**Appendices**

1. STROBE guidelines
2. Potential risk factors for CLABSI developed by literature review and expert consensus
3. Clinical variable definitions
4. Clinical variables with >5% discrepancy rate during data validation
5. Sensitivity analysis
6. STROBE statement—Checklist of items that should be included in reports of case-control studies

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| --- | --- | --- | --- |
|  | Item No | Recommendation | Location in manuscript |
| **Title and abstract** | 1 | (*a*) Indicate the study’s design with a commonly used term in the title or the abstract | Page 2 |
| (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | Page 2 |
| Introduction | | |  |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | Pages 4-5 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | Pages 4-5 |
| Methods | | |  |
| Study design | 4 | Present key elements of study design early in the paper | Pages 5-7 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | Pages 5-7 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls | Pages 5-7 |
| (*b*)For matched studies, give matching criteria and the number of controls per case | Pages 5-6 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | Pages 5-7 + Appendix |
| Data sources/ measurement | 8\* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | Appendix |
| Bias | 9 | Describe any efforts to address potential sources of bias | Page 14-15 |
| Study size | 10 | Explain how the study size was arrived at | Pages 5, 8 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | Pages 7-8 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | Page 7-8 |
| (*b*) Describe any methods used to examine subgroups and interactions | Page 7-8 |
| (*c*) Explain how missing data were addressed | Not applicable |
| (*d*) If applicable, explain how matching of cases and controls was addressed | Pages 5-6 |
| (*e*) Describe any sensitivity analyses | Page 8 |
| Results | | |  |
| Participants | 13\* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed | Page8 |
| (b) Give reasons for non-participation at each stage | Not applicable |
| (c) Consider use of a flow diagram | Figure 1 |
| Descriptive data | 14\* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | Table 1 |
| (b) Indicate number of participants with missing data for each variable of interest | Tables |
| Outcome data | 15\* | Report numbers in each exposure category, or summary measures of exposure | Page 8 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | Pages 8-9 |
| (*b*) Report category boundaries when continuous variables were categorized | Pages 8-9 |
| (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | Pages 8-9 |

1. Potential risk factors for CLABSI developed by literature review and expert consensus

* Demographics – age at admission, age at central line-associated bloodstream infection (CLABSI) diagnosis, gender, ethnicity, survival to discharge, Pediatric Index of Mortality Score, intensive care unit (ICU) length of stay, unit of admission, emergent or planned admission, PICU Up! score at time of CLABSI
* Line characteristics – type of central venous catheter (CVC), anatomic location of CVC, location of CVC placement, credentials of provider placing CVC, number of lumens, duration of dwell, number of times accessed, number of CVCs present
* Concurrent invasive medical devices - tracheostomy, external ventricular drain (EVD), chest tube, arterial line, endotracheal tube (ETT), nephrostomy, ileostomy/jejunostomy, Foley catheter
* Concerns of malnutrition – body mass index (BMI) category at admission and time of CLABSI diagnosis
* Infectious risk factors – methicillin-resistant *Staphylococcus aureus* (MRSA)/vancomycin-resistant *Enterococcus* (VRE)/other multidrug-resistant (MDR) organism colonization, history of CLABSI, receiving empiric or prophylactic antibiotics (for risk of candidemia or MDR bacteria), Braden QD score, administration of glucocorticoids
* Intrahospital transport < 72 hours prior to CLABSI
* Administration of alteplase < 72 hours prior to CLABSI
* Signs of altered gut function - gastrostomy tube continuous vented/Sump to continuous low wall suction, diarrhea (>3 episodes/day) or stool volume (mL/kg/day), vomiting (>2 episodes/day) or gastric output (mL/kg/day), increase in abdominal girth (>2 increases in 24 hours), promotility agents ordered, anti-emetics ordered, positive fecal or gastric occult blood test, intra-abdominal surgical procedure < 72 hours prior to CLABSI, need for vasoactive agents
* Enteral feeding - enteral feed initiation, enteral feeds at 50% goal, enteral feeds at 100% goal, enteral feeding modality (mouth, nasogastric tube, nasojejunal tube, gastrostomy tube, gastrojejunostomy tube, continuous, bolus)
* Time from parenteral nutrition discontinuation
* Medication administration - No parenteral medications on medication administration record (MAR), enteral and parenteral medications on MAR, continuous sedative infusion

1. Clinical variable definitions

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| --- | --- |
| **Variable** | **Definition** |
| Survival to discharge | Discharge disposition as indicated in discharge summary for hospitalization stay that included ICU encounter of interest.  Survival to discharge included dispositions of: home, home with visiting nurse services, non-acute facility, skilled nursing facility, and other acute hospital. |
| Duration of ICU stay | For case patients, duration of ICU stay was measured from date of CLABSI to date of ICU discharge. For control patients, duration of ICU stay was measured from date of ICU admission to date of ICU discharge. |
| Type of admission | Type of admission was determined by manual review of the ICU admission note.  Surgical admissions included: admissions directly from the operating room/interventional radiology/cardiac catheterization laboratory/ electrophysiology laboratory, neonates with known congenital anomalies requiring surgical intervention (i.e. congenital heart defects, omphalocele, gastroschisis, congenital diaphragmatic hernia, esophageal atresia), surgical emergencies, and trauma patients.  Medical Admissions included: oncology, sepsis, respiratory failure, medical management of congenital heart disease.  Elective admissions included: ​​patients coming for second opinions from other hospitals, babies with prenatally known congenital heart disease admitted to the CICU, babies with known congenital diaphragmatic hernia (CDH), babies with known congenital anomalies admitted to the NICU, organ transplants, and patients presenting for planned admission from procedural areas.  Emergent admissions included: from the emergency department, admission from other hospitals for higher level of care/service not offered there, postnatally diagnosed congenital anomalies admitted to any of the ICUs, admission from post anesthesia care unit for some complication from anesthesia/surgical, admission from floor after ICU evaluation or code event. |
| Pediatric Index of Mortality (PIM) score | Calculated based on laboratory values and vital signs during first 24 hours of admission. Composite score associated with mortality risk during ICU stay. |
| Anatomic location of central venous catheter (CVC) | As noted in the CVC insertion procedure note in the medical record: internal jugular vein, subclavian vein, upper extremity vein (includes basilic, brachial, cephalic, antecubital, axillary, and documentation of upper extremity from outside hospital notes), lower extremity vein (includes femoral, saphenous, and documentation of lower extremity from outside hospital records). |
| Concurrent CVCs | Presence of more than one CVC during time period of interest. |
| Presence of chest tube | Defined as the presence of a chest tube as noted in the “Lines and Tubes” section of the electronic medical record (EMR) or in the “Ins and Outs” section of the EMR during time period of interest. |
| Presence of endotracheal tube | Defined as the presence of an endotracheal tube as noted in the “Respiratory/Ventilator Support” section of the EMR during time period of interest. |
| Presence of Foley catheter | Defined as the presence of a Foley catheter as noted in the “Lines and Tubes” section of the EMR or in the “Ins and Outs” section of the EMR during time period of interest. |
| Presence of enteral feeding tube | Defined as the presence of a gastrostomy tube, gastrojejunostomy tube, nasogastric tube, nasoduodenal tube, or nasojejunal tube as noted in the “Lines and Tubes” section of the EMR or in the “Ins and Outs” section of the EMR during time period of interest. |
| Presence of tracheostomy | Defined as the presence of a tracheostomy noted in the “Respiratory/Ventilator Support” section of the EMR or in Admission History & Physical Exam or Discharge Summary during time period of interest. |
| Presence of ostomy | Defined as the presence of an ileostomy, colostomy, or mucous fistula noted in the “Lines and Tubes” section of the EMR or in the “Ins and Outs” section of the EMR during time period of interest. |
| Neutropenia | Defined as an absolute neutrophil count (ANC) < 500 cells/µL for ≥3 consecutive days. |
| Oncologic condition | Any mention of a history of an oncologic condition including but not limited to acute lymphoblastic leukemia, acute myelocytic leukemia, neuroblastoma, medulloblastoma, Wilms tumor, hepatoblastoma, craniopharyngiomas, or lymphoma prior to ICU encounter of interest on patient’s problem list or in ICU admission note. |
| History of solid organ transplant | Any mention of a history of kidney, liver, lung, heart, or small bowel transplant prior to ICU encounter of interest on patient’s problem list or in ICU admission note. Included encounters that were immediately after transplantation (e.g., patient’s ICU admission was after heart transplantation). |
| History of stem cell transplant | Any mention of a history of stem cell transplant prior to ICU encounter of interest on patient’s problem list or in ICU admission note. |
| History of short bowel syndrome | Any mention of a history of short bowel syndrome prior to ICU encounter of interest on patient’s problem list or in ICU admission note. |
| History of gastrointestinal graft-vs-host disease (GvHD) | Any mention of a history of gastrointestinal GvHD prior to ICU encounter of interest on patient’s problem list or in ICU admission note. |
| Transport to radiology | Presence of a radiology report from magnetic resonance imaging, computed tomography imaging (CT), Nuclear Medicine, or Fluoroscopy in the results tab of the EMR during time period of interest. Ultrasounds were not included as they are almost exclusively performed at the bedside in the ICU at BCH. Head CTs without contrast were reviewed to ensure they did not occur at the bedside. |
| Transport to interventional radiology (IR) | Presence of “IR” reports in the results tab of the EMR during time period of interest. Notes were searched for “bedside” and “sedation by ICU” and “in the ICU” to ensure bedside procedures were not included. |
| Transport to operating room | Presence of “Brief Op Note” or “Operative Report” in the EMR during time period of interest stating patient went to the main operating room or cardiac operating room. Notes were searched for “bedside” and “sedation by ICU” and “in the ICU” to ensure bedside procedures were not included. |
| Transport to cardiac catheterization lab | Presence of “Catheterization Note” in the EMR during time period of interest stating patient went to the cardiac catheterization laboratory. |
| Parenteral nutrition (TPN) | Active orders for parenteral nutrition listed as administered on the patient’s MAR during time period of interest.  If duration greater than or equal to 21 days, defined as parenteral nutrition dependent. This designation included patients on home parenteral nutrition. |
| Enteral nutrition | Included documentation of enteral nutrition in the form of oral or tube feeds as noted in the “Ins and Outs” section of the EMR during time period of interest. |
| Post-pyloric feeds | Included documentation of enteral nutrition as noted in the “Ins and Outs” section of the EMR during time period of interest. |
| Lactic acidosis | Lactic acid value greater than or equal to 3.0 mmol/L during time period of interest. |
| Extracorporeal membrane oxygenation (ECMO) | Documentation of “ECMO Cannulation” or “ECMO Decannulation  or “eCPR” in “Brief Operative Note” 30 days prior to CLABSI. As per the NHSN definition, no CLABSI during an ECMO run were included. |
| Cardiac arrest | Documentation of cardiac arrest in Discharge Summary or chart search with results for “CPR”, “cardiac arrest”, or “respiratory arrest” 30 days prior to CLABSI. |
| Admission weight | Weight and associated percentile as documented in the “Growth Chart” section of the EMR on day of ICU admission. If not available, values from date closest to admission were selected. |
| Discharge weight | Weight and associated percentile as documented in the “Growth Chart” section of the EMR on day of ICU discharge. If not available, values from date closest to discharge were selected. |
| Elemental formula | Included documentation of receiving one of the following formulas as noted in the “Ins and Outs” section of the EMR during time period of interest: Nutramigen, Alimentum, Pregestimil, Neocate, Elecare, Pure Amino, Tolerex. |
| Continuous opioid infusions | Any of the following medications listed as administered on the patient’s MAR under continuous infusions section during time period of interest: morphine, fentanyl, hydromorphone.  Nurse-controlled analgesia (NCA) and patient-controlled analgesia (PCA) orders of these medications were excluded. |
| Continuous non-opioid infusions | Any of the following medications listed as administered on the patient’s MAR under continuous infusions section during time period of interest: ketamine, dexmedetomidine, midazolam, propofol. |
| Continuous neuromuscular blockade | Any of the following medications listed as administered on the patient’s MAR under continuous infusions section during time period of interest: vecuronium, cisatracurium. |
| Vasoactive inotropic score | Any of the following medications listed as administered on the patient’s MAR under continuous infusions section during time period of interest: dopamine, norepinephrine, epinephrine, vasopressin, dobutamine, milrinone, phenylephrine.  Highest hourly rate for each medication was used to calculate the vasoactive inotropic score for each patient. |
| Stress ulcer prophylaxis | Any of the following medications listed as administered during time period of interest: cimetidine, famotidine, ranitidine, nizatidine, dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole.  Included continuous infusions of pantoprazole listed as administered on the patient’s MAR during time period of interest.  TPN orders were searched to look for inclusions of famotidine or ranitidine during time period of interest. |
| Alteplase | Documented administration of one-time alteplase doses for partial or complete CVC occlusion during time period of interest.  Alteplase infusions were excluded. Doses written for but documented as not given were excluded. |
| Ileus | Composite variable included patients who had one or more of the following during the time period of interest: parenteral nutrition dependence, need for post-pyloric feeds, need for elemental formula, presence of nasogastric or gastrostomy tube to continuous low wall suction or gravity. |
| Ischemia | Composite variable included patients who had one or more of the following during the time period of interest: lactic acidosis, vasoactive inotropic score >0, ECMO within 30 days, cardiac arrest within 30 days, positive fecal occult blood, diagnosis of necrotizing enterocolitis (NEC) within 30 days. |
| Intestinal insufficiency | Composite variable included patients who had one or more of the following during the time period of interest: presence of ostomy, diagnosis of short bowel syndrome, or parenteral nutrition dependence. |
| Blood product administration | Included documentation of packed red blood cells, cryoprecipitate, platelets, or fresh frozen plasma in the “Ins and Outs” section of the EMR during time period of interest.  Excluded all patients who had an EMCO run during ICU course of interest when calculating this variable. |
| Chronic CVC | Defined as a CVC that was in place for greater than or equal to 21 days. |

1. Clinical variables with >5% discrepancy rate during data validation+

|  |  |  |
| --- | --- | --- |
| **Variable** | **Control Discrepancy Rate** | **Case Discrepancy Rate** |
| Ethnicity | 8.5% | n/a |
| Race | 6.6% | n/a |
| Admission weight | 12.3% | 8.0% |
| Admission weight percentile | 29.2% | 46.0% |
| Discharge condition | 25.5% | 19.0% |
| Alteplase administration | 11.3% | n/a |
| Radiology transport | 22.6% | n/a |
| Operating room transport | 33.0% | n/a |
| Cardiac cath or electrophysiology transport | 8.5% | n/a |
| Interventional radiology transport | 13.2% | n/a |
| Fresh Frozen Plasma administration | 6.6% | n/a |
| Packed Red Blood Cell administration | 31.1% | n/a |
| Platelet administration | n/a | 12.0% |
| Discharge weight percentile | 34.9% | n/a |
| Elemental formula | 19.8% | 8.0% |
| Post-pyloric feeds | 25.5% | n/a |
| Parenteral nutrition dependence | 13.2% | 15.0% |
| Lactic acid ≥ 3 mmol/L | 10.4% | 8.0% |
| Cardiac arrest | 5.7% | n/a |
| Promotility agent | 13.2% | 12.0% |
| Proton pump inhibitor | 12.3% | 15.0% |
| Histamine H2 blocker | 24.5% | 15.0% |
| Continuous opioid infusion | 11.3% | n/a |
| Continuous non-opioid infusion | 16.0% | n/a |
| Continuous neuromuscular blockade | 7.5% | n/a |
| Parenteral Nutrition administration | 5.7% | n/a |
| Enteral feeding | 19.8% | n/a |
| Vasoactive inotropic score | n/a | 19.0% |

+20% of randomly selected study participants had all recorded variables manually double checked in electronic medical record and updated if incorrect. The percentage of incorrect fields for each variable were then calculated.

Abbreviations: “n/a” = variable not manually double checked

1. Sensitivity analysis independent risk factors for the development of central line-associated bloodstream infections in the pediatric intensive care setting excluding matched sets that contained one patient with a gap of one or more calendar days without a CVC in place during their ICU stay

|  |  |  |
| --- | --- | --- |
| **Predictor** | **Adjusted Odds Ratio**  **(95% CI)** | ***P* value** |
| Anatomic location of placement |  |  |
| Upper extremity vein | 0.07 (0.01, 0.32) | 0.001 |
| Type of CVC |  |  |
| Non-tunneled | 0.09 (0.02, 0.46) | 0.003 |
| Number of days with one or more CVC(s) in place | 1.59 per 10 days (1.23, 2.07) | 0.001 |
| Concurrent invasive medical devices |  |  |
| Endotracheal tube | 0.19 (0.06, 0.59) | 0.005 |
| Foley catheter | 0.29 (0.12, 0.75) | 0.01 |
| Nasogastric tube | 0.34 (0.14, 0.83) | 0.018 |
| Intra-hospital transport <72 hours prior to CLABSI | |  |
| Radiology | 0.12 (0.03, 0.47) | 0.003 |
| Presence of GI tract dysfunction |  |  |
| Insufficiency | Omitted due to collinearity |  |
| Continuous neuromuscular blockade infusion at time of CLABSI | 0.26 (0.08, 0.89) | 0.032 |
| Continuous opioid sedative infusion at time of CLABSI | Omitted due to collinearity |  |
| Continuous non-opioid sedative infusion at time of CLABSI | 3 (1.09, 8.25) | 0.033 |
| Stress ulcer prophylaxis |  |  |
| H2 blockers | 0.22 (0.07, 0.69) | 0.01 |

Abbreviations: CLABSI = central line associated bloodstream infection, CVC = central venous catheter, EP = electrophysiology, GI = gastrointestinal, PPI = proton pump inhibitor, H2 = histamine H2 receptor