CLINICAL INVESTIGATION

# Analysis of 72-Hour Sterility of Common Pediatric Continuous Intravenous Infusions

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**OBJECTIVES** Patient morbidity and mortality associated with contaminated and improperly prepared sterile products has captured national attention. In response, both the United States Pharmacopeia (USP) and Centers for Disease Control (CDC) have published recommendations in an effort to minimize the risk of infection. While the CDC recommends that administration sets are not changed more frequently than every 72 hours, the USP recommends a maximum beyond use date of 48 hours. Neither organization provides specific guidance on expiration dating once the intravenous drug is dispensed. Likewise, neither addresses the length of time that a bag containing medication for continuous infusion may hang once administration to the patient has begun. We evaluated the sterility of medications that are commonly administered by continuous infusion to pediatric patients. Because frequent manipulation of infusion and administration sets may predispose the patient to adverse events, we evaluated sterility for extended beyond use dating up to 72 hours.

**METHODS** Thirty-five common intravenous (IV) continuous infusions using 94 standard concentrations and diluents were identified. IV solutions were mixed using sterile technique in the laminar flow hood in accordance with USP guidelines. Medications were excluded for short stability, short durations of use or high cost. A sample from each solution was tested for contamination or bacterial growth at 72 hours. Any visible discoloration suggesting physical instability was also evaluated.

**RESULTS** None of the syringes or chambers resulted in contamination, bacterial growth or discoloration after 72 hours.

**CONCLUSIONS** This study provides sufficient data that these compounded sterile products may be stored using a beyond use date up to 72 hours for a number of commonly used continuous IV infusions in pediatric patients. In our institution, this allows for a more convenient and consistent change of both administration sets and continuous infusions at 72 hours to potentially minimize adverse events, workload and cost.

**KEYWORDS** continuous infusions, expiration, pediatric, sterility

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## INTRODUCTION

Compounding sterile products is a major component of hospital pharmacy practice. Increasing patient morbidity and mortality associated with contamination or improper preparation has prompted national attention. Despite published guidelines establishing practice standards for compounding sterile products, pharmacy as a profession has not adopted a practice standard

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**ABBREVIATIONS** BUD, beyond use date; CDC, Centers for Disease Control and Prevention; CPT, certified pharmacy technician; CSP, compounded sterile product; D5W, dextrose 5% in water; ICU, intensive care unit; IV, intravenous; NS, normal saline; USP, United States Pharmacopeia

for key components of sterile compounding such as minimizing contamination, aseptic technique, and quality assurance.[1] Pediatric hospitals are faced with additional challenges due to the uniqueness of their patient population. Compared to adults, pediatric patients typically require special compounds and dilutions that are often not available through regular manufacturers. As a result, hospital pharmacies serving pedia-tric patients are commonly asked to prepare specialized compounds which may increase the risk of contamination and limit the quality of these products. Nosocomial infections caused by likely multi-drug resistant Gram-negative bacteria such as *Enterobacter cloacae*, *Pseudomonas aeruginosa, Pseudomonas putida,* and *Serratia marcescens* are well described in pediatric patients due to contaminated compounded sterile products (CSPs).[2-8]

In 2001, The United States Pharmacopeia (USP) began its efforts to establish an enforceable standard for pharmacies that prepare CSPs.[9] Recently, USP published final revisions for practice standards which will be mandated by regulatory agencies for health care settings that compound sterile products including: hospitals, community pharmacies, home infusion services, ambulatory care services, physician offices and nursing homes. The intent of these practice guidelines is to prevent morbidity or mortality as a result of contamination or improperly prepared CSPs. USP 797 provides specific requirements for the sterile preparation of CSPs and also requires that all personnel involved in the preparation process are adequately educated and trained.[10] Aseptic technique has been identified as the most important variable to minimize contamination.[11] Under these guidelines, beyond use dates (BUD) are assigned to CSPs based on the number of manipulations and contamination risk during drug preparation or storage. There are two major factors in establishing CSP beyond use dating. This includes, first, the stability of the drug and then the sterility of the drug. For CSPs with the lowest risk, a BUD maximum of 48 hours may be assigned, given it is stable when stored at room temperature, unless further sterility testing is done.[10,12]

In 2002, the Centers for Disease Control and Prevention (CDC) published enforceable guidelines for adult and pediatric patients for the prevention of intravascular catheter-related infections. The incidence of catheter-related infections varies by catheter type, frequency of catheter manipulation, and patient-related factors. Each infection increases the risk of mortality and health care costs.[13] The intensive care unit (ICU) setting often carries a higher risk of infection due to increased use of central as opposed to peripheral line placement, the need for frequent manipulation, and extended durations of use for indwelling lines. Additionally, ICU patients are often colonized with hospital-acquired organisms. In order to minimize the risk for infection, the CDC recommends that administration sets are changed no more frequently than every 72 hours.[13]

Although their intent is the same, USP and the CDC have two sets of standards that are difficult to adhere to when combined in clinical practice for each institution. At our institution, we change administration sets every 72 hours per CDC recommendations and hospital policy. Per USP, pharmacy provides a BUD in accordance with the standard up to a maximum of 48 hours based on contamination risk. A BUD only addresses storage conditions before the CSP is attached to the patient and is not to be confused with expiration dating or hang time. Once dispensed from the pharmacy, USP 797 guidelines no longer apply. Further recommendations on hang times or expiration dating may be better explained by the CDC or the Infusion Nurses Society (INS); however, to our knowledge no specific recommendations are suggested to date.[10,13,14] Therefore, in clinical practice at our institution, the nursing staff often use the BUD assigned by the pharmacy as the "expiration date." When infusions must be changed every 24 to 48 hours it becomes difficult to manage changing CSPs without manipulation or changing of the administration set simultaneously, increasing the likelihood a patient may experience an adverse event. As a result, our administration sets are often changed more frequently than every 72 hours, contrary to the CDC recommendations, potentially increasing adverse events, workload and cost.

USP allows for extension of the BUD for storage prior to administration if the medication is stable and further sterility testing has been performed.[10] Since more frequent manipulation of infusions and administration sets may predispose the patient to hemodynamic instability, infection, air emboli and other adverse events we chose to

**Table.** Sterility of Commonly Used IV Continuous Infusions Medications In Pediatric Patients

| Drug | Concentrations | Diluents, Volume or Additive Concentration | Contamination Risk | Growth | Visual Precipitate | Color Change |
|---|---|---|---|---|---|---|
| Dobutamine | 800, 1600, 3200, 6400 µg/mL | NS, D5W | Medium | None | None* | None |
| Dopamine | 800, 1600, 3200, 6400 µg/mL | NS, D5W, D10W | Medium | None | None | None |
| Epinephrine | 16, 32, 64 µg/mL | D5W | Medium | None | None | None |
| Milrinone | 100, 200, 800 µg/mL | NS, D5W | Low | None | None | None |
| Lidocaine | 5 mg/mL | 10 mL Syringe | Low | None | None | None |
| Phenylephrine | 10 µg/mL | 10 mL Syringe | Low | None | None | None |
| Epinephrine | 10 µg/mL | 10 mL Syringe | Low | None | None | None |
| Fentanyl | 2.5, 5, 10, 25 µg/mL | NS, D5W, D10W | Low | None | None | None |
| Fentanyl | 50 µg/mL | Undiluted<br>20 mL and 50 mL syringes and 100 mL bags | Low | None | None | None |
| Hydromorphone | 1 mg/mL | PCA in NS (30mL) | Low | None | None | None |
| Hydromorphone | 50, 100 µg/mL | NS, D5W | Low | None | None | None |
| Ketamine | 1, 5 mg/mL | D5W | Low | None | None | None |
| Morphine | 0.25, 0.5 mg/mL | NS, D5W | Low | None | None | None |
| Midazolam | 0.25, 0.5, 1 mg/mL | NS, D5W | Low | None | None | None |
| Midazolam | 5 mg/mL | Undiluted | Low or Medium (depending on volume) | None | None | None |
| Pentobarbital | 50 mg/mL | Undiluted | Low | None | None | None |
| PICU Arterial Line | NS and ½ unit/mL Heparin | 250 mL | Low | None | None | None |

**Table.** Sterility of Commonly Used IV Continuous Infusions Medications In Pediatric Patients (cont.)

| Drug | Concentrations | Diluents, Volume or Additive Concentration | Contamination Risk | Growth | Visual Precipitate | Color Change |
|---|---|---|---|---|---|---|
| PICU Arterial Line | NS and ½ unit/mL Heparin and 15 mg Papaverine | 250 mL | Low | None | None | None |
| NICU Flush | NS, ½ Na Acetate | 50 mL | Low | None | None | None |
| UAC/UVC | ½ NS and ¼ Heparin | 100 mL | Low | None | None | None |
| NICU Arterial Line | ½ NS and ¼ Heparin and 4 mg Lidocaine | 100 mL | Medium | None | None | None |
| D10W Fluids | NaCL | 20 mEq/L | Low | None | None | None |
| D10W Fluids | NaCL/KCL | 20 mEq/L; 20 mEq/L | Low | None | None | None |
| D10W Fluids | NaCL, KCl, Ca Gluc | 20 mEq/L; 20 mEq/L; 10 mEq/L | Medium | None | None | None |
| D10W Fluids | NaCL, KCL, Ca Gluc, Heparin | 20 mEq/L; 20 mEq/L; 10 mEq/L; ¼ unit/mL | Medium | None | None | None |
| D20W Fluids | NaCL | 20 mEq/L | Low if made from mfg D20W | None | None | None |
| D20W Fluids | NaCL/KCL | 20 mEq/L; 20 mEq/L | Low | None | None | None |
| D20W Fluids | NaCL, KCL, Ca Gluc | 20 mEq/L; 20 mEq/L; 10 mEq/L | Medium | None | None | None |
| D20W Fluids | NaCL, KCL, Ca Gluc, Heparin | 20 mEq/L; 20 mEq/L; 10 mEq/L; ¼ unit/mL | Medium | None | None | None |
| D5W Fluids | NaCL | 20 mEq/L | Low | None | None | None |
| D5W Fluids | NaCL/KCL | 20 mEq/L; 20 mEq/L | Low | None | None | None |
| D5W Fluids | NaCL, KCL, Ca Gluc | 20 mEq/L; 20 mEq/L; 10 mEq/L | Medium | None | None | None |
| D5W Fluids | NaCL, KCL, Ca Gluc, Heparin | 20 mEq/L; 20 mEq/L; 10 mEq/L; ¼ unit/mL | Medium | None | None | None |

** Denotes brown precipitate likely due to chemical reaction between drug and growth medium*

evaluate the 72-hour sterility of common continuous infusions shown to be stable for at least 72 hours. The purpose of this study was to establish a longer BUD for common continuous infusions used in the pediatric population to propose an evidence-based standard for our institution that would allow both drug and administration sets to be changed no more frequently than every 72 hours, when appropriate, to better comply with both the CDC and USP recommendations.

## MATERIALS AND METHODS

A thorough search through primary literature and standard references was done to verify stability.[15-19] Some clinical judgment was made for extrapolation of stability using available data of concentrations that were not our institution specific standards. For example, if stability was documented for a concentration both less than and greater than our standard, then our standard concentration was reported to be stable. All stability information including clinical judgment extrapolations were reviewed and verified by a team of pharmacists.

Common IV continuous infusions used in pediatric patients were identified and evaluated (Table). Contamination risk was assigned by the number of manipulations required to make a CSP and designated as low, medium or high.[10] At our institution, low risk CSPs may contain up to three commercially available products which could have up to three manipulations. Medium risk products contain more than three commercially available products but the number of manipulations is not specified. All medium and high risk products must be prepared in the pharmacy using aseptic technique by trained personnel. Lower contamination risk is provided when using premixed solutions or commercially available products as a result of less manipulation. IV solutions were mixed by only one certified pharmacy technician (CPT) using sterile technique in a laminar flow hood in accordance with USP guidelines.[10,20] Medications were excluded for short stability (less than 72 hours), short durations of use, or high cost. One sample from each solution was tested using a full filtration contamination growth medium chamber (QT Micro Systems #TM6000, QI Medical, Inc.) and tryptic soy broth for aerobic and facultative testing.[21] Sterility testing began within 60 minutes after preparation of each solution.

The syringes were kept at 22.5ºC ± 2.5ºC for the duration of the 14-day evaluation period. No other temperature ranges were tested and samples were not tested for fungi. Positive and negative controls were used for sampling comparison and training was provided by the microbiology company to the study pharmacist and CPT. At our institution, all pharmacists and technicians are tested for sterile technique at least annually for competency. Both syringe and chamber were examined by the study pharmacist for growth or turbidity (indicating a positive growth) at 72 hours and then daily up to 14 days. Any visible discoloration suggesting physical instability was also evaluated.

## RESULTS

Sterility results are summarized in Table. None of the syringes or chamber samples demonstrated contamination, bacterial growth or discoloration after 72 hours. A brown precipitate was noted in the chamber of dobutamine 6400 µg/mL in normal saline (NS) and dextrose 5% in water (D5W) sample. However, there was no contamination or bacterial growth in the sample and the syringe showed no visible precipitate or color change. The company indicated that this was most likely a result from a chemical instability with the growth medium and not consistent with a positive indication for contamination (QI Medical, personal communication, February 26, 2008).

## DISCUSSION

Both the USP and CDC have common initiatives to prevent the likelihood of contaminated CSPs or catheter-related infections through a variety of pertinent and evidence-based recommendations.[10,13] However, in order to comply with both standards, our institution was faced with a therapeutic dilemma in which some clinical judgment was required. USP allows some clinical judgment from the pharmacist when assigning BUD, however, to extend beyond the 48-hour maximum, further sterility testing in accordance with USP must be performed.[1,10,13-14,20]

The likelihood for potential adverse events as a result of more frequent manipulation of infusions and administration sets led our department to investigate extended beyond use dating of com-

monly used continuous infusions for patients most likely used in the ICU settings. By establishing a 72-hour BUD for CSPs, the pharmacy workload would likely be decreased and cause a reduction in drug cost associated with more frequent compounding and wastage.

This study provides sufficient data that these CSPs may be stored using a BUD up to 72 hours for a number of commonly used continuous IV infusions in pediatric patients. The methodology of our study was not sufficient to extrapolate a conclusion that these CSPs are safe to hang for 72 hours once dispensed from the pharmacy. Possible contamination from nursing and patient manipulation and contamination was not evaluated but may be subjects of future research. Continuous and diligent monitoring of line infections by our infection control team can provide needed quality assurance to determine this need for the future. Additionally, continuous quality assurance within our department to ensure sterility consistent with our 72-hour BUD is currently being considered. In our institution, this data used in conjunction with clinical judgment and hospital policy allows for a more convenient and consistent change of both administration sets and continuous infusions at 72 hours to minimize potential adverse events, workload and cost.

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