

Probiotic administration and the incidence of nosocomial infection in pediatric intensive care: A randomized placebo-controlled trial*

Travis C. B. Honeycutt, MD, FAAP, FCCM; Mohamed El Khashab, MD; Richard M. Wardrop III, MD, PhD; Kenya McNeal-Trice, MD; Andrea L. B. Honeycutt, PharmD, MD; Claudia G. Christy, RN, MSN; Kshitij Mistry, MD; Bradford D. Harris, MD; Jon N. Meliones, MD, MS, FCCM; Keith C. Kocis, MD, MS, FCCM

LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. Identify the mechanisms by which probiotics are thought to confer beneficial effects in critically ill adults and children.
2. Define the potential interaction between probiotics and the immune system in critically ill adults and children.
3. Recall that there are a variety of probiotic preparations and that each may have differing safety and efficacy profiles in critically ill adults and children.

All authors have disclosed that they have no financial relationships with or interests in any commercial companies pertaining to this educational activity.

The authors disclosed that probiotics have not been approved by the U.S. Food and Drug Administration for use in the prevention of nosocomial infection. Please consult product labeling for the approved usage of this drug.

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Objective: To evaluate the efficacy of probiotics in reducing the rates of nosocomial infection in pediatric intensive care.

Design: Randomized, double-blind, placebo-controlled trial.

Setting: A 16-bed pediatric intensive care unit in a university-affiliated children's hospital.

Patients: Sixty-one pediatric patients were enrolled from April 2004 until December 2004. Screening of all patients admitted occurred on a daily basis. Patients were excluded if they had the following: evidence/suspicion of intestinal perforation, evidence/suspicion of mechanical gastrointestinal obstruction, absolute neutrophil count $\leq 0.5 \times 10^9$ cells/L, judgment by the attending physician that unable to tolerate the enteral volume necessary for administration, use of a probiotic preparation at any time in the week before study entry, participation in another clinical trial, lack of parental presence, or lack of parental consent.

Interventions: Patients were randomized to receive either one capsule of *Lactobacillus rhamnosus* strain GG (Culturelle, Con-Agra Foods, Omaha, NE) or placebo capsule of insulin once a day until discharge from the hospital.

Results: Sixty-one patients were randomized: 31 in the treatment group and 30 on the placebo group. Three patients in the control group developed four infections. Six patients in the treat-

ment group developed 11 infections. The relative risk of developing infection in the treatment group was 1.94 (confidence interval [CI], 0.53 to 7.04; $p = .31$). The mean number of infections in the treatment and control groups was 1.83 and 1.33, respectively, with a difference of 0.5 ($p = .52$). No serious adverse effects in the study population were noted. However, due to recent safety concerns regarding the administration of *L. rhamnosus* strain GG and a lack of benefit in this interim analysis, the study was terminated by the study investigators.

Conclusions: The results of this preliminary investigation were unexpected but important in view of the increased use of probiotic preparations in medically fragile pediatric patients. In this randomized, placebo-controlled trial, *L. rhamnosus* strain GG was not shown to be effective in reducing the incidence of nosocomial infections. In fact, a statistically nonsignificant trend toward an increase in infection was seen (four vs. 11). Further studies with a larger patient population are needed to establish both safety and efficacy of probiotics in pediatric critical care. (*Pediatr Crit Care Med* 2007; 8:452-458)

KEY WORDS: intensive care units; pediatric; cross infection; bacteremia; pneumonia; urinary tract infection; probiotics

Despite marked improvements in antimicrobial therapy and critical care technology, nosocomial infection remains a significant cause of morbidity and mortality in critically ill patients (1–4). Because the final common pathway of Gram-negative bloodstream infection, ventilator-associated pneumonia, and urinary tract infection (UTI) involves pathogenic enteric organisms, recent interest has emerged in how to suppress the growth of these organisms. Multiple studies have demonstrated that the colonization of the bowel with nonpathogenic commensal bacteria (probiotics) competitively inhibits the attachment of these pathogenic organisms (5–7). In addition, probiotics have been shown to augment the local gut immunity by enhancing immunoglobulin (Ig)-A-specific responses to enteric pathogens (8, 9). Probiotics also are thought to produce a variety of antimicrobial substances that may interfere with the growth of pathogenic bacteria (10–13). Finally, probiotics have been shown in numerous animal models to reduce intestinal permeability and decrease the bacterial translocation of pathogenic bacteria (14–16).

Moreover, probiotics also have been shown to nonspecifically stimulate the systemic immune system. Probiotic bacteria have been shown in several studies to enhance the phagocytic ability of neutrophils (17, 18). Multiple trials also have demonstrated an improvement in natural killer cell activity following the administration of various probiotic agents (19). Probiotic intake also has been shown to modulate production of interleukin-6 and -10, as well as tumor necrosis factor- α (20). Specific stimulation of the systemic immune system also has been shown using probiotic bacteria as vehicles for vaccines with resultant increases in antigen specific T-cell and immunoglobulin G responses (21, 22).

As a result of these studies demonstrating stimulation of local and systemic

immune defenses and a reduction in bacterial translocation, there has been a rapidly growing interest in the clinical applications of probiotics. A few small clinical trials in intensive care settings have begun looking at the incidence of nosocomial infections with probiotic use and have demonstrated promising results (23). Therefore, the purpose of this study was to evaluate the hypothesis that the administration of probiotics in infants and children admitted to a pediatric intensive care unit setting would reduce the incidence of nosocomial infection, bloodstream infection, pneumonia, tracheobronchitis, and UTI.

METHODS

This investigation was a prospective, double-blinded, randomized, placebo-controlled trial that was conducted from April 2004 to December 2004 in a 16-bed multidisciplinary medical-surgical pediatric intensive care unit in a university-affiliated children's hospital. The study was approved by the institutional internal review board. All patients were considered eligible if they were admitted to the pediatric intensive care unit. There were 650 eligible patients during the study period. We screened all patients on a daily basis. Patients were excluded if they had one of the following: evidence or suspicion of intestinal perforation, evidence or suspicion of mechanical gastrointestinal obstruction (such as volvulus, intestinal atresia, etc.), absolute neutrophil count $\leq 0.5 \times 10^9$ cells/L, judgment of attending physician that the patient is unable to tolerate the enteral volume necessary for administration, admitted to the pediatric intensive care unit >72 hrs, use of a probiotic preparation at any time in the week before study entry, participation in a trial for activated protein C, lack of parental presence, or lack of parental consent. Inotropic support was not a contraindication to begin or continue the protocol.

Randomization with blocks of four was done by the University of North Carolina Hospitals Investigational Drug Services. For those randomized to the treatment arm, patients received one capsule of *Lactobacillus rham-*

nosus strain GG (Culturelle, 10×10^9 cells/capsule, ConAgra Foods, Omaha, NE) once a day. For those randomized to the placebo arm, patients received one capsule of insulin once a day. The capsules were indistinguishable in appearance from one another. Thus, the study investigators and the clinical team caring for the patient were blinded to the treatment group. The probiotic and placebo capsules were prepared in a suspension of 5 mL of 5% dextrose. They were administered by mouth in those patients able to orally feed or by orogastric/nasogastric tube. An appropriate normal saline flush was administered in patients with an orogastric/nasogastric tube as follows: patients 0–2 yrs, 3–5 mL; 2–5 yrs, 5–10 mL; >5 yrs, 10–15 mL. If the patient had a functional ileus requiring decompressive gastric tube, the stomach was emptied before administration of the study mixture and the patient was placed in the right lateral decubitus position with the tube closed for 2 hrs. Patients continued the protocol until discharge from the hospital, parental request to withdraw from the study, or the death of the patient. Any patient who missed more than two doses of *Lactobacillus* GG did not have the probiotic regimen restarted. All enrolled patients were evaluated as intent-to-treat in the final data analysis.

Daily pertinent clinical and demographic data were collected prospectively by the study investigators until hospital discharge or death of the patient. In addition, patients also were followed for 48 hrs after discharge/transfer from the hospital to monitor for the development of nosocomial infections that would have been acquired just before patient discharge/transfer. This was done by reviewing the patient electronic medical record for ongoing culture results, phone calls from parents, hospital readmission, or emergency department/clinic visits to our institution. Families were not directly contacted for follow-up by phone.

Specific demographic and clinical information obtained at study entry included age of the patient, sex of the patient, and admission diagnostic category. Admission diagnostic categories, as defined by the attending pediatric intensivist of record, are shown in Table 1. The miscellaneous category was composed of small

*See also p. 499.

WakeMed Faculty Physicians, Pediatric Critical Care, WakeMed Hospital, Raleigh, NC (TCBH, KM-T); Clinical Assistant Professor of Pediatrics (TCBH), Pediatric Hospitalist, Assistant Professor of Pediatrics (KM-T), Assistant Professor (BDH), Professor of Pediatrics, Pediatric Cardiology (KCK), The University of North Carolina School of Medicine, Chapel Hill, NC; Senior Assistant, Pediatric Intensive Care Unit, Department of Pediatrics, Cairo University Hospital, Cairo, Egypt

(MEK); Assistant Clinical Professor, Professor of Internal Medicine, Carilion Medical Center/Carilion Clinic, Roanoke, VA (RMW); Resident Physician, Department of Internal Medicine (ALBH), Nurse Clinician I, Pediatric Critical Care Medicine (CGC), University of North Carolina, Chapel Hill, NC; Medical Instructor in Pediatrics, Pediatric Critical Care Medicine, Duke University School of Medicine, Durham, NC (KM); Director, Pediatric Critical Care Unit, Duke University Medical Center, Durham, NC (JNM).

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For information regarding this article, E-mail: thoneycu@unch.unc.edu or thoneycutt@wakemed.org
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Table 1. Patient population

Variable (Mean or n)	Total Patients (n = 61)	Treatment Group (n = 31)	Placebo Group (n = 30)
Age, mos			
0–1	12	6	6
1–24	24	13	11
>24	25	12	13
Gender			
Male	40	21	19
Female	21	10	11
Admission diagnosis			
Cardiac disease	20	8	12
Respiratory disease	12	6	6
Postoperative (noncardiac)	10	5	5
Miscellaneous	7	3	4
Neurologic disease	5	4	1
Trauma	5	3	2
Sepsis/SIRS	2	2	0
Length of PICU stay, days	9.7	12.2	7.0
Length of hospitalization, days	14.4	17.6	11.1
Enteral feeds of any type	61	31	30
Formula	44	25	19
Breast milk	12	7	5
TPN	13	5	8
H ₂ blocker/PPI	57	29	28
Antibiotic use >2 days	47	26	21
Steroid use >2 days	7	4	3
Vasoactive drug use	20	9	11
Device utilization ratio	1.5	1.4	1.6

SIRS, systemic inflammatory response syndrome; PICU, pediatric intensive care unit; TPN, total parenteral nutrition; H₂ blocker, histamine receptor 2 antagonist; PPI, proton pump inhibitor.

numbers of a variety of diagnoses including renal insufficiency, liver disease, metabolic disorders, etc. All patients in the study were followed closely by the study investigators for signs and symptoms of nosocomial infection. Blood cultures, radiographic studies, tracheal aspirates, quantitative bronchoalveolar lavage cultures, viral antigen detection/cultures, and urine cultures were obtained at the clinical discretion of the pediatric intensivist caring for the patient.

Variables assessed on a daily basis included the following: invasive device utilization (mechanical ventilation, arterial catheter, central venous catheter, urinary catheter), vasoactive infusions, total parenteral nutrition, steroids, antibiotics, H₂-receptor antagonist/proton-pump inhibitor medications, enteral feeds of any type, human milk, formula, and length of stay in the pediatric intensive care unit. Vasoactive infusion use included the use of dobutamine, dopamine, epinephrine, milrinone, norepinephrine, or vasopressin. Enteral feed use was defined as any use of any type of enteral feed in a 24-hr period. Formula use was defined as any commercial formula preparation use in a 24-hr period. Breast milk use was defined as any use of breast milk in a 24-hr period. Steroid and antibiotic use only were statistically analyzed if >2 days duration. Device utilization ratios were calculated using the following equation: (central venous catheter days) plus (urinary catheter days) plus

(arterial catheter days) plus (mechanical ventilation days)/(days in pediatric intensive care unit). We collected information on a daily basis on all patients enrolled in the study, obtained from medical records, daily flow sheets, and laboratory results. This information was documented using scannable data collection forms. These forms were then scanned and entered into a Microsoft Excel database for subsequent statistical analysis.

Because of safety concerns raised by recent reports in the medical literature (24–27), a data safety monitoring board was convened and a blinded early interim analysis was performed. The age of the patient was divided into age bands *a priori* for statistical analysis as follows: age <1 month (neonate), age 1–24 months, and age >24 months. Categorical variables were evaluated in the univariate setting using the chi-square test. A two-group unpaired Student's *t*-test was used to compare the number of infections in each group. Statistical tests were performed using SAS software (SAS, Cary, NC).

Only cases of nosocomial pneumonia, bloodstream infection, tracheobronchitis, or UTI occurring after 48 hrs of study entry were included in our data analysis. Infections in the first 48 hrs after any hospital admission were considered community-acquired in origin. Such a period of time is based on the methods used by the Centers for Disease Control and the National Nosocomial Infection Surveil-

lance system (28). Infections diagnosed in the first 48 hrs after inpatient transfer to the pediatric intensive care unit and study entry were not analyzed, as these likely represent nosocomial infections acquired before study entry. The diagnostic criteria for bloodstream infection, UTI, pneumonia, and tracheobronchitis were simple modifications of the CDC criteria and are listed in the Appendix of this manuscript. Modifications were made so as to more accurately reflect the standard of care in the study institution. Any such deviations from the CDC criteria are noted with an *a*. All diagnoses of nosocomial infection were reviewed independently by two study investigators using these criteria.

RESULTS

There were 61 patients in this prospective, randomized, double-blinded, placebo-controlled trial. Thirty-one patients were randomized to the treatment arm and 30 to the placebo arm. The study population characteristics of the two treatment groups are shown in Table 1. Nine patients in the study population developed 15 nosocomial infections. Of these 15 infections, six (40%) were bloodstream infections, five (33%) tracheobronchitis, two (13%) pneumonia, and two (13%) UTI. Overall, of the 15 infections, six (40%) were caused by Gram-positive organisms. Gram-negative bacteria accounted for six (40%) of the nosocomial infections. *Candida* species were responsible for three (20%) of the infections.

Of the 31 patients randomized to the treatment group, six patients developed 11 nosocomial infections. Three patients in the control group developed four infections. The relative risk of developing a nosocomial infection in the treatment group was 1.94 (confidence interval [CI], 0.53–7.04; *p* = .31). The mean numbers of infections in the treatment and control groups were 1.83 and 1.33 in the two groups, respectively, with a difference of 0.5 (*p* = .52). The clinical characteristics of the infected patients in both the treatment and control groups are shown in Table 2. The number and type of nosocomial infections in each group are shown in Table 3.

There were six deaths during the study period with four in the placebo group and two in the treatment group. None of these deaths were associated with a nosocomial infection. Two patients (one each in placebo and treatment) were withdrawn from the study because of parent perception of the intervention causing

Table 2. Clinical characteristics of patients with nosocomial infection

Variable	Treatment Group (n = 6)	Placebo Group (n = 3)
Age, mos		
0–1	1	1
1–24	2	2
>24	3	0
Gender		
Male	4	1
Female	2	2
Admission diagnosis		
Cardiac disease	1	0
Respiratory disease	0	1
Postoperative (noncardiac)	2	1
Miscellaneous	1	1
Neurologic disease	1	0
Trauma	0	0
Sepsis/SIRS	1	0
Length of PICU stay, days	36.7	13.7
Length of hospitalization, days	41	24.7
Enteral feeds of any type	6	3
Formula	6	3
Breast milk	2	1
TPN	2	1
H ₂ blocker/PPI	6	3
Antibiotic use >2 days	6	3
Steroid use >2 days	2	0
Vasoactive drug use	3	1
Device utilization ratio	2.0	1.7

SIRS, systemic inflammatory response syndrome; PICU, pediatric intensive care unit; TPN, total parenteral nutrition; H₂ blocker, histamine receptor 2 antagonist; PPI, proton pump inhibitor.

nausea. One study patient who missed more than two doses of *Lactobacillus* GG did not have the probiotic regimen restarted. All patients were included in the final data analysis. There were no cases of *L. bacteremia* in the study population. No known serious adverse effects occurred in any subject during the study period. However, because of recent safety concerns regarding the administration of *Lactobacillus* GG in critically ill pediatric patients and a lack of benefit in this interim analysis, the study was terminated by the study investigators.

DISCUSSION

Numerous clinical trials recently have examined the effect of probiotics on various infectious and inflammatory conditions. The efficacy of probiotics in the treatment of gastrointestinal disease is well established (29). Multiple clinical trials have confirmed the efficacy and safety of probiotic administration in the treatment and prevention of acute viral diar-

Table 3. Types of nosocomial infections

Type of infection	No. of Infections Treatment Group (n = 11)	No. of Infections Placebo Group (n = 4)
Bloodstream infection	2	4
Pneumonia	2	0
Tracheobronchitis	5	0
Urinary tract infection	2	0

rheal disorders (30–33). Probiotics also have been shown to reduce both the incidence and recurrence of *Clostridium difficile* colitis (34, 35). In addition, the prophylactic use of probiotics has proven to be effective in reducing the incidence of non-*C. difficile* antibiotic-associated diarrhea (36–38). Several studies also suggest that probiotics may be helpful in the prevention of traveler's diarrhea (39, 40). Emerging data exists concerning the efficacy of probiotics in controlling bacterial overgrowth in chronic pouchitis in children with short bowel syndrome (41, 42). Finally, two experimental animal models and two clinical trials in human neonates showed a marked reduction in the incidence of necrotizing enterocolitis with the administration of probiotics (43–46).

Data also exist for the use of probiotics in the prevention of infections outside the gastrointestinal tract. Several studies have demonstrated a reduction in the incidence of upper respiratory infections in daycare settings with the prophylactic use of probiotic preparations (47–49). Limited data also exists for the prevention of lower respiratory infection with probiotics (50, 51). In addition, one study in patients with cystic fibrosis showed a reduction in the frequency of recurrent pulmonary infections with probiotic use (52). Both animal studies and limited human trials demonstrate evidence for the use of probiotics in reducing recurrent urinary tract infections (53–57). Preliminary data also demonstrate a role for probiotics in reducing sepsis and endotoxemia after surgery and in patients with primary gastrointestinal disease (58–61). Finally, small clinical trials in intensive care settings have begun looking at the incidence of nosocomial infections with probiotic use and have demonstrated promising results (24). A prospective randomized trial of 172 patients after major abdominal surgery or liver transplantation demonstrated a 31% incidence of nosocomial infection in the control group compared with 4% in

those that received a postoperative probiotic preparation (62). A subgroup analysis of the 95 liver transplant patients demonstrated a statistically significant combined decrease of 21% in the incidence of nosocomial infections including sepsis, pneumonia, UTI, and cholangitis with *Lactobacillus* vs. placebo, and 35% combined decrease compared with selective bowel decontamination (63).

In this randomized, double-blinded, placebo-controlled trial, *L. rhamnosus* strain GG was not proven to be effective in reducing the incidence of nosocomial infections. A nonsignificant trend toward increased infections was seen in the treatment group (four vs. 11). However, this is likely due to insufficient sample size and an early analysis of the study data. A weakness of this study is that no assessment of severity of illness on admission was done to compare the two randomized groups. Except for the risk of bacteremia from the probiotic itself, there is no known plausible explanation for an increased nosocomial infection rate in the treatment group.

Significant safety concerns arose near the end of the study with the first published report of proven sepsis due to the *L. rhamnosus* strain GG in two debilitated pediatric patients with underlying chronic disease (64). In addition, two more pediatric case reports of *Lactobacillus* GG bacteremia during probiotic therapy were described in three patients with short gut syndrome requiring total parenteral nutrition (26, 27). A similar case then occurred in a nonstudy patient with multiple chronic medical conditions at our own institution. Finally, at the same time, a case series was published of 11 adult patients with proven sepsis from the probiotic *L. rhamnosus* strain GG (28). These publications and a lack of benefit seen in this preliminary analysis led the review board and us to terminate the study prematurely.

Given the enormous potential benefits of probiotic use outlined in this manuscript, one could argue that the study

should have been continued. A large epidemiologic study in Finland found no increase in cases of *L. bacteremia* during a 10-yr period, despite a marked increase in the use of the probiotic *L. rhamnosus* strain GG (65). However, in that population-based study, the vast majority of patients consuming probiotics preparations were otherwise healthy subjects. Therefore, there is now more debate about the use of probiotics in medically fragile pediatric patients (66). Of note, a recent large, randomized, placebo-controlled trial demonstrated both safety and efficacy of a different probiotic preparation (Infloran, *L. acidophilus* and *Bifidobacter infantis*) against necrotizing enterocolitis in critically ill preterm infants weighing <1500 g (67). It is very plausible that different probiotic preparations may have differing safety and efficacy profiles. A larger multicentered trial with a different probiotic preparation is under consideration.

CONCLUSIONS

The results of this investigation were unexpected but important in view of the increased use of probiotic preparations in medically fragile pediatric patients. In this randomized, placebo-controlled trial, *L. rhamnosus* strain GG was not shown to be effective in reducing the incidence of nosocomial infections. In fact, a statistically nonsignificant trend toward an increase in infection was seen (four vs. 11). Further studies with a larger patient population are needed to establish both safety and efficacy of probiotics in pediatric critical care.

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APPENDIX

A bloodstream infection must meet one of the following three criteria:

1. Recognized pathogen isolated from blood culture and pathogen is not related to infection at another site.
2. One of the following: fever (>38°C), chills, or hypotension (systolic blood pressure ≤90 mm Hg) and any of the following:
 - a. Common skin contaminant isolated from two blood cultures drawn on separate occasion and organism is not related to infection at another site
 - b. Common skin contaminant isolated from blood culture from patient with intravascular access device and physician institutes appropriate antimicrobial therapy
 - c. Positive antigen test on blood and organism is not related to infection at another site
3. Patient <12 months of age has one of the following: fever (>38°C), temperature instability, hypothermia (<37°C), lethargy, apnea, or bradycardia (rate <60 beats/min) and any of the following:
 - a. Common skin contaminant isolated from two blood cultures drawn on separate occasions (or separate sites) and organism is not related to infection at another site

- b. Common skin contaminant isolated from blood culture from patient with intravascular access device and physician institutes appropriate antimicrobial therapy
- c. Positive antigen test on blood and pathogen is not related to infection at another site

A urinary tract infection must meet the following criteria:

One of the following: fever ($>38^{\circ}\text{C}$), urgency, frequency, dysuria, or suprapubic tenderness and a urine culture of $\geq 10^5$ colonies/mL of urine obtained by catheterization or mid-stream "clean catch" method with no more than two species of organisms present.

Nosocomial pneumonia is defined as radiographic evidence of a new infiltrate, consolidation, or cavitation. In addition, the patient also must have the following:

1. If patient needs mechanical ventilation, a tracheal aspirate must demonstrate organisms on Gram-negative stain under oil immersion field and <10 epithelial cells/high-powered field or >25

polymorphonuclear leukocytes and <10 epithelial cells/high-powered field with subsequent culture of a known respiratory pathogen. Alternatively, recovery of a known respiratory pathogen by a quantitative culture ($>10^4$ CFU/mL) of a bronchoalveolar lavage specimen, isolation of a known respiratory virus by culture or antigen detection, or histopathologic evidence of pneumonia will suffice.

2. If the patient no longer requires mechanical ventilation, there must be either new onset or increased purulent sputum, increased work of breathing or tachypnea, isolation of a known respiratory pathogen from the bloodstream, isolation of a known respiratory pathogen from a quantitative bronchoalveolar lavage specimen, isolation of known respiratory virus by culture or antigen detection, or histopathologic evidence of pneumonia.

Tracheobronchitis is defined as a lower respiratory infection without radiographic evidence of pneumonia and must meet the following criteria:

1. If the patient needs mechanical ventilation, a tracheal aspirate must demonstrate organisms on Gram-negative stain under oil immersion and <10 epithelial cells/high-powered field or >25 polymorphonuclear leukocytes and <10 epithelial cells with subsequent culture of a known respiratory pathogen. Alternatively, recovery of a known respiratory pathogen by a quantitative bronchoalveolar lavage specimen, isolation of a known respiratory virus by culture or antigen detection, or histopathologic evidence of tracheobronchitis will suffice.
2. If the patient no longer requires mechanical ventilation, there must be one of the following: new onset/increased purulent sputum, increased work of breathing/tachypnea, or wheezing and one of the following: isolation of a known respiratory pathogen from a quantitative bronchoalveolar lavage specimen, isolation of known respiratory virus by culture, or antigen detection.