i>Pseudomonas aeruginosa</i>	Routine replacement	Yes	Yes	No	Urine: <i>Pseudomonas aeruginosa</i>
Coagulase negative staphylococci	Routine replacement	Yes	Yes	No	Wound: Coagulase negative staphylococci
<i>S aureus</i>	Routine replacement	Yes	Yes	No	Wound: <i>S aureus</i>
<i>Escherichia coli</i>	Routine replacement	Yes	Yes	No	No
<i>Enterobacter cloacae</i> *	Routine replacement	Yes	Yes	<i>Enterobacter cloacae</i> >100 CFU	No
<i>Escherichia coli</i> †	Routine replacement	Yes	Yes	No	Urine: <i>Escherichia coli</i>
Coagulase negative staphylococci†	Routine replacement	No	No	No	No
<i>Bacteroides fragilis</i> ‡	Routine replacement	Yes	Yes	No	No
Coagulase negative staphylococci‡	Routine replacement	No	No	No	No
Coagulase negative staphylococci	Routine replacement	Yes	Yes	No	No
<i>Klebsiella oxytoca</i>	Routine replacement	Yes	Yes	No	No§

CFU=colony forming units. *Only case of peripheral intravenous catheter-related bloodstream infection.¹⁴ †Two separate episodes from one patient. ‡Two separate episodes from one patient. §Intraperitoneal pus was identified in the operating theatre at the time of the bloodstream infection and was clinically suspected as the source.

Table 4: Microbiological and clinical information for 15 positive blood cultures from 13 patients

[eight of 143, 6% of intravenous catheters]; routine replacement 12.4/1000 catheter days [six of 155, 4% of intravenous catheters]; HR 1.05 [95% CI 0.32–3.68]). None of these colonised tips were associated with a bloodstream infection.

Rates of infiltration, occlusion, accidental removal, total infusion failure, and in-hospital mortality were all equivalent between groups (table 3). The groups had equivalent overall duration of intravenous treatment; however, the clinically indicated group required significantly fewer intravenous catheters per patient, with significantly reduced hospital costs (both $p < 0.0001$, table 5). No serious adverse events were related to the trial intervention.

Discussion

Phlebitis occurred in 7% of patients when intravenous catheters were removed when clinically indicated and when they were removed routinely every 3 days. The absolute difference was small (0.41%) and within the prestated 3% equivalence margin. We accepted the equivalence hypothesis and results were consistent across all analyses including per patient, per protocol, per catheter, and per 1000 catheter days. Likewise, study groups had equivalent occurrence of catheter-related bloodstream infections and all-cause bloodstream infections, with no local infections in either group.

Catheter-related bloodstream infections were rare in our study at one per 3283 (0.03%) patients or one per 5907 (0.02%) catheters. This finding is reassuring, with no suggestion that clinically indicated replacement increased risk of bloodstream infection; this is a major

	Clinically indicated (n=1593)	Routine replacement (n=1690)	Difference (95% CI)	p value
Duration of therapy (h)*	98 (69–161)	96 (66–162)	..	0.12
Intravenous catheters used	1.7 (1.0)	1.9 (1.2)	0.21 (0.13–0.29)	<0.0001
Cost of therapy (AU\$)†	\$61.66 (\$39.46)	\$69.24 (\$43.45)	\$7.58 (\$4.78–10.38)	<0.0001

Data are median (IQR) or mean (SD). *Cumulative of all intravenous catheters per patient. †2011 cost.

Table 5: Comparison of resource use and costs by treatment group (per patient analysis)

piece of evidence that routine removal is not warranted. Our results confirm the low occurrence of catheter-related bloodstream infections in peripheral intravenous catheters identified in previous prospective studies of none in 2088,¹⁷ none in 1054,¹³ and none in 6538 intravenous catheters.¹⁸

Consideration of the pathogenesis of catheter-related bloodstream infection might assist in understanding of our results. Such infections are initially related to the insertion procedure (poor hand hygiene or skin preparation) with later infections caused by colonisation along the skin tract, or contaminated hubs or fluids.¹⁹ Although routine replacement of intravenous catheters theoretically could reduce later infections, conversely it exposes the patient to the contamination risk of another insertion procedure. One study reported 16% of central catheter tips as already colonised immediately after insertion,²⁰ and initial contamination might also be common for intravenous catheters. Our substudy rate of 5% tip colonisation with no associated bloodstream infections is consistent with results of previous studies showing

Panel: Research in context**Systematic review**

We searched the Medline and CINAHL databases for studies comparing any duration of peripheral intravenous catheter replacement with any other duration of peripheral catheter replacement. Our search terms were “peripheral”, “intravenous”, “catheter/device/cannula”, “replacement”, “removal”, “resite”, “timing”, “duration”, “routine”, “phlebitis”, and “infection”. The search was not restricted by date or language. We also searched reference lists of articles identified by this strategy, and updated the search during write-up of our study. The date of the last search was May 14, 2012. Previous studies were smaller than ours and did not provide a conclusive answer as to whether clinically indicated replacement is equivalent to routine replacement. Some studies were limited to catheters inserted in particular groups of patients, and outcome measures were often composites. Our recent systematic review³⁵ summarised six trials (including unpublished interim data from this trial) with a total of 3455 patients and showed no difference in phlebitis or bloodstream infection between routine and clinically indicated replacement groups. We concluded that a large trial focusing on phlebitis as the primary outcome was needed.

Interpretation

Our study was powered to answer the question of equivalence in phlebitis for clinically indicated replacement versus routine third day replacement of peripheral intravenous catheters in general hospital patients. Bloodstream infections were confirmed as a rare complication in patients with peripheral catheters and did not differ between groups. Our results confirm previous smaller studies' findings that clinically indicated peripheral intravenous catheter replacement is safe.

colonisation as a poor predictor of infection.^{6,13} With the role of surface preconditioning and biofilm development now attaining increased prominence, new molecular-based diagnostics might offer improved insights.²¹

We recruited 3283 patients with intravenous catheters who were predicted by the research nurses at enrolment to require intravenous treatment for more than 4 days. However, this was a pragmatic clinical trial: we did not expect that all patients would actually have intravenous catheters remaining in situ for this length of time, and we recruited additional patients to allow for this attrition. Ultimately, only 2537 patients (77%) adhered to the protocol, and adherence was disproportionately lower in the routine replacement group than in the clinically indicated group (70% vs 85%) because for staff to always replace catheters on day 3 was more difficult than leaving them in situ in the clinically indicated group. The per-protocol analysis showed that even in patients with intravenous catheters in situ on day 3, and when clinically indicated or routine replacement was consistently applied, phlebitis was equivalent between groups, with adequate statistical power for this analysis.

Intravenous catheters are already frequently left in place beyond the currently recommended 72–96 h, typically as the result of a complex clinical judgment, rather than a policy violation.^{22,23} Prospective studies^{23–25} report that 21–62% of intravenous catheters remain in situ beyond the routine time for removal, and they are usually left for appropriate reasons—eg, treatment soon to be completed, poor veins, or no available staff to

cannulate.^{22–25} The CDC itself tempers its 72–96 h replacement recommendations with “if sites for venous access are limited and no evidence of phlebitis or infection is present, intravenous catheters can be left in place for longer”.¹⁴ Thus, a change to policies of clinically indicated removal of intravenous catheters might not be very far from the current real-world approach that occurs despite policies and recommendations.

Our data predict how intravenous catheter dwell times and numbers of intravenous catheters used would change with a clinically indicated replacement approach. Intravenous catheter use will be extended, on average, by a little more than 1 day, with the IQR showing that about a quarter will remain in use for longer than 5 days. The longest intravenous catheter duration we recorded was 3 weeks, without complications. Importantly, our study was not testing intravenous catheter dwell for short versus very lengthy periods per se (because we could not force intravenous catheters to remain in situ for set periods), but rather whether the policy of routine replacement reduces complications. Our data strongly suggest that routine replacement does not, but rather causes many unnecessary invasive procedures. The average reduction of 0.2 intravenous catheters per patient inserted in the clinically indicated group meant a number needed to treat of 5; that is, under a clinically indicated removal policy, one in every five patients will avoid an unnecessary procedure.

Because globally a high number of patients need intravenous catheters, clinically indicated replacement would have worldwide effects on health-care costs each year. Of the 200 million catheters estimated to be inserted each year in the USA alone,¹ if even 15% are needed for more than 3 days, then a change to clinically required replacement would prevent up to 6 million unnecessary intravenous catheter insertions, and would save about 2 million hours of staff time, and up to US\$60 million in health costs each year for that country alone. These savings could then be redirected to other health interventions with better evidence of effectiveness than routine replacement.

Routine replacement of intravenous catheters has been practised for four decades, during which time catheter materials have changed from steel, polyvinylchloride, polyethylene, and tetrafluoroethylene-hexafluoropropylene to more biocompatible polyurethane.^{13,26} This change might partly explain why intravenous catheters can now be tolerated for longer periods than previously and why our 7% phlebitis occurrence was lower than that reported with other catheter materials,^{6–8,13} but consistent with rates of 1–7% reported with polyurethane intravenous catheters.^{11,18,27–31} Our rates might have been somewhat lowered by the 40% of intravenous catheters placed by intravenous insertion teams, although our teams did no post-insertion care, the main factor by which such teams are believed to reduce complications.³² Our phlebitis occurrence was also affected by a strict

definition whereby pain or tenderness was one criterion rather than two, and many criteria were quantitatively restricted, compared with other definitions. Similarly, our identification of catheter-related bloodstream infections was affected by the stringent CDC definition; we required confirmed microbiological evidence of the intravenous catheter as the source of infection. Our findings might not be generalisable to settings where the incidence of phlebitis or catheter-related bloodstream infection is high.

The major strengths of this study were the processes used to eliminate selection, allocation, and detection bias, and the large sample size with 100% follow-up for the primary endpoint. We included a broad range of hospital patients and did not restrict intravenous catheters by their use or by inserter. Most patients had several comorbidities and received vein-irritant drugs such as intravenous antibiotics. Most catheters in our sample were inserted by medical and nursing staff, not intravenous teams, and we included those inserted in general wards, emergency, or operating departments. These factors promote generalisability to other acute, complex hospital populations. Our results do not apply to intravenous catheters inserted under emergency conditions, where aseptic insertion is not achieved because such insertions were not included in our study.

The study's main limitation was its non-blinded design. Blinding was not possible because of the obvious nature of catheter placement to patients and staff. We considered using a second set of blinded research nurses for phlebitis assessments, but this procedure would be prohibitively expensive, in view of the large sample and daily measures. We recorded high phlebitis inter-rater agreement rates in a blinded substudy, suggesting our approach was acceptable. The phlebitis measures involved some subjectivity but that was reduced by use of a structured phlebitis instrument, continued training, and audit of research nurses. Patient-reported ratings were only one item (pain or tenderness) on the five-item list, and because two items were required concurrently for diagnosis, patients' perceptions alone were unable to affect phlebitis rates. Another limitation was our inability to culture all intravenous catheter tips because of restrictions of the hospital laboratories and budget. Instead we monitored all tips cultured on clinical indication, a method that produces much the same identification of catheter-related bloodstream infections,^{3,19} and undertook a substudy. Additionally, we could not use catheter-related bloodstream infection as the primary endpoint since rates with intravenous catheters are typically close to 0%.

Worries about phlebitis and bloodstream infections have sustained routine replacement policies, with these two complications generally the focus of intravenous catheter literature, yet our data show that the more frequent reasons for modern catheter failure are infiltration, occlusion, and accidental removal. In total, nearly 30% of intravenous catheters had some form of failure.

This finding is not indicative of particularly poor outcomes in our institutions—similarly high, and higher rates of up to 92%, have been reported in previous studies.^{27,28,33,34} Since routine replacement is ineffective, research attention should now focus on other interventions to reduce these complications. Improved survival of intravenous catheters for even small increments of time would further reduce the number of insertions, staff workloads, and costs. Improved insertion, securement, and flushing strategies could be key.

Our findings are consistent with previous smaller randomised controlled trials,^{9–12} and a systematic review showed no benefit of routine replacement for phlebitis or catheter-related bloodstream infections (panel).³⁵ Thus, much evidence now suggests that clinically indicated replacement is safe. Updated intravenous catheter policies should advocate clinically indicated removal—ie, to monitor and immediately remove intravenous catheters for complications or as soon as treatment is complete. The CDC guidelines already recommend clinically indicated replacement in children,⁴ citing two non-randomised studies (total n=589).¹⁴ Thus, despite a scarcity of large randomised controlled trials, paediatric patients are not subjected to routine replacement, perhaps because of the sensitivities of cannulating children. Our data support extension of these recommendations, and this sensitivity, to the management of adult patients. Insertion of an intravenous catheter is painful, requiring piercing of skin, tissue, and vein with a steel needle at least once, or several times for a difficult insertion. Investigation of patients' perspectives of strategies for replacement of intravenous catheters has been recommended,²⁵ but patients are presumably unlikely to want routine replacement since it has no proven benefit.

Contributors

CR and JW did the scientific literature search, study design, and grant writing. CR recruited sites, wrote the first and final drafts of the report, and consulted with all authors about the article. MM, who is a statistician, analysed data and prepared figures. All authors contributed to data collection and substantially to interpretation and analysis of data and approved the final version of the report.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

The Australian National Health and Medical Research Council funded this study through the national competitive grants scheme. We received in-kind support from Griffith University, Royal Brisbane and Women's Hospital, Princess Alexandra Hospital, Gold Coast Hospital, and Monash University. We acknowledge the participants, and the clinical and research staff of the three hospitals. In particular, the research nurses: Kaye Sayed, Catherine Gale, and Wendy Jackman (Royal Brisbane and Women's Hospital); Rebecca Kim, Jan Hine, Joanne Peters, and Mark Wood, (Princess Alexandra Hospital); Kenneth Boag, Tanya Clark, Tracey Patrick, Lyn Jenyns, Julie Pitman, and Melissa Medina (Gold Coast Hospital) for recruitment of patients and data collection. We also thank Nicolas Rossow for development and assistance with the database and David McMillan for microbiology advice. We thank Lukman Thalib and Damhnat McCann for advice on the grant proposal.

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