Clinical Investigation

# Antibiotics Before Removal of Percutaneously Inserted Central Venous Catheters Reduces Clinical Sepsis in Premature Infants

*Gail E. Reynolds, DNP, MSN,[1] Sarah B. Tierney, PharmD,[2] and Jonathan M. Klein, MD[1]*

*[1]Stead Family Department of Pediatrics, [2]Department of Pharmaceutical Care, University of Iowa Children's Hospital, Iowa City, Iowa*

**OBJECTIVES:** Evaluate the incidence of postcatheter removal clinical sepsis when antibiotics were infused prior to the removal of percutaneously inserted central venous catheters (PICCs).
**METHODS:** A retrospective chart review of premature neonates (n = 196) weighing ≤1250 g at birth with 218 PICC line removals in the presence or absence of antibiotics at a tertiary level neonatal intensive care unit (NICU) between January 1, 2010, and May 31, 2012. Charts were reviewed looking for the presence of clinical sepsis defined as a sepsis workup including white blood cell count, differential, C-reactive protein, blood and/or cerebral spinal fluid (CSF), and urine cultures along with at least 48 hours of antibiotic therapy given within 72 hours after removal of a PICC line. Antibiotics were considered present at line removal if given within 12 hours before catheter removal either electively or at completion of a planned course.
**RESULTS:** When antibiotics were given within 12 hours before PICC line removal, only 2% of the line removal episodes (1/48) resulted in a neonate developing clinical sepsis versus 13% (21/165) when no antibiotics were given prior to removal (p = 0.03, Fisher's exact test). Despite the increased use of elective antibiotics with line removal, there was no increase in total antibiotic usage due to the overall decrease in episodes of clinical sepsis or changes in antibiogram susceptibility patterns.
**CONCLUSIONS:** There was an 11% absolute decrease and a 6-fold relative decrease in postcatheter removal clinical sepsis events in premature neonates who received antibiotics prior to PICC line removal.

**INDEX TERMS:** neonatal sepsis, PICC removal, prophylactic antibiotics

J Pediatr Pharmacol Ther 2015;20(3):203–209

## INTRODUCTION

Peripherally inserted central venous catheters (PICCs) are critical in caring for preterm neonates. A significant number of these neonates require long-term intravenous (IV) access for medications and neonatal venous nutrition. The use of a PICC line in preterm infants is not without risk. Hospital acquired or associated central line infection or sepsis in the neonatal population is life threatening. Low birth weight infants have immature immune responses making them vulnerable to sepsis. Preventing central line blood stream infections (CLABSIs) and postcatheter removal clinical sepsis is essential in reducing complications and associated costs incurred with these events including the diagnostic evaluation for sepsis, cost of additional medications needed for treatment, increased length of stay, as well as increased mortality and morbidity associated with sepsis.

When a PICC is placed, bacteria can colonize at the tip of the catheter. Upon removal of the catheter, there is a risk of bacteria being released into the bloodstream from the biofilm becoming dislodged and the neonate may become septic.[1] Coagulase negative staphylococci is the most common pathogen identified in late onset sepsis in neonates admitted to the neonatal intensive care unit (NICU) and the use of indwelling central lines increase the risk of hospital acquired infections[2–11] with gram positive pathogens accounting for as much as 80% of CLABSIs.[12] Furthermore, coagulase negative staphylococci are particularly adept at adhering to catheters and forming biofilms[13] leading to this organism being responsible for the majority of catheter-associated sepsis; other organisms associated

with sepsis in the presence of central venous catheters include: S*taphylococcus aureus*, *Enterobacter, Klebsiella*, and *Escherichia coli*.[11]

There are other factors that may increase a neonate's risk for CLABSI. Sengupta et al[14] and Njere et al[15] reported that the length of time the PICC was in place was the main predictor for PICC infection. Njere et al[15] saw an increased incidence of infection if the catheter was *in situ* for a period of greater than 9 days. Sengupta et al[14] showed that having an indwelling catheter *in situ* for greater than 35 days was an important risk factor to predict infection as compared to lines in for less than 35 days. Hoang et al[16] reported the median time to infection associated with a PICC line was 9 days when placed in an upper extremity and 15 days when placement was in a lower extremity. Thus the possibility of biofilm formation may increase with catheter duration. Due to these known risks of infection, the use of prophylactic antibiotics given during the removal phase has been studied.

In a retrospective study by van den Hoogen et al,[11] only 2% of patients (2/132) had postcatheter removal sepsis when given cefazolin (Ancef, Apotex Corp, Weston, FL) and gentamicin (Garamycin, APP Pharmaceuticals, LLC, Schaumburg, IL) at the time of removal compared with 10% of the patients (22/213) who did not receive antibiotics at the time of PICC removal. Hemels et al[6] conducted a prospective, randomized study where the group who received cefazolin both 1 hour before and 12 hours after PICC removal had zero cases (0/44) of PICC removal-associated sepsis compared to 11% in the group who received no antibiotics (5/44).

The aim of our study was to analyze our variance in practice behavior regarding the use of elective antibiotics given within 12 hours prior to PICC line removal to see if there was a reduction in the number of postcatheter removal clinical sepsis as well as culture positive sepsis events. If true, this would minimize the use of antibiotics for these patients and in turn decrease the overall antibiotic exposure for the entire unit, as well as potentially decrease mortality and morbidity associated with postcatheter removal clinical sepsis.

## MATERIALS AND METHODS

We performed a retrospective chart review to evaluate the incidence of clinical sepsis within 72 hours of PICC line removal in all premature infants ≤ 1250 g. Eligible patients included inborn and outborn patients at the University of Iowa Children's Hospital NICU between January 1, 2010, and May 31, 2012. Episodes of line removal were excluded from analysis if the line was present during early onset sepsis (defined as either a positive blood or cerebral spinal fluid (CSF) culture obtained in the first 3 days of life), emergently removed due to occlusion, or still in place when the infant died or was transferred.

PICC lines were inserted under sterile technique per The University of Iowa Children's Hospital Policy and Procedure using a standardized central line bundle made up of insertion and maintenance components based on guidelines from the Centers for Disease Control and Prevention, Institute for Healthcare Improvement, and The Joint Commission. No changes were made in central line bundle practices during the period studied. All lines were placed percutaneously and monitored by weekly radiographs for placement and daily via clear 100% occlusive dressings. No IV antibiotic prophylaxis was administered for PICC placement. PICC line dressings were changed when wet or when nonocclusive. PICC line tubing was changed every 4 days and lines were removed when no longer needed clinically as determined by review on daily medical rounds. If a CLABSI developed, the medical team, on an individualized basis, determined if the PICC line needed to be removed or if the infection could be treated through the line.

Data points were identified before collection started and included: birth weight ≤1250 g, gestational age at birth, length of time PICC was indwelling, purpose of line, if any antibiotics were infused within 12 hours before PICC line removal, or if a one-time dose of vancomycin (Vancocin, Hospira, Inc, Lake Forest, IL) was given 2 hours prior to line removal. The elective use of vancomycin was at the discretion of the provider and based upon an individualized decision and not per unit protocol. The dose of vancomycin (15 mg/kg) was infused through the PICC line over 90 minutes followed by a 1-mL normal saline flush over 30 minutes. For patients with more than 1 PICC line, each removal episode was analyzed as a separate event.

We defined a postcatheter removal clinical sepsis event as the performance of a sepsis workup (white blood cell count, differential, C-reactive

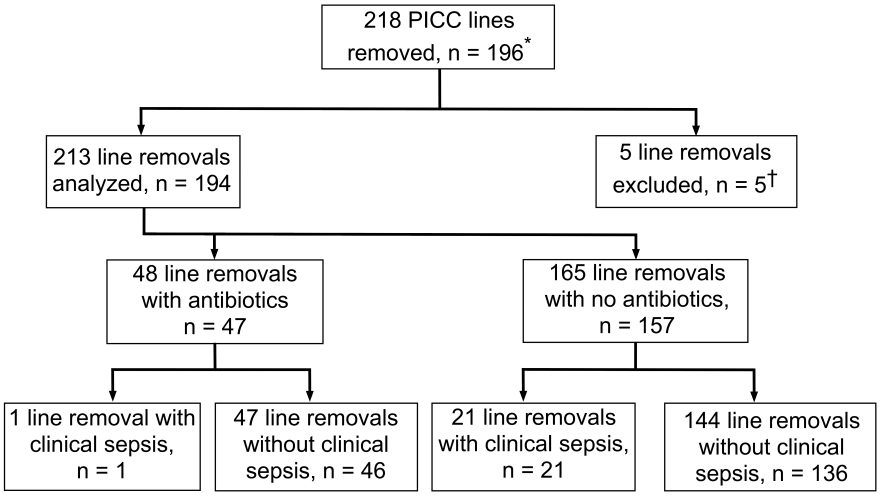


**Figure.** Flow chart distribution of PICC line removal episodes. PICC, percutaneously inserted central venous catheter. *Eighteen patients had more than 1 removal episode: 14 patients with 2 removal episodes and 4 patients with 3 removal episodes; †Three of the 5 patients with excluded line removal episodes had a second line whose removal was analyzed leaving only 2 patients completely excluded from analysis.

protein, blood and/or CSF, and urine cultures) along with antibiotics given for more than 48 hours initiated within 72 hours of line removal as indicated by the medical team. This time frame was chosen based on the observation by van den Hoogen et al[11] that more than half of the cases of line removal sepsis occurred within 5 days after removal with the peak incidence occurring within 24 to 72 hours. Furthermore, Hemels et al[6] found that when coagulase negative staphylococci sepsis occurred in neonates, 23% of the time it occurred within 72 hours after removal of a central venous catheter. The type and number of doses of antibiotics given for this sepsis event were recorded as well as culture results obtained and organisms identified.

Statistical analysis of the incidence of postcatheter removal clinical sepsis was performed by Fisher's exact test, and analysis of the number of antibiotic exposures as well as differences in patient characteristics between the 2 groups were compared by unpaired *t*-test. Unless noted, data are presented as mean ± standard deviation. The university's Institutional Review Board exempted the study from formal review as part of a quality improvement project.

## RESULTS

We evaluated 196 neonates with 218 PICC line removal episodes (Figure). The gestational age of our population was 26.8 ± 2.5 weeks (range, 22-34 weeks), and birth weight was 862 ± 212 g (range, 364-1236 g). The duration of the PICC lines was 24.3 ± 11.4 days (range, 8-67 days). Overall, we found that postcatheter removal clinical sepsis events were decreased by 11% from 13% (21/165) to 2% (1/48; p = 0.03 by Fisher's exact test), a 6-fold relative reduction, when a dose of antibiotics was given 12 hours prior to the removal of a PICC line (Figure).

Five line removal episodes were excluded from analysis for the following reasons: 1 line was present when the patient died, 1 line was present when the patient transferred, 1 line was placed soon after birth and removed when the patient had confirmed early onset sepsis with *E coli*, and 2 lines were emergently removed after occlusion, leaving a total of 213 line removal episodes to be analyzed (Figure). Three of the patients with excluded line removal episodes had a second line placed later whose removal was elective and thus was included in the analysis.

There were a total of 18 patients who had more than 1 PICC line removal episode, so individual patients with multiple line removal episodes were placed in more than 1 outcome group since each line removal was counted as a separate event. Out of the 18 with multiple lines during their hospitalization, there were 14 patients with 2 line removal episodes and 4 patients with 3 removal episodes.

The line removal episodes were separated into 2 groups for analysis based on whether or not a dose of antibiotics was given within 12 hours prior to line removal. Clinical characteristics of patients within these 2 groups are shown in the Table. The infants in the group that received antibiotics within 12 hours prior to line removal

**Table.** Clinical Characteristics of Infants at the Time of PICC Line Removal

| | Antibiotics Given Within 12 hr Prior to Removal Episode n = 48 lines | No Antibiotics Given With Removal Episode n = 165 lines | *P* value |
|---|---|---|---|
| Gestational age, wk | 25.7 ± 2.1 | 27.1 ± 2.5 | 0.0002 |
| Birth weight, g | 743 ± 225 | 897 ± 197 | <0.0001 |
| Postnatal age, days | 30.1 ± 14.5 | 26.1 ± 14.2 | 0.087 |
| PICC line duration, days | 27.2 ± 11.4 | 23.4 ± 11.3 | 0.044 |

*PICC, percutaneously inserted central venous catheter*

were significantly more premature with both a lower gestational age ($p = 0.0002$) and birth weight ($p < 0.0001$) compared to the infants who did not receive antibiotics prior to line removal. Additionally, the group that received antibiotics had their PICC lines in place for a significantly longer duration ($p = 0.044$). There was no statistically significant difference between the groups in postnatal age at the time of line removal. Again, there were 18 patients who had more than 1 PICC line removal episode so individual patients with multiple line removal episodes are represented more than once in this table based on their clinical characteristics at the time of line removal.

There were 48 out of 213 PICC lines removed (23%), in which a dose of antibiotics was given within 12 hours prior to removal from 47 patients (1 patient had 2 PICC line removal episodes). Of these 48 line removal episodes, 98% (47/48) had no postcatheter removal clinical sepsis events. Twenty-seven were electively given a dose of vancomycin 2 hours before PICC line removal, while the other 21 just completed a course of antibiotics with gentamicin, cefotaxime (Claforan, Sanofi-Aventis, Bridgewater, NJ), or vancomycin given within 12 hours before line removal (10, 2, and 9 removal episodes, respectively). Thus, vancomycin was used 36 of the 48 times a dose of antibiotics was given within 12 hours before PICC line removal. The 1 patient who had a postcatheter removal clinical sepsis event did not have a positive blood culture, but received 7 days of vancomycin, gentamicin, and piperacillin/tazobactam (Zosyn, The Wyeth Pharmaceuticals Incorporated, Philadelphia, PA) for clinical sepsis based on physical exam and laboratory findings.

There were 165 out of 213 PICC lines removed (77%) from 157 patients who received no antibiotics within 12 hours prior to removal. Of these removal episodes, 13% (21/165) of the time the patient had a postcatheter removal clinical sepsis event. There were no positive blood cultures, but there were 5 positive urine cultures obtained by catheterization (enterococcus species [4], coagulase negative staphylococci [1]). In the 21 patients who required antibiotics for a postcatheter removal clinical sepsis event, the length of antibiotic therapy ranged from 3 to 14 days as determined by the medical team.

A total of 103 doses of antibiotics were administered to the 47 patients who had 48 line removal episodes when antibiotics were given within 12 hours prior to catheter removal. This included elective doses of vancomycin, the final dose of a course of antibiotics as well as any doses given for postcatheter removal clinical sepsis. One patient in this group, after PICC line removal, received less than 48 hours of antibiotics (10 doses); and 1 patient with postcatheter removal clinical sepsis received 7 days of antibiotics (45 total doses) for a total of 2.2 antibiotic exposures per patient for the entire group (2.15 ± 0.96, mean ± standard error of the mean [SEM]).

A total of 729 doses of antibiotics were administered to the 157 patients who had 165 line removal episodes who did not receive antibiotics within 12 hours prior to catheter removal. This resulted in a total of 4.4 antibiotic doses per patient (4.42 ± 1.03, mean ± SEM) primarily due to the increased occurrence and subsequent treatment of postcatheter removal clinical sepsis. Thus, the population of patients who were given either elective vancomycin or had their last dose of antibiotics within 12 hours of line removal were not exposed to more antibiotics but received fewer total doses of antibiotics per patient compared to the group who did not receive elective antibiotics, although the decrease in antibiotic usage averaged per patient did not reach significance ($p = 0.25$). Furthermore, there was no change

in our Antibiogram (Pharmacy & Therapeutics Subcommittee University of Iowa Hospitals and Clinics) susceptibility pattern for vancomycin from during the first year of the study (2010) compared to after the study (2013) for coagulase negative staphylococci (100% susceptible).

## DISCUSSION

This retrospective chart review demonstrated a statistically significant reduction for an important infectious complication of PICC lines; postcatheter removal clinical sepsis. We observed a 6-fold decrease (13% to 2%) in postcatheter removal clinical sepsis events when a PICC line was removed with antibiotics given within 12 hours prior to removal. Despite the use of elective antibiotics, average antibiotic exposure for this population was less due to the decreased incidence of clinical sepsis after catheter removal.

Our results were consistent with the study by van den Hoogen et al[11] that showed the incidence of sepsis associated with the removal of a PICC was significantly less in patients who received antibiotics at the time of removal; 2% (2/132) versus 10% in patients (22/213) who did not receive antibiotics. Their 5-fold decrease with antibiotics prior to removal is consistent with our finding of a 6-fold decrease in clinical sepsis events postcatheter removal.

In a prospective randomized controlled study of the use of prophylactic antibiotics with PICC line removal, Hemels et al[6] also showed a decrease in postcatheter removal sepsis similar to our results. They found no cases of postcatheter removal sepsis in the prophylactic antibiotic intervention group (0/44) compared to 11% in the control group (5/44). For prophylaxis, they gave cefazolin with PICC line removal. In their study, the median duration of catheter insertion was 9 days (range, 7-15), and all cases of sepsis were caused by coagulase negative staphylococci, which occurred within 48 hours of line removal. Thus, we chose the time frame of within 72 hours after removal as a point in time that would ensure that we would capture all catheter removal clinical sepsis events.

To date, there is limited evidence supporting prophylactic use of vancomycin for prevention of postcatheter removal clinical sepsis. A Cochrane Review showed that the use of prophylactic vancomycin in preterm infants with central lines decreased the incidence of CLABSI.[17] Lodha et al[8] in a systematic review of the literature, also concluded that prophylactic vancomycin is effective in preventing catheter related sepsis in preterm neonates. Cooke et al[4] in a prospective randomized control trial found that the use of twice-daily low-dose vancomycin in infants less than 1500 g reduced coagulase negative staphylococci infections, but the decrease did not reach significance due to small numbers of patients. Garland et al[5] in a randomized prospective trial found that a vancomycin-heparin lock solution significantly decreased the incidence of CLABSI in the NICU.

Catheter related sepsis was decreased from 15% to 0%, and colonization of central line catheters by coagulase negative staphylococci decreased from 40% to 22% when low dose vancomycin was added to parenteral nutrition in a randomized, controlled trial and no adverse effects were noted in the vancomycin infusion group.[18] An additional study showed that adding vancomycin to parenteral nutrition led to a significant decrease in the colonization of central venous catheters, from 67% to 16%, without the development of vancomycin resistant strains of coagulase negative staphylococci.[2] However, there was no difference between the control and vancomycin groups in the number of infants who underwent an evaluation for suspected sepsis. Overall, to minimize PICC line associated sepsis, the literature is supportive of using prophylactic vancomycin at the time of central line catheter removal rather than via administration in parenteral nutrition.

There are always concerns for the development of antibiotic resistance when an antibiotic is given. The key to minimizing the development of vancomycin resistance is to achieve optimal drug exposure. It is possible to select for vancomycin resistant mutants by using low doses along with prolonged exposure to vancomycin.[19] However, our experience with the individualized elective use of vancomycin given as a 1-time dose (15 mg/kg) prior to the removal of a PICC line minimized this risk since we did not use low doses or give vancomycin prophylactically for a prolonged period of time. Furthermore, we found that the elective use of vancomycin did not increase the average number of antibiotic exposures per patient; instead there were fewer antibiotic doses given in the elective group. However, there will always be some patients who will be given a dose

of elective vancomycin, who otherwise would possibly not be exposed.

Limitations of our study include the use of retrospective data and that outcomes were based on clinical sepsis events and not positive blood cultures. However, clinically ill premature infants, even with negative blood cultures, often receive many days of antibiotics before they are deemed well enough to discontinue therapy. Furthermore, due to the small blood volume of premature infants, our practice of drawing a single blood culture containing 0.5 to 1.0 mL of blood may have contributed to the lack of efficacy in obtaining a positive blood culture from a clinically ill appearing infant. A third limitation is that we included all patients who had received antibiotics within 12 hours before PICC line removal within the antibiotic group for analysis whether or not the antibiotic was given electively or was the final dose from a prolonged course. We felt that combining these groups was acceptable based on the concept of inhibiting any potential bacterial spread into the bloodstream from the biofilm becoming dislodged during catheter removal. A fourth limitation is that the 2 groups of infants were clinically different in that infants who received antibiotics prior to PICC line removal had significantly lower gestational ages and birth weights as well as longer duration of line placement. Yet, despite these known risk factors for line sepsis, the antibiotic before removal group still had a 6-fold lower incidence of postcatheter removal clinical sepsis.

We conclude that the elective use of vancomycin prior to removal of a PICC, or catheter removal within 12 hours of the last dose of a planned course of antibiotics, significantly reduces the number of postcatheter removal clinical sepsis events in premature infants without increasing the total antibiotic burden.

**Disclosure** The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

**Acknowledgments** Data presented in part at the National Association of Neonatal Nurses Summit in April 2014 in Scottsdale, Arizona. We also thank Susan J. Carlson, MMSc, RD, CSP, LD, CNSD, for assistance in providing specific information for this patient population.

**Abbreviations** CLABSI, central line blood stream infection; CSF, cerebral spinal fluid; IV, intravenous; NICU, neonatal intensive care unit; PICC, percutaneously inserted central venous catheter; SEM, standard error of the mean

**Correspondence** Jonathan M. Klein, MD, Professor of Pediatrics, University of Iowa, Roy J. and Lucille A. Carver College of Medicine, 200 Hawkins Drive, 8806 JPP, Iowa City, IA 52242, email: jonathan-klein@uiowa.edu

## REFERENCES

1. de Silva GD, Kantzanou M, Justice A, et al. The ica operon and biofilm production in coagulase-negative Staphylococci associated with carriage and disease in a neonatal intensive care unit. *J Clin Microbiol.* 2002;40(2):382-388.
2. Baier RJ, Bocchini JA Jr, Brown EG. Selective use of vancomycin to prevent coagulase-negative staphylococcal nosocomial bacteremia in high risk very low birth weight infants. *Pediatr Infect Dis J.* 1998;17(3):179-183.
3. Borghesi A, Stronati M. Strategies for the prevention of hospital-acquired infections in the neonatal intensive care unit. *J Hosp Infect.* 2008;68(4):293-300.
4. Cooke RW, Nycyk JA, Okuonghuae H, et al. Low-dose vancomycin prophylaxis reduces coagulase-negative staphylococcal bacteraemia in very low birthweight infants. *J Hosp Infect.* 1997;37(4):297-303.
5. Garland JS, Alex CP, Henrickson KJ, et al. A vancomycin-heparin lock solution for prevention of nosocomial bloodstream infection in critically ill neonates with peripherally inserted central venous catheters: a prospective, randomized trial. *Pediatrics.* 2005;116(2):e198-e205.
6. Hemels MA, van den Hoogen A, Verboon-Maciolek MA, et al. Prevention of neonatal late-onset sepsis associated with the removal of percutaneously inserted central venous catheters in preterm infants. *Pediatr Crit Care Med.* 2011;12(4):445-448.
7. Lee JH. Catheter-related bloodstream infections in neonatal intensive care units. *Korean J Pediatr.* 2011;54(9):363-367.
8. Lodha A, Furlan AD, Whyte H, et al. Prophylactic antibiotics in the prevention of catheter-associated bloodstream bacterial infection in preterm neonates: a systematic review. *J Perinatol.* 2008;28(8):526-533.

9. Powers RJ, Wirtschafter DW. Decreasing central line associated bloodstream infection in neonatal intensive care. *Clin Perinatol* 2010;37(1):247-272.
10. Stoll BJ, Hansen N, Fanaroff AA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. *Pediatrics.* 2002;110(2 pt 1):285-291.
11. van den Hoogen A, Brouwer MJ, Gerards LJ, et al. Removal of percutaneously inserted central venous catheters in neonates is associated with the occurrence of sepsis. *Acta Paediatr.* 2008;97(9):1250-1252.
12. Garland JS, Uhing MR. Strategies to prevent bacterial and fungal infection in the neonatal intensive care unit. *Clin Perinatol.* 2009;36(1):1-13.
13. Marchant EA, Boyce GK, Sadarangani M, et al. Neonatal sepsis due to coagulase-negative staphylococci. *Clin Dev Immunol.* 2013;2013:586076.
14. Sengupta A, Lehmann C, Diener-West M, et al. Catheter duration and risk of CLABSI in neonates with PICCs. *Pediatrics.* 2010;125(4):648-653.
15. Njere I, Islam S, Parish D, et al. Outcome of peripherally inserted central venous catheters in surgical and medical neonates. *J Pediatr Surg.* 2011;46(5):946-950.
16. Hoang V, Sills J, Chandler M, et al. Percutaneously inserted central catheter for total parenteral nutrition in neonates: complications rates related to upper versus lower extremity insertion. *Pediatrics.* 2008;121(5):e1152-e1159.
17. Craft AP, Finer NN, Barrington KJ. Vancomycin for prophylaxis against sepsis in preterm neonates. *Cochrane Database Syst Rev.* 2009(2):CD001971.
18. Spafford PS, Sinkin RA, Cox C, et al. Prevention of central venous catheter-related coagulase-negative staphylococcal sepsis in neonates. *J Pediatr.* 1994;125(2):259-263.
19. Rybak MJ. Pharmacodynamics: relation to antimicrobial resistance. *Am J Infect Control.* 2006;34(5 suppl 1):S38-S45; discussion S64-S73.