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Title: Comparison of midline catheters and peripherally inserted central catheters to reduce the need for general anesthesia in children with respiratory disease: A feasibility randomized controlled trial.

Running title: Vascular access in pediatric respiratory disease

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Abstract

Background: The optimal intravenous device for antibiotic administration for children with respiratory disease is uncertain. We assessed the feasibility of a randomized controlled trial (RCT) comparing midline catheters with peripherally inserted central catheters (PICCs).

Methods: Prospective, 2-arm, feasibility RCT in an Australian tertiary, pediatric hospital. Random assignment of 110 children (< 18 years) to receive (i) midline catheter, (ii) PICC. Primary outcome was feasibility (eligibility, recruitment, retention, protocol adherence and acceptability), and the primary clinical outcome was general anesthesia requirement for intravenous catheter insertion. Secondary outcomes: insertion time, treatment delays, infusion efficiency, device failure, complications, and cost.

Results: There was 80% recruitment, 100% retention, no missing data, and high patient/staff acceptability. Mean patient experience assessed on a 0–10 numeric rating scale was 8.0 (PICC) and 9.0 (midline catheters) respectively. Participant eligibility was not achieved (49% of screened patients) and moderate protocol-adherence across groups (89% PICC vs 76% midline catheter). Insertion of midline catheter for pulmonary optimisation reduced the requirement for general anesthesia compared to PICCs (10% vs 69%; odds ratio=0.01, 95% confidence interval: 0.00–0.09). Midline catheters failed more frequently (18.1 vs 5.5 PICCs per 1,000 catheter-days), however this reduced over trial duration. Midline catheter insertion compared to PICCs saved AUD$1,451 per pulmonary optimisation episode.

Conclusions: An efficacy trial is feasible with expanded eligibility criteria and intensive staff training when introducing a new device. Midline catheter for peripherally compatible infusions is acceptable to patients and staff, might negate the need for general anesthesia and results in significant cost savings.

Key words:
anesthesia, general; central venous catheterization; cystic fibrosis; midline; pediatrics; PICC; randomized controlled trial

Data sharing:

Data generated and/or analysed will be available from the chief investigator (TMK) on reasonable request and after agreement by ethics."

a. **What is already known about the topic**

- Children who require insertion of a vascular access device to administer >7 days of intravenous antibiotics for pulmonary optimization typically require general anesthesia.

- General anesthesia can cause further deterioration in lung function in the already compromised respiratory patient.

b. **What new information this study adds**

- This is the first pediatric study to investigate the safety, acceptability and effectiveness of inserting midline catheters compared to PICCs to administer intravenous antibiotics for pulmonary optimization, while reducing the requirement for general anesthesia.

- The insertion of a midline catheter without general anesthesia is well tolerated and safe.

Introduction

Suppurative lung diseases, such as cystic fibrosis (CF) and non-CF bronchiectasis, are life-limiting disorders of the respiratory tract.[1] Incidence varies across Europe and America, however its occurrence in Australia is estimated in 1 in 2,500 births.[1-3] Currently no cure exists, however aggressive, intravenous antibiotic therapy to treat pulmonary exacerbation helps maintain lung function and extend life expectancy.[3] Reliable intravenous access is necessary to administer these intravenous antibiotics.[3]

Peripherally inserted central catheters (PICCs) are traditionally inserted to administer this intermittent, but vital therapy.[4-6] PICCs are presumably reliable (in comparison to peripheral intravenous catheters), and easy to insert (in comparison to other central devices)[5,6] however, complications including thrombosis, infection, and occlusion are reported.[7-10] To aid procedural compliance and comfort, local practice has historically offered all children a general anesthesia for PICC insertion however, globally, children >12 years often do not require GA.[11-14] Despite improved recovery with modern anesthetic agents[15], children with chronic respiratory conditions are still advised to avoid *unnecessary* GAs.[16] Comparatively, insertion of a midline catheter is less complex and quicker to insert, potentially negating the need for GA.[5,14]

Internationally, midline catheters are inserted as an alternative intravenous device to administer short- to mid-term peripherally compatible therapies.[17-21] A midline catheter is inserted into a peripheral vein of the upper arm with the terminal tip at the level of the axilla. In an observational study, Sharp, Esterman, McCutcheon, Hearse, Cummings [5] described similar rates of midline catheter and PICC complications (15.5% vs 18.2%) in adult patients with CF, and concluded midline catheters are a safe, and lower cost alternative to PICCs. However, no robust clinical trials have compared similar outcomes in pediatrics.[22,23] The aim of this trial was to assess the feasibility of a randomized controlled trial comparing midline catheters with PICCs for children requiring pulmonary optimization.

Methods

Design

A single center, two-arm, parallel group, pilot randomized controlled trial (RCT) involving children requiring parenteral antibiotic administration for pulmonary optimization. The trial was

prospectively registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12618001642279).

Setting and participants

The trial was conducted across Children's Health Queensland (Australia), including Queensland Children's Hospital (QCH) inpatients and home-care settings. QCH is a tertiary referral metropolitan hospital. Children were eligible if they were aged 1 to <18 years and required peripherally compatible intravenous antibiotics for pulmonary optimization due to chronic respiratory condition[24], and upper arm vessel size >3mm (as measured with ultrasound, without tourniquet by proceduralist). We excluded children with non-English speaking parents or guardians where a translator was not available, those unable to provide consent, and children previously enrolled in the trial.

Interventions

Children were randomly assigned to receive either:

1. standard care: **PICC**: 3fr, 4fr; BioFlo® PICC with PASV®; AngioDynamics Inc (Queensbury, New York, USA), or
2. intervention: **midline catheter**: 3fr, 4fr Powerwand™ midline catheter; Smiths Medical (Minneapolis, Minnesota, USA).

Intervention insertion procedures

All device insertion, care and management were standardized across both groups, as per hospital policy and international guidelines.[25] Catheters were inserted by clinicians who were competent in PICC and midline catheter insertion or were supervised by a competent practitioner. The catheters were inserted with full barrier precautions, 2% chlorhexidine gluconate in 70% alcohol for skin antisepsis, catheter-to-vessel ratio of <45%, and devices were removed when clinically-indicated.[25]

The need for GA was determined by patient preference after a collaborative discussion between patient, parent, proceduralist and occupational therapist prior to all device insertion, regardless of randomized device. Procedures not requiring a GA/imaging occurred in a treatment room[26].

Procedures requiring GA and/or use of imaging equipment occurred in an angiography suite or operating theatre. Where a device was complicated by failure and a replacement catheter required, the decision was left to the discretion of the treating clinician and patient preference.

Outcomes

The primary outcomes were feasibility of an efficacy trial and GA requirement for catheter insertion. Feasibility was determined through a composite analysis of eligibility, recruitment, retention, protocol adherence, missing data, patient, parent/clinician experience, and acceptability[27,28]. Secondary outcomes were insertion time, treatment delays, infusion efficiency[1,29], device failure[5,8,20], complications[5,8,20], and cost. Outcome definitions are provided in Table 1.

Total healthcare resource use and associated costs were estimated for each participant (Table 2). Cost-analysis was carried out from the perspective of the hospital including; equipment (negotiated contract prices for public hospitals), staff time to insert and monitor the catheter (published enterprise agreements), GA costs, replacement products, imaging (Ultrasound or X-ray), and treatment of complications (2020 Australian Dollars; Supplementary Table 1).[30]

Sample size

Target recruitment was 50 children per group, adding 10% for potential attrition (total *N*=110). Sample sizes were based upon requirements for feasibility testing and informing sample size calculations for a definitive trial.[28,31]

Study procedures

Research nurses (ReN) screened children for PICC insertion for pulmonary optimization, obtained written informed consent, and performed randomization. Randomisation and allocation concealment were achieved using a web-based central randomization service (https://randomisation.griffith.edu.au/). Patient-level randomization was generated in a 1:1 ratio between groups, with randomly varied block sizes. The randomized device was provided to inserting staff by ReNs, to ensure protocol fidelity. It was not possible to blind clinicians or patients/parents or caregivers, however the data analyst and health economist were blinded to

study group, and all infection and thrombosis end points were assessed by a blinded infectious disease physician and radiologist respectively.

Study data were collected and entered directly into the secure web-based data platform REDCap™ (Research Electronic Data Capture)[32] hosted at Griffith University. Feasibility outcomes were collected from screening logs. ReNs collected patient (age, gender, weight), clinical (diagnosis, co-morbidities, prior venous thrombosis), device (insertion site, vessel size, catheter size), and treatment (antibiotics, dose delivered, inpatient or home-based) characteristics. Study participants were visited daily (Mondays to Fridays) by the ReN until completion of treatment or device failure. Patients discharged to homecare had data collected at respiratory outpatient clinic, during home-care visit, or by phone.

On insertion and device removal ReNs asked the patient/parent to rate the child's procedural anxiety and pain, and the parent's procedural anxiety on an 11-point scale (0=none, 10=maximum). On insertion or within 24 hours of insertion, ReNs asked the inserting clinician to rate the ease of insertion on the same scale, and previous experience with the device. Within 24 hours of device removal, reason for removal was collected and children >8 years of age and their parents were asked to rate their device experience on an 11-point scale.

Statistical methods

The data were exported to Stata 16 for analysis. All randomized patients were analyzed by intention-to-treat, irrespective of treatment. The patient was the unit of measurement with one device per patient recruited and analyzed. Descriptive statistics, appropriate to data characteristics, reported feasibility outcomes and explored clinical outcomes. Comparisons between control and intervention groups were made using chi-square (general anesthesia for device insertion, device failure), rank-sum (duration of insertion procedure), and independent sample t-tests (anxiety, difficulty and experience). To enable an expression of between-group failure rates over device dwell, results were reported per 1,000 catheter-days with 95% confidence intervals (CIs), and graphs of the Kaplan-Meier survival function by group and the cumulative proportion of device failure were generated. Uni- and multivariable Cox regression assessed the effect of *a priori* chosen patients and treatment characteristics on GA use, with hazard ratios (HRs) and 95% CIs

calculated. Based on the results of univariable analyzes, covariates were deemed ineligible for multivariable analysis at $p \geq 0.20$, or if the proportional-hazards-assumption-test was significant. The final regression model was derived using manual backward/forward stepwise removal/addition of covariates analysis.

Comparative cost-analysis was assessed on a per patient episode of pulmonary optimization basis. Costs identified for the analysis included: purchase price of devices, staff time, operating room costs, inpatient bed days, and cost of complications and re-insertion of device if necessary, for completion of care. The mean cost per patient in both treatment groups were compared using *t*-test with 95% CI computed using non-parametric bootstrapping. All costs are reported in 2020 Australian Dollars. No discounting was applied as the time horizon of analysis was <1 year. Statistical significance was declared at $p < 0.05$.

Ethical statement

Ethical approval was received from Children's Health Services Queensland and Griffith University Human Research Ethics Committees (HREC/18/QRCH/160, (GU 2018/668), respectively and a Data Safety Monitoring Committee was convened mid-trial.

Results

Study participants

Between January 2019 to April 2020, 110 patients were randomized. Baseline demographic, device, and clinical characteristics are outlined in Table 3. The median age was higher for midline catheters (11 years, inter-quartile range [IQR]: 3–11) compared to PICCs (6, 5–14). Midline catheters had more comorbidities than PICCs: 42 (82%) vs 32 (58%). Inserters were more familiar with PICCs than midline catheters. All inserters had previously inserted PICCs, and 39 (85%) had inserted PICCs >20 times. Comparatively, 6 (14%) had never inserted a midline catheter and only 23 (55%) had inserted midline catheters >20 times. A total of 1,223 catheter-days was studied. (Table 4)

Insert Table 1. Participant and clinical characteristics

Primary outcome: feasibility

Two hundred and twenty-four children were assessed for trial eligibility, 110 (49%) were randomized (Figure 1). Of the 138 families approached for consent, 80% agreed to participate. Twenty-one potential participants were missed due to emergent admission outside ReN hours. There was moderate protocol compliance, six patients in each group (total 11%) did not receive their allocated intervention: 8 due to patient or clinician preference, 3 due to inappropriate vasculature (irregularly small vessels for age or undiagnosed narrowing at axillar), and 1 participant randomized to PICC was too unwell for GA and received a midline catheter while fully conscious. Seven patients were excluded from analysis in the midline catheter group due to change in intravenous therapy that was not peripherally compatible (*n*=3), or the planned intravenous therapy was cancelled (*n*=4). There were no missing data for primary or secondary outcomes, and no children were lost to follow-up.

Staff reported acceptable ease of insertion for midline catheters (median 10, IQR: 9–10) and PICCs (10, 8–10) (Table 3). Parents and children reported a greater experience score in midline catheters (median 9, IQR: 5.5–10) compared to PICCs (8, 7–10). Median parent–anxiety score for PICCs pre-GA was 4/10 (IQR: 2–7, *n*=47), median child-pain score when the midline catheter was inserted awake was 1/10 (IQR: 1–4, *n*=29). (Table 4)

Insert Figure 1. CONSORT Flowchart of study participants

Primary outcome: requirement for GA

Thirty-four (69%) of the 49 children allocated to PICCs required GA for device insertion compared to 4 (10%) of 42 children allocated to midline catheters (odds ratio [OR]=0.05, 95% CI: 0.01–0.15, $p<0.001$). Other factors significantly associated with need for GA for device insertion included; age (OR=0.89, 95% CI: 0.82–0.97), weight (OR=0.96, 95% CI: 0.93–0.99), and insertion by anesthetist compared to VA specialist (OR=3.38, 95% CI: 1.42–8.08) (Table 4, Supplementary Table 2).

Insert Table 2. Study outcomes

Secondary clinical and safety outcomes

Insertion procedure time was significantly shorter for midline catheters (median: 18 minutes, IQR: 12–25) compared to PICCs (45, 29–71, $p<0.001$). GA wait was the most common reason for delay associated with non-elective admissions, occurring in 17 (35%) PICCs and 8 (19%) midline catheters. Most patients received uninterrupted medication administration: 43 (88%) PICCs and 33 (79%) midline catheters. Midline catheters more reliably delivered a therapeutic dose in home care settings (100% elastomeric and 97% battery operated pump) compared to PICCs (76% and 89% respectively) (Table 4).

The mean PICC and midline catheter dwell was 14.8 and 11.9 days respectively. Overall, 9 (21%) midline catheters failed prior to therapy completion, compared to 4 (8%) PICCs, corresponding to 18.1 and 5.5 failures per 1,000 catheter-days (incidence rate ratio [IRR]=3.28, 95% CI: 0.91–14.6) (Table 4). The Kaplan-Meier curve showed longer survival by PICCs (Figure 2a). Figure 2b demonstrates most midline catheters failed in the first four months of the study and failure reduced as the study progressed.

Insert Figure 2a (Kaplan-Meir curve of device failure) and 2b (Kaplan-Meir curve of device failure over time).

Economic evaluation

The total cost per patient episode of pulmonary optimization was significantly lower for midline catheters (mean AU$ 1,322, 95% CI: 894–1,749) compared with PICCs (mean AU$ 2,773, 95% CI: 2,355–3,191, $p<0.001$) (Table 2). The mean cost-saving per patient episode of pulmonary optimization was AU$1,451 (95% CI: 884–2,018). The largest cost-saving was GA costs which was significantly lower for midline catheters (mean AU$780, 95% CI: 386–1,173) than PICCs (mean AU$2,087, 95% CI: 1,718–2,455).

Discussion

Reliable vascular access for children with chronic health conditions is necessary, however neither the consequence of the insertion procedure (GA, traumatic insertion) or dwell (thrombosed vessels, extravasation) should result in harm. Clinical guidelines recommend insertion of midline

catheter when peripherally compatible infusion is planned for up 4 weeks[25], however recent guidelines caution implementation in pediatrics without careful monitoring due to limited clinical data.[4,22,23] Our results confirm the safety and acceptability of midline catheters for peripherally-compatible antibiotic therapy up to 14 days for children with respiratory conditions.

Internationally, this is the first RCT to assess the role of midline catheters to administer intravenous therapy for children with chronic lung disease. These results demonstrate a large efficacy trial would be feasible with the following protocol modifications. The existing eligibility criteria was not feasible due to patient (i.e. vessel size <3mm) and procedural (i.e. patients could only participate once) factors. Protocol adherence was difficult to achieve, as this cohort of chronic healthcare consumers had existing preferences for device and procedural sedation[33]. Future efficacy trials might still be feasible if other clinical groups with prototypical peripherally compatible parenteral therapy are included. The addition of age stratification at randomization might improve balance between groups at baseline, as well as the exclusion of children already having general anesthesia for additional procedures at the time of device insertion such as bronchoscopy. All other feasibility criteria were achieved.

Although midline catheters had increased risk of needing replacement to complete treatment, the prompt insertion of a midline catheter without GA enabled early initiation of treatment. Antos, Quintero, Walsh-Kelly, Noe, Schechter [34] report a recent quality improvement initiative to reduce delays to initiation of intravenous antibiotic therapy for children requiring pulmonary optimization. This was in response to parental reports that delayed initiation of intravenous medication was the most significant cause of stress.

Sharp, Esterman, McCutcheon, Hearse, Cummings [5] demonstrated in an observational study of adult patients with CF (n=328) similar rates of adverse events: 14 (PICC) and 11 (midline catheters) per 1,000 devices (IRR=1.18, 95% CI: 0.62–2.22, p=0.617). Despite greater removal of midline catheters (IRR=2.24, 95% CI: 0.91–5.56, p=0.079) they concluded midline catheters are an acceptable clinical and economical alternative to PICCs.

Our study demonstrated midline catheter selection was associated with a significant reduction in total health care costs, saving an average of AU $1,451 per patient. That is, despite increased cost associated with midline catheter replacement, this was countered by cost savings associated with lower device insertion costs. Whilst most cost savings are associated with reduced costs of GA (-$1,307, 95%CI: -1,839–-775), midline catheters are still considered cost saving even in the absence of these savings due to other cost saving elements including device cost, cost of inserting including associated staff costs and avoiding the need for x-ray. Presently, approximately four PICCs are inserted every week for children requiring pulmonary optimization at QCH (350 beds). Were midline catheters used instead, the annual savings for this one hospital alone are estimated at AU $301,808.

Implications for practice and future research recommendations

This study has important patient safety and practice implications. Insertion of a midline catheter without a GA enabled early initiation of treatment, early discharge with more reliable in-home infusion of a therapeutic medication dose, and negated the need for fluoroscopy to confirm catheter tip position; reducing the overall radiation burden in this patient population.

Additionally, the temporal relationship between learning a new procedure and attaining proficiency in a generalist medical model is unclear, but likely to be more protracted than training specialist clinicians.[35] Within the current study more midline catheters failed at the beginning of the study. Comparatively, the same generalist staff have been inserting PICCs since 2014 when the failure rate was 22%.[8] By perfecting insertion and maintenance technique PICC failure has reduced to the current rate of 8%. Notwithstanding the learning curve for successful device insertion, Chopra, Kaatz, Swaminathan, Boldenow, Snyder, Burris, Bernstein, Flanders [36] reports wide variation in midline catheter use across their hospital group and conclude more studies are needed to define appropriate indications for use, optimal insertion technique, and best care and maintenance practices to ensure longevity and ultimately patient safety.

Strengths and limitations

Although we used robust methods, our trial had some limitations. The study was undertaken in a single, pediatric hospital, in a specific sub-set of patients, limiting external generalizability. Clinicians, participants, family members, and research staff were not blinded to the intervention,

due to obvious visual differences. When assessing patient pain and procedural anxiety, we used the numeric rating scale which is validated for children >8 years of age[37,38] only, future trials should consider use of additional pain and anxiety scales validated for various pediatric age groups such as the Face Legs Activity Cry and Consolability (FLACC) behavioral pain assessment tool in children with cognitive impairment[39,40] and/or aged 0–5 years, and the Faces Pain Score (FPS) tool for children >5 – to 8 years of age[41]. Finally, a knowledge/practice imbalance existed between the well-established PICC and newly introduced midline catheter, potentially impacting management of complications and escalation to device removal rather than symptom management.[42,43]

Our study had important strengths. This is the first pediatric RCT to establish the safety and efficacy of substituting PICC for less invasive midline catheter to reduce harmful effects of anesthesia. Furthermore, we report an economic evaluation using a micro-costing approach enabling pragmatic and more comprehensive cost estimates including the cost of interventions and those of managing complications and adverse events. These findings have substantial implications for clinical decision-making and patient safety. Future studies should consider additional patient cohorts that might benefit from insertion of a less invasive catheter when peripherally compatible therapies are prescribed.

Conclusion

This study demonstrated the feasibility of an efficacy trial to compare midline catheter to PICC for peripherally compatible therapy, with protocol modifications to widen participant eligibility criteria. We also demonstrated the need to consider the varied learning curve when introducing a new device into a healthcare service that is based on a generalist insertion model. Finally, midline catheters can be safely inserted without GA, and staff and patients consider this an acceptable treatment alternative.

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Potential Conflicts of Interests

Except for the above financial disclosures, the authors have indicated they have no potential conflicts of interest to disclose.

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Authors' contributions

TMK conceptualized and designed the study and data collection instruments, carried out the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript.

JS carried out the initial analyses, drafted the initial manuscript, critically reviewed and revised the manuscript for important intellectual content.

CW provided intellectual content on the study design, carried out the initial analyses, critically reviewed and revised the manuscript for important intellectual content.

GM, carried out the initial analyses, and critically reviewed the manuscript for important intellectual content.

VG designed the data collection instruments coordinated and supervised data collection, collected data, reviewed and revised the manuscript.

MS, JB provided advice on the health economic component of the study design, were responsible for the health economics analyses, reviewed and revised the manuscript.

PC, FMacF, NG, ES provided intellectual content for the study design and reviewed and revised the final manuscript.

AJU conceptualized and designed the study, carried out the initial analyses, reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Table 1. Outcome definitions

Primary outcomes

The primary outcomes of the trial are (i) feasibility and (ii) GA during pulmonary optimization.

(i) Feasibility of a full-scale efficacy trial will be established by a demonstration that:

- Greater than 75% of patients screened are eligible and,
- Greater than 80% of eligible participants agree to enrol and,
- Greater than 80% of participants receive their allocated treatment and,
- Less than 5% of participants are lost to follow up and,
- There is less than 5% missing data and,
- Parents and healthcare staff report > 80% satisfaction and acceptability with the study intervention.

(ii) Requirement for GA will be established by the VAD insertion necessitating a GA, that would not otherwise be required.

Secondary outcomes

- *Time to insert:* Time from the start of the PICC or ML placement until radiographic confirmation of tip position and device ready for use
- *Delays to initiation of treatment: Time between decision made to administer treatment and treatment commenced.*
- *Delays throughout treatment:* Any delay that occurs from the time the antibiotic was due to be administered to the time the antibiotic was actually administered.
- *Efficiency of device to deliver therapeutic dose via infusor in 24 hour period:* Weight of infusor at beginning of 24 hour period, compared to weight of infusor at the end of 24 hour period. Dose delivery of more than 90% over 24 hour period is considered optimal.
- *Cost analysis:* Estimates of direct product costs, healthcare resource utilisation (including additional equipment, staff time) and failure-associated resource usage using previously established cost estimates;
- *Device failure:* Cessation of device function due to any complication (CABSI,

thrombosis, occlusion, fracture, infiltration, dislodgement) prior to completion of therapy;

- *Patient, parent and clinician experience:* Using 0-10 numeric rating scales for child anxiety and pain (self-report and/or parent-report), parental anxiety, and clinician difficulty

Table 2: Cost comparison between the trial groups (2020 AU$)

Costs	PICCs (95% CI)	Midline (95% CI)	Difference (95% CI)	p-value[a]
Device insertion	2,710 (2,293 to 2,318)	1,219 (798 to 1,640)	-1,491 (-2,077 to -905)	<0.001
Devices	256 (211 to 300)	179 (161 to 196)	-76 (-125 to -28)	<0.001
Inserting staff	149 (110 to 188)	72 (38 to 105)	-77 (-128 to -26)	0.001
Assisting staff	47 (37 to 56)	27 (19 to 34)	-20 (-32 to -7)	0.001
GA theatre/procedure	2,087 (1,718 to 2,455)	780 (386 to 1,173)	-1,307 (-1,839 to -775)	<0.001
Ultrasound	133 (123 to 141)	128 (120 to 135)	-5 (-16 to -7)	0.43
X-ray	36 (31 to 41)	7 (2 to 11)	-29 (-36 to -22)	<0.001
Local anesthesia	4 (3 to 5)	0.5 (0.0 to 1)	3 (2 to 5)	<0.001
Non-GA consumables	2 (1 to 3)	22 (18 to 26)	20 (16 to 24)	<0.001
Device maintenance	43 (39 to 46)	37 (33 to 39)	-6 (-11 to -2)	0.004
Replacement device	0.5 (0.0 to 1)	41 (11 to 70)	40 (13 to 68)	0.007
Device removal	9 (NE)	9 (NE)	0 (NE)	NE
Complications	11 (4 to 18)	17 (5 to 28)	6 (-7 to 19)	0.39
Total procedure cost[b]	2,773 (2,355 to 3,191)	1,322 (894 to 1,749)	-1,451 (-884 to -2,018)	<0.001

[a] t-test with bootstrapping confidence intervals; CI = confidence interval; GA = general anesthetic; NE= not estimable; PICC = peripherally inserted central catheter; [b] does not add due to rounding error

Table 3: Participant (N=106, as randomized; unless otherwise noted) and Clinical characteristics (N=91, per-protocol analysis)

	PICC	Midline	Total
Participant characteristics (*N*=106)			
Group size[a]	55 (52)	51 (48)	106 (100)
Age group (years):	6.0 (3.0–11.0)[d]	11.0 (5.0–14.0)[d]	8.0 (3.0–13.0)[d]
1 to <2	4 (7)	1 (2)	5 (5)
2 to <5	18 (33)	12 (24)	30 (28)
5 to <13	21 (38)	22 (43)	43 (41)
13 to <18	12 (22)	16 (31)	28 (26)
Gender (females)	30 (55)	30 (59)	60 (57)
Insertion on dominant side (*N*=101)	17 (33)	25 (51)	42 (42)
Diagnosis:			
cystic fibrosis	39 (71)	39 (76)	78 (74)
non-cystic fibrosis bronchiectasis	7 (13)	2 (4)	9 (8)
other chronic respiratory	9 (16)	10 (20)	19 (18)
Previous venous thrombosis^ (*N*=103)	5 (9)	8 (16)	13 (13)
Previous vessel occlusion* (*N*=102)	16 (31)	24 (48)	40 (39)
Clinical characteristics (*N*=91)			
Placement:			
basilica	36 (74)	19 (45)	55 (60)
brachial	10 (20)	18 (43)	28 (31)
cephalic	1 (2)	5 (12)	6 (7)
axilla	2 (4)	0 (0)	2 (2)
Multiple insertion attempts:			
one (success at first attempt)	37 (76)	38 (90)	75 (82)
two	6 (12)	3 (7)	9 (10)
three or more	6 (12)	1 (2)	7 (8)
Successful insertion by (*N*=90):			
nurse practitioner	12 (25)	33 (79)	45 (50)
medical officer/anesthetist	36 (75)	9 (21)	45 (50)

	PICC	Midline	Total
No. of times clinician used product (*N*=88):			
first-time user	0 (0)	6 (14)	6 (7)
1 to 5 times	4 (9)	2 (5)	6 (7)
6 to 19 times	3 (7)	11 (26)	14 (16)
20 times or more often	39 (85)	23 (55)	62 (70)
Ease of insertion (0=worst, 10=best, *N*=85)	10 (9–10)[d]	10 (8–10)[d]	10 (9–10)[d]
Technology: ultrasound[c]	48 (98)	41 (98)	89 (98)
Technology: X-ray[c] (catheter tip confirmation	46 (94)	2 (5)	48 (53)
Catheter tip position:			
superior vena cava-right atrial junction	41 (84)	0 (0)	41 (45)
axilla	0 (0)	42 (100)	42 (46)
superior vena cava	8 (16)	0 (0)	8 (9)
Catheter size (French):			
3	43 (88)	31 (74)	74 (81)
4	6 (12)	11 (26)	17 (19)
Department of insertion:			
interventional radiology	26 (53)	14 (33)	40 (44)
operating theatre	23 (47)	5 (12)	28 (31)
procedure room/treatment room	0 (0)	23 (55)	23 (25)
Medication (ever): IV antibiotic	49 (100)	41 (98)	90 (99)
Medication (ever): IV fluid	4 (8)	3 (7)	7 (8)
Medication (ever): parenteral nutrition/lipid	2 (4)	1 (2)	3 (3)

*frequencies and column percentages shown unless otherwise noted; ^ patient-reported; * reported on ultrasound; [a] row percentages shown in brackets; [b] other than PICC [c] category of 'no' omitted; [d] median (25th–75th percentiles) shown; PIVC = Peripheral Intravenous Catheter: PICC = Peripherally Inserted Central Catheter; CVAD = Central Venous Access Device; IV = intravenous;*

Table 4: Study outcomes (*N*=91, per-protocol analysis)

	PICC *n*=49	Midline *n*=42	p-value
GA required:			
yes, for insertion of IVAD only	34 (69)	4 (10)	<0.001[a]
no, fully conscious	1 (2)	29 (69)	
yes, for additional procedures	14 (29)	7 (17)	
no, non-fasting sedation	0 (0)	2 (5)	
Duration of insertion procedure (minutes)[b]	45 (29–71)	18 (12–25)	<0.001[c]
Duration of general anesthesia (minutes, *N*=59)[b]	57 (42–83)	57 (51–63)	
Tx not delayed: device promptly inserted	26 (53)	27 (64)	
Tx delayed: no PICC list/theatre space	17 (35)	8 (19)	
Tx delayed: no inpatient beds	4 (8)	8 (19)	
Delay to medication:			
none	43 (88%)	33 (79%)	
up to 4 hours	3 (6%)	4 (10%)	
>4 hours	3 (6%)	5 (12%)	
Therapeutic dose[g] (Elastomeric): (*N*=24 checks)	13 (76%)	7 (100%)	
Therapeutic dose[g] (Ambit TM) (*N*=50 checks)	17 (89%)	30 (97%)	
Therapeutic dose[g] (syringe driver) (*N*=262 checks)	153 (99%)	104 (97%)	
Failure	4 (8)	9 (21)	0.071[a]
Dwell time[b] (days)	14 (13–15)	14 (9–14)	
Catheter-days	725	498	
Incidence rate (per 1,000 catheter-days, 95% CI)	5.52 (2.07–14.7)	18.1 (9.40–34.7)	
Incidence rate ratio (95% CI)	reference	3.28 (0.91–14.6)	0.041[d]
Hazard ratio (unadjusted, 95% CI)	reference	3.22 (0.98–10.6)	0.054[e]
Reason for removal[f]:			
completed treatment or elective	45 (92)	33 (79)	
patient reported pain/discomfort	0 (0)	4 (10)	
complete dislodgement	2 (4)	1 (2)	

	PICC *n*=49	Midline *n*=42	p-value
occlusion	0 (0)	3 (7)	
leaking	0 (0)	2 (5)	
rupture/fracture	2 (4)	0 (0)	
infiltration	0 (0)	1 (2)	
confirmed thrombosis	0 (0)	1 (2)	
Complications during dwell (ever)[f]:			
occlusion	5 (10)	12 (29)	
skin injury/pressure area	5 (10)	5 (12)	
pain/discomfort	0 (0)	5 (12)	
leaking	1 (2)	2 (5)	
partial dislodgement	2 (4)	2 (5)	
fracture	2 (4)	0 (0)	
internal malposition	0 (0)	1 (2)	
phlebitis	0 (0)	1 (2)	
infiltration	0 (0)	1 (2)	
Suspected CABSI	1 (2)	0 (0)	
Confirmed CABSI	0 (0)	0 (0)	
Child pain, midline awake (max. 10, *N*=29)[d]	-	1 (1–4)	
Parent anxiety, midline awake (max. 10, *N*=30)[d]	-	2 (0–4)	
Parent anxiety, PICC GA (max. 10, *N*=47)[d]	4 (2–7)	-	
Patient experience (worst 0 to best 10, *N*=70)[d]	8 (7–10)	9 (5.5–10)	

frequencies and column percentages shown unless otherwise noted; [a] chi-squared test; [b] median (25th–75th percentiles) shown; [c] rank-sum test; [d] log-rank test; [e] Cox regression; [f] multiple answers allowed; [g] >80% of dose in last 24 hours; GA = general anaesthetic; CI = confidence interval; CABSI = catheter-associated bloodstream infection; tx = treatment;

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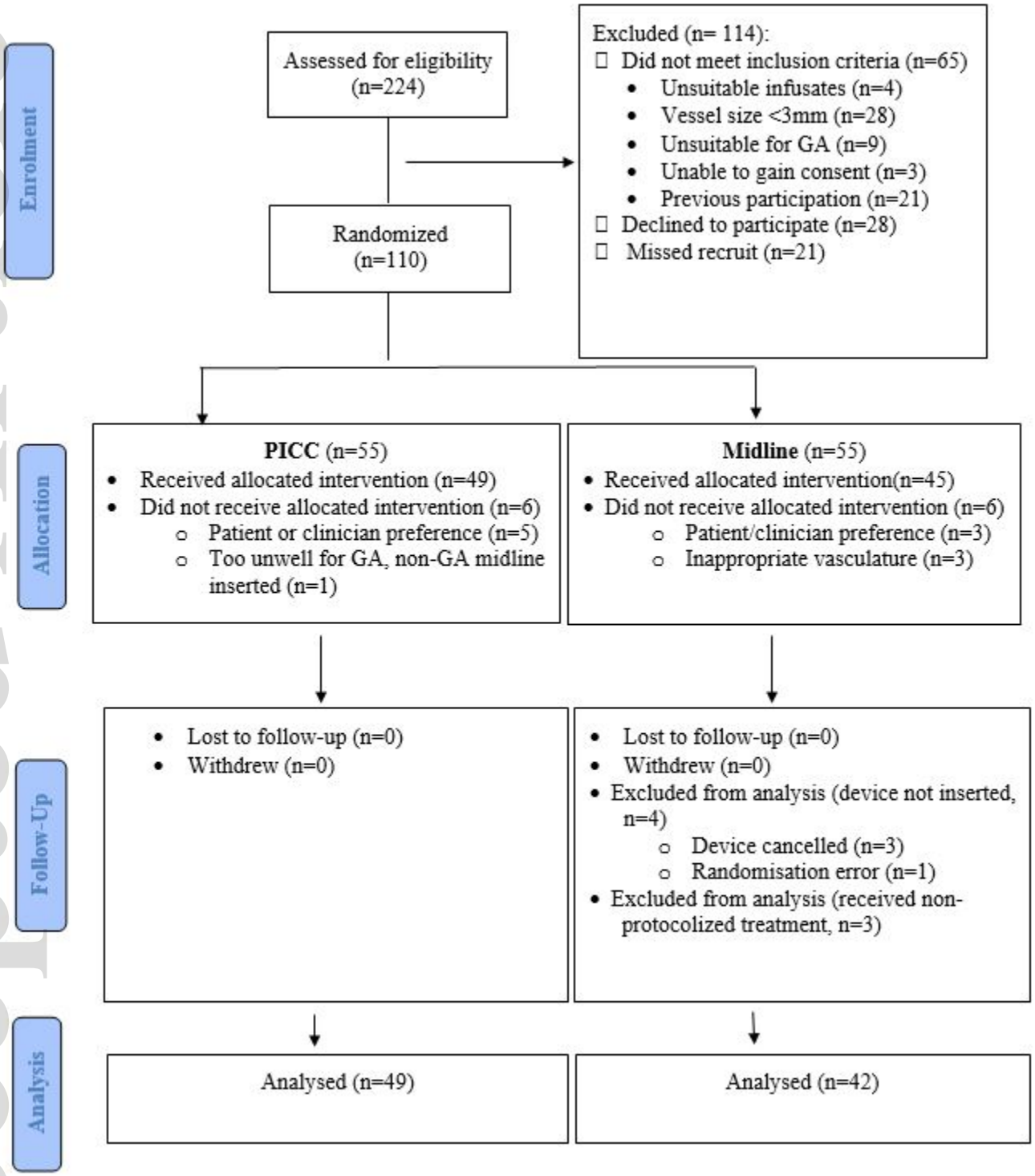

Figure 1

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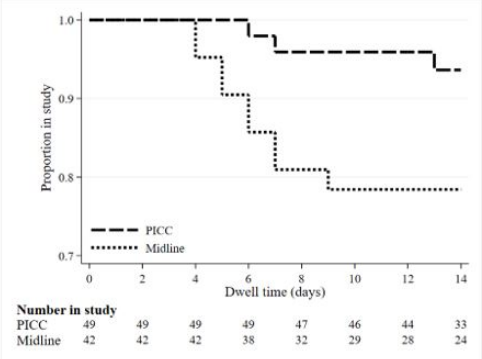
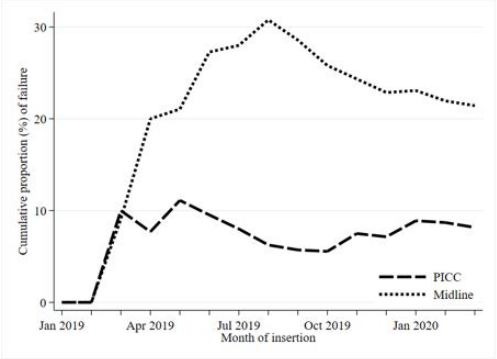


Figure 2a.



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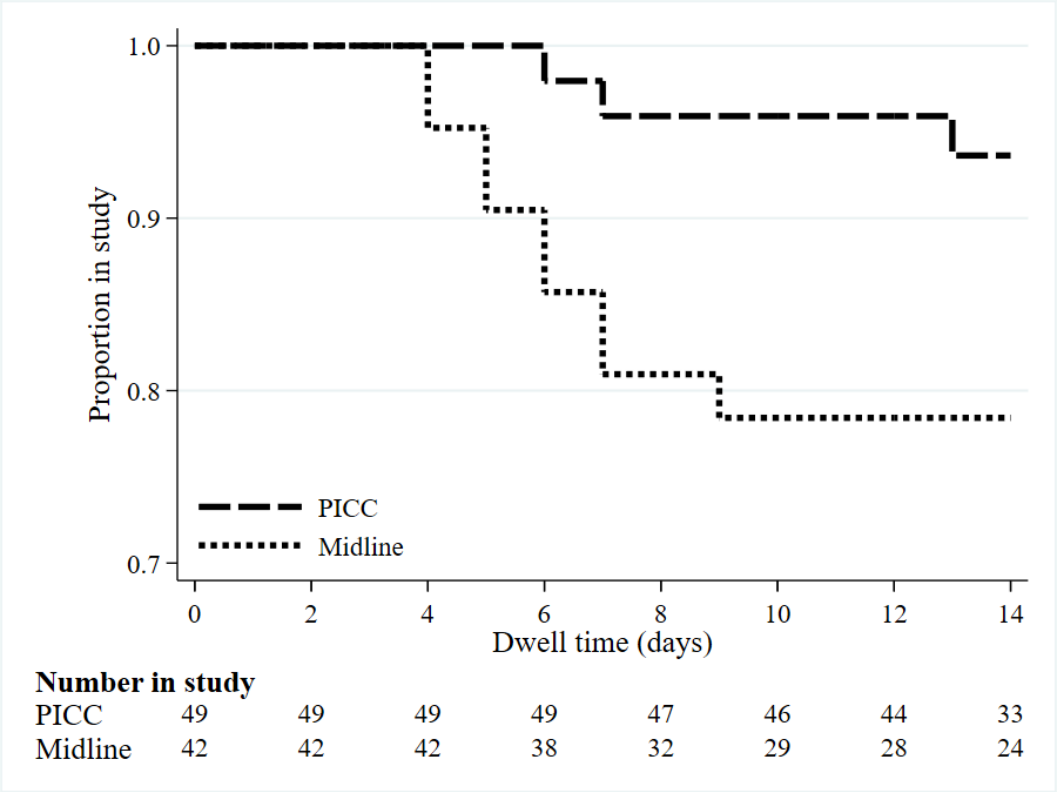

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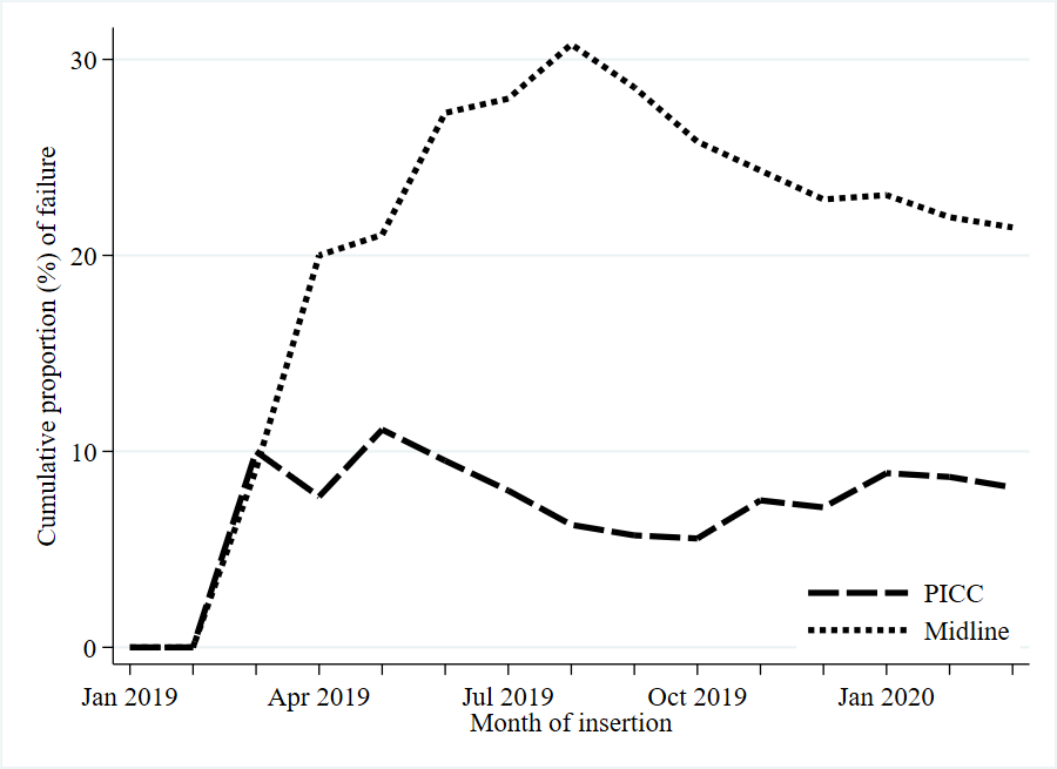

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