Prevention of Nosocomial Infections in Neonatal Intensive Care Units

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Abstract

Neonatal sepsis causes a huge burden of morbidity and mortality and includes bloodstream, urine, cerebrospinal, peritoneal, and lung infections as well as infections starting from burns and wounds, or from any other usually sterile sites. It is associated with cytokine - and biomediator-induced disorders of respiratory, hemodynamic, and metabolic processes. Neonates in the neonatal intensive care unit feature many specific risk factors for bacterial and fungal sepsis. Loss of gut commensals such as *Bifidobacteria* and *Lactobacilli spp.*, as occurs with prolonged antibiotic treatments, delayed enteral feeding, or nursing in incubators, translates into proliferation of pathogenic microflora and abnormal gut colonization. Prompt diagnosis and effective treatment do not protect septic neonates form the risk of late neurodevelopmental impairment in the survivors. Thus prevention of bacterial and fungal infection is crucial in these settings of unique patients. In this view, improving neonatal management is a key step, and this includes promotion of breast-feeding and hygiene measures, adoption of a cautious central venous catheter policy, enhancement of the enteric microbiota composition with the supplementation of probiotics, and medical stewardship concerning H2 blockers with restriction of their use. Additional measures may include the use of lactoferrin, fluconazole, and nystatin and specific measures to prevent ventilator associated pneumonia.

Keywords
- neonate
- fluconazole
- lactoferrin
- sepsis
- candida
- infection
- probiotics

Sepsis-related morbidity and mortality is an increasing concern in all neonatal intensive care units (NICUs), and the reported incidences are dramatically high regardless of the improvements in the quality of neonatal assistance.[1]

Neonatal sepsis includes bloodstream, urine, cerebrospinal, peritoneal, and lung infections, as well as infections starting from burns and wounds or from any other usually sterile site. It is associated with cytokine- and biomediator-induced disorders of respiratory, hemodynamic, and metabolic processes that are triggered by infections.

Many specific risk factors account for the increased risk of bacterial and fungal sepsis in such patients, including the use

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of broad-spectrum antimicrobial drugs, parenteral nutrition, acid inhibitors, and steroids, as well as the systematic and long-lasting use of invasive devices such as central venous catheter (CVC) and endotracheal tube.

Preterm neonates in NICU are at high risk of intestinal disorders with proliferation of a pathogenic microflora, because treatment with antibiotics, total parenteral nutrition (TPN), or nursing in incubators may delay or impair the intestinal colonization process. Loss of gut commensals such as *Bifidobacteria spp.* and *Lactobacilli spp.*, due to the difficulties in oral feeding or a slower acquisition of them in preterm neonates, translates into an increased susceptibility to abnormal gut colonization. For all these reasons, the digestive tract is regarded as an important reservoir and site for colonization by all kinds of pathogens and subsequent sepsis in preterm infants.

Immature or injured skin and impaired gut barriers allow dissemination of many organisms (among them, *Staphylococci* and *Candida spp.*) from various colonizing sites.

Infants with complicated gastrointestinal diseases are at increased risk due to abdominal surgery and prolonged periods of TPN and ileus. In addition, many critically ill infants subjected to mechanical ventilation are at high risk of ventilator-associated pneumonia (VAP) that may in turn determine sepsis and other long-term negative outcomes.

Due to the high incidence of negative outcomes in sepsis survivors,[2] prevention of bacterial and fungal colonization and infection is the key in these settings.

In this article, the currently available strategies to prevent infections in NICU patients will be reviewed (►**Table 1**).

Table 1 Overview of Preventive Measures to Reduce Risk for Sepsis in NICU

Neonatal management
• Breast-feeding with fresh human milk • Promotion of enteral feeding • Hygiene measures • CVC management policies • CVC bundles • In-line filters • Enteric microbiota composition enhancement with the use of probiotics • H2 blockers and steroids restrictions • Antibiotic stewardship • Stewardship in TPN use • Prevention of VAP
Pharmacological prophylactic interventions
• General anti-infective prophylaxis: bioactive substances, probiotics, lactoferrin • Specific antifungal prophylaxis: fluconazole, nystatin • Specific anti-RSV prophylaxis: palivizumab

Abbreviations: CVC, central venous catheter; NICU, neonatal intensive care unit; RSV, Respiratory Syncitial Virus; TPN, total parenteral nutrition; VAP, ventilator-associated pneumonia.

Prevention of Sepsis: What Does Not Work

In the last years, several promising strategies have been assessed and have been ineffective in preventing sepsis.

Recent evidence provided by large, multicenter trials showed that the administration of glutamine, immunoglobulins (either pooled immunoglobulins or specific antistaphylococcal enriched donor's immunoglobulins, or the monoclonal antibody pagibaximab) had no benefits in preventing the incidence and severity of neonatal late-onset sepsis. As a result, these potential approaches are not currently recommended.

Glutamine is one of the most abundant amino acids in both plasma and human milk, with trophic actions on enterocytes and gut integrity,[3] but it is still not routinely included in standard amino acid solutions. Some studies suggested that parenteral nutrition supplemented with glutamine may reduce sepsis and mortality in critically ill adults.[4] Some reports advocated a similar benefit also in extremely low-birthweight (ELBW) infants.[5] A multicenter, randomized, double-masked, clinical trial was thus conducted to reveal possible beneficial effects of glutamine in preterm infants.[6] ELBW infants (weighing between 401 and 1000 g) were randomized to receive within 72 hours of birth either a usual amino acid solution with no glutamine (control) or an isonitrogenous amino acid solution with 20% glutamine whenever they received TPN. Primary outcome was death or late-onset sepsis. Of the 721 infants who were assigned to glutamine supplementation, 370 (51%) died or developed late-onset sepsis, as compared with 343 of the 712 infants (48%) assigned to control (relative risk: 1.07; 95% confidence interval: 0.97 to 1.17). Glutamine had no effect on tolerance of enteral feeds, necrotizing enterocolitis, or growth. No significant adverse events were observed with glutamine supplementation. The conclusion was that parenteral glutamine supplementation did not decrease mortality or the incidence of late-onset sepsis in ELBW infants. Similar results have been obtained by other two trials of glutamine supplementation.[7,8] Consequently, routine use of parenteral glutamine supplementation cannot be recommended in this population.

Also therapy with intravenous immune globulins (either pooled or specifically enriched against some pathogen) has proved to be not effective both in prevention and on the outcomes of suspected or proven neonatal sepsis.

The Immunoglobulin Neonatal International Study (INIS) Collaborative group conducted an International Multicenter trial involving 113 hospitals in 9 countries.[9] In all, 3,493 infants were randomized to receive two infusions of either polyvalent immunoglobulin G (IgG) immune globulin (at a dose of 500 mg/kg) or a matching placebo 48 hours apart. No effect, in terms of death or major disability at the age of two years, could be demonstrated.

Similar disappointing findings were so far obtained by studies addressing the potential benefit of antistaphylococcal immunoglobulins for the prevention of staphylococcal infection in very low-birth-weight (VLBW) infants. A recent Cochrane review analyzed all eligible randomized and quasi-randomized studies in this area.[10] Three eligible studies were

included involving a total of 2,701 VLBW neonates. No significant differences in the risk of staphylococcal infection between two antistaphylococcal studied drugs (INH A-21 Veronate,[11] Inhibitex Inc., Alpharetta, GA, USA and also Altastaph, Nabi Biopharmaceuticals Inc., Rockville, MD, USA) versus placebo could be demonstrated. The authors concluded that both types of antistaphylococcal immunoglobulins are not recommended for prevention of staphylococcal infections in preterm or VLBW neonates and that further research to investigate the efficacy and the impact on long-term neurodevelopmental outcome of other products, such as pagibaximab, was needed.

Pagibaximab is a recently developed chimeric monoclonal antibody against lipoteichoic acid, a component of the cell membrane of many gram-positive organisms, particularly represented in all *Staphylococcus spp.* It reacts with coagulase-negative staphylococci and *Staphylococcus aureus* isolate strains and was granted "orphan drug status" in 2000. An investigational pipeline has been developed over the last decade to provide evidence supporting the claim of prevention of staphylococcal sepsis in VLBW infants.

In a preliminary phase I study, the safety, pharmacokinetics, and pharmacodynamics of pagibaximab were assessed and no major adverse effects were noticed.[12] The antibody was effective against staphylococci preclinically and seemed safe and well tolerated.

A phase IIa, randomized, double-blind, placebo-controlled trial was therefore conducted evaluating also the effects on staphylococcal sepsis. Some dozens of VLBW neonates were randomized to receive once-a-week pagibaximab (90 or 60 mg/kg) or placebo infusions since the early days of life. The results showed that infants who received 90 mg/kg did not feature any staphylococcal sepsis episode. Pagibaximab had a linear pharmacokinetic trend with a 14.5-day half-life and was not immunogenic. However, the target protective levels < 500 µg/mL were only consistently achieved after two to three doses.[13]

These promising findings prompted the organization of a large phase IIb, multicenter, randomized, double-blind, controlled trial that was performed in 100 NICUs across North America and Europe, enrolling 1,579 VLBW infants weighing 600 to 1200 g at birth. The protocol and the preliminary results are described and accessible at www.clinicaltrials.gov.[14]

The primary endpoint was the incidence of infections by *Staphylococcus spp.* from study days 0 to 35. The report posted at www.clinicaltrials.gov states that no significantly different adverse events occurred in the two groups and that no safety concerns arose. The same report declares that out of 1579 infants analyzed (792 in the pagibaximab and 787 in the placebo groups), 85 in the pagibaximab group versus 79 in the placebo group had staphylococcal sepsis in the first 35 days of study, thus nearly the same.[14]

These findings seem to be consistent with the already reported lack of effectiveness of other strategies based on administration of specific antistaphylococcal immunoglobulins, either pooled from donors or enriched,[9,12] and seem confirming that administration of specific antistaphylococcal antibodies, whichever the type, is not effective in preventing neonatal late-onset sepsis by *Staphylococcus spp.* in the nursery.

Prevention of Sepsis—What Does Work

Nutrition: Human Milk

Availability of essential nutrients is critical for a proper development and maturation of all organs, both in the fetus and in the neonate. Several nutrients play both direct and indirect roles in conditioning the onset of sepsis and infection during the neonatal period. For some nutrients, there is evidence of a protective role against infections also in early infancy (i.e., after the neonatal period).

Human milk contains several substances with putative anti-infective actions, such as lactoferrin (LF), lactoperoxidase, lysozyme, immunoglobulin A (IgA), IgG, immunoglobulin M (IgM), cytokines, interferon, oligosaccharides, bifidogenic factors, platelet-activating factor acetylhydrolase, vitamin E, beta carotene, ascorbic acid.

Also the mucosal trophic effect of human milk on the gut can be seen as an anti-infective mechanism because human milk has a known impact on gut permeability, which changes as a function of age and type of feeding.[15] The feeding of human milk is associated with decreased gut permeability at 28 days of age,[16] meaning that human milk-fed neonates have a more rapid maturation of intestinal epithelium, leading to lower intestinal permeability. This might cause less translocations of pathogens from the gut and ultimately less infections and necrotizing enterocolitis (NEC).

Which factors in maternal milk could account for this? LF possibly plays a major role. Experimental data obtained in human gut cell lines showed that enterocytes exposed to high LF concentrations respond with a potent and rapid increase in cell proliferation, whereas the same cells when exposed to low LF concentrations show enhancement and stimulation of intestinal differentiation. These experiments also reported that bovine LF has the same extent of activity as human LF.[17] LF is thus a key modulator of intestinal epithelium development, and the speculation is that the higher concentrations of LF in colostrum contribute to the early proliferation of intestinal cells, which then differentiate as a result of its decreased concentrations in mature milk.

Of importance, beneficial effects of breast milk in prevention of infections depend on the amounts of human milk ingested. Only average intakes higher than 50 mL/kg/d have been associated with a protective effect,[18] as well as only fresh (and not donor) milk has been found to be protective. Pasteurization at 62.5°C for 30 minutes (Holder method) decreases many anti-infective milk substances, and this might explain why in a recent randomized trial of donor human versus preterm formula, the two different types of milk were shown to have the same lack of effect on prevention of sepsis.[19]

CVC Policy

Strict policies in the management of the CVC are mandatory to prevent or reduce line-associated infections. The duration of a CVC should be correctly monitored as it impacts on the occurrence of a line-associated infection. After 15 days of maintenance, the odds of developing a bloodstream infection increase abruptly.[20] Therefore, scheduled removal of

percutaneously inserted CVC should be considered, at least in at-risk ELBW neonates, even in absence of signs of suspected sepsis. This recommendation is different from the usual practice in adult and pediatric critical care, and the difference in patient populations (the need for a long-term Total Parenteral Nutrition (TPN) in preemies) may explain this situation. Anyway, further, more robust evidence has to be produced to really clarify this issue.

In terms of best use of human resources, "proactive" management of percutaneously inserted central catheters results in decreased incidence of infection in the ELBW population. In a single NICU study, the creation of a dedicated task force for the CVC management produced a two-third reduction in the incidence of line-associated infections (from 15.8 infections/1000 catheters per day to only 5.1 infections/1000 catheters per day).[21] Additionally, recent evidence confirmed that standardization of CVC placement and maintenance can reduce the risk for bloodstream infection by 50%.[22]

The use of "in-line filters" is also a promising approach. Particulate contamination due to infusion therapy carries a potential health risk, in terms of occurrence of systemic inflammatory response syndrome, organ failure, thrombosis, and ultimately sepsis. A recent single-center, prospective, randomized controlled trial conducted in a pediatric intensive care unit assessed the effects of filtration of intravenous fluids on the reduction of complications in critically ill children.[23] The authors demonstrated a significant reduction in the overall complication rate (40.9% versus 30.9%; $p = 0.003$) for the filter group. In detail, the incidence of systemic inflammatory response syndrome was significantly lower (30.3% versus 22.4%; $p = 0.01$). Pediatric intensive care unit stay and duration of mechanical ventilation were also significantly reduced. However, no significant impact could be shown on the incidence of sepsis. This strategy needs further evaluation specifically designed for sepsis prevention and neonatal settings.

Another option to consider is an "intraremoval" prophylactic strategy. In a recent trial, the administration of two doses of cefazolin during CVC removal and change reduced from 11 to 0% the incidence of coagulase-negative staphylococcal sepsis (number needed to treat: 9).[24] These data might have limited generalizability due to the fact that in many NICUs the proportion of coagulase-negative staphylococci resistant to cefazolin is high. Nevertheless, this is interesting information and deserves further confirmation addressing also the possible differences in risk between various types of catheters: in fact, umbilical central catheter seems at much lower risk than peripherally inserted CVC.[25]

Restriction of H2-Blockers

Use of H2 blockers is associated with increased rates of infections in preterm neonates in NICU and should therefore be limited or avoided. The acid gastric barrier is the most primitive way of contrasting pathogens, and its impairment is obviously detrimental for the preterm host.

In a retrospective study of 569 infants in NICU over 3 years, Bianconi et al examined the effect of ranitidine on the incidence of late-onset sepsis and concluded that after controlling for all possible confounding factors, infants receiving ranitidine were at approximately 7 times greater risk of late-onset sepsis (odds ratio [OR] 6.99; 95% confidence interval [CI]: 3.78 to 12.94; $p < 0.0001$).[26] More recently, other reports confirmed these findings, suggesting that the use of ranitidine or other H2 blockers in the nursery should be avoided.[27,28] In this view, no data are currently available on the impact of proton pump inhibitors (e.g., omeprazole). This class of antacid drugs operate by a different pharmacological mechanism but still result in increased gastric pH and probable altered gastrointestinal flora, thus—at least in theory—its use should be carefully considered in neonates at high risk for sepsis.

Probiotics

Probiotics colonize the neonate since the early moments of life, starting from labor when the offspring ingests microorganisms belonging to the normal commensal flora of the maternal genitourinary tract. Should the baby be prematurely born, or through cesarean section, or exposed to antibiotics since the early moments of life, this natural process may not occur or be impaired.

Probiotics have known immunomodulating and anti-infective activities, as they produce substances with bacteriostatic/bactericidal actions (e.g., the *Lactobacillus reuterii* produce the so-called reutericyclin, an antibiotic peptide[29]), compete for adhesion to gut cells displacing the pathogens,[30] and finally influence intestinal permeability.[31]

The impact of healthy gut colonization has been confirmed by studies that showed how colonization with *Bacteroides spp*. increases the number of gut cells producing IgA, IgG, and IgM in the first months of life.[32]

Probiotics have a known effect in the prevention of NEC, which is often related to sepsis.[33] A recent Cochrane review stated that enteral supplementation of probiotics prevents severe NEC (risk ratio 0.35), sepsis (risk ratio 0.9), and all-cause mortality (risk ratio 0.4) in preterm infants.[34]

Moreover, *Lactobacillus rhamnosus GG* and *L. reuterii* proved effective in preventing gut colonization by *Candida spp*.,[35] a process that often precedes fungal sepsis. ►**Table 2**[36,37,63–71] summarizes the results from the main trials of probiotics for prevention of *Candida* colonization. The safety of probiotics has been recently confirmed in a retrospective, two-center study reporting on the absence of any adverse effect or microbiologic issue over 6 years of routine *L. rhamnosus LGG.* administration in VLBW neonates admitted in two large Italian NICUs.[36]

Despite the important available evidence, major areas are still in need of further studies and clarifications before probiotics can be more broadly embraced, including the scattered availability of well-defined pharmacological-grade products (as opposed to nutritional supplement grade) in many countries/settings, the lack of data on long-term neurodevelopmental follow-up in infants fed probiotics since birth, and the identification of which species of probiotics is preferable for each different clinical purpose, given that that different probiotic species may have different actions and targets.

Table 2 Main Rrials of Probiotics to Prevent LOS or Colonization by *Candida spp.* in Preterm Infants in NICU

	Probiotic used	Primary outcome	Incidence in the probiotic group (%)	Incidence in the placebo group (%)	*p* value
Manzoni et al, 2006[35]	*Lactobacillus rhamnosus GG*	*Candida* gut colonization in <1500-g neonates	23.1	48.8	0.01
Romeo et al, 2011[37]	*Lactobacillus reuterii*	*Candida* gut colonization in <2500-g neonates	7.1	22.9	0.01
Romeo et al, 2011[37]	*Lactobacillus rhamnosus GG*	*Candida* gut colonization in <2500-g neonates	10.7	22.9	0.01
Manzoni et al, 2006[35]	*Lactobacillus rhamnosus GG*	LOS in <1500-g neonates	48.7	53.6	NS
Kitajima et al, 1997[63]	*Bifidobacterium breve*	LOS in <1500 g neonates	2.2	0	NS
Dani et al, 2002[64]	*Lactobacillus rhamnosus GG*	LOS in <1500-g neonates	4.7	4.1	NS
Costalos et al, 2003[65]	*Saccharomyces boulardii*	LOS in <1500-g neonates	5.8	8.3	NS
Bin-Nun et al, 2005[66]	*Bifidobacterium infantis*; *Streptococcus thermophilus*; *Bifidobacterium bifidus*	LOS in <1500-g neonates	43	32.89	NS
Lin et al, 2005[67]	*Lactobacillus acidophilus*, *Bifidobacterium infantis*	LOS in <1500-g neonates	12.2	19.2	NS
Stratiki et al, 2007[68]	*Bifidobacterium longum*	LOS in <1500-g neonates	0	9.7	0.09
Lin et al, 2008[69]	*Lactobacillus acidophilus*, *Bifidobacterium bifidus*	LOS in <1500-g neonates	19.8	11.5	0.06
Samanta et al, 2009[70]	*Bifidobacterium lactis*; *Lactobacillus acidophilus*, *Bifidobacterium bifidus*	LOS in <1500-g neonates	14.2	29.5	0.02
Rougé et al, 2009[71]	*Lactobacillus rhamnosus GG* *Bifidobacterium longum*	LOS in <1500-g neonates	33.3	26.5	NS

Abbreviations: LOS, late-onset sepsis; NICU, neonatal intensive care unit; NS, not significant.

Fluconazole

Fluconazole prophylaxis is effective in preventing *Candida spp.* infection in infants < 1500 g. A recent meta-analysis with Mantel-Haenszel methods including 10 studies (7 retrospective studies and 3 randomized controlled trials)[37] shows that fluconazole prophylaxis reduces:

- ∀ the chance of developing invasive fungal infection (IFI) in high-risk infants <1000 g (odds ratio (OR) 0.10; 95% confidence interval (CI) 0.05–0.22; $p < 0.0001$)
- ∀ the chance of developing IFI in all infants <1500 g (OR 0.15; 95% CI 0.09–0.26; $p < 0.0001$)
- ∀ the overall mortality rate (11% versus 16.3%) in all infants <1500 g (OR 0.74; 95% CI 0.58–0.95; $p = 0.017$)
- ∀ the Candida-related mortality (from 25 non-treated infants to 1 fluconazole-treated patient among the 4,208 VLBW infants included in the published studies so far).

Overall, fluconazole prophylaxis decreases invasive fungal infections by 90% in ELBW and by 85% in VLBW infants with all cause mortality decreased by 24%. Fluconazole is currently recommended as a strategy in NICU having a high incidence of fungal infections, and in all those subgroups of neonates with high odds of developing such a devastating disease.[38,39]

Nystatin

Nystatin is a nonabsorbed antifungal drug that has been proposed since the 1990s as a feasible approach for prevention of fungal infections in neonates.[38,40–44] The highest-quality evidence comes from one only recent comparative trial in which 278 babies were randomized to three arms receiving nystatin, fluconazole, or placebo. The efficacy of nystatin in preventing fungal colonization and invasive infections was deemed similar to that of fluconazole.[45] When grouping together all the other nystatin studies, however, the overall level of evidence reached is lower, as compared with that of fluconazole. However, most data come from retrospective, nonrandomized, or low-quality studies with few of the smallest preterm infants and do not report data on mortality, nor on other major outcomes and on resistances development.

Of note, although intravenous fluconazole acts on many levels, oral nystatin may only reduce intestinal colonization. Moreover, nystatin has an extremely high osmolarity (10 times higher than fluconazole) and this paradoxically might be a relevant risk factor for NEC.[46]

Lactoferrin

A new approach toward reduction of sepsis and NEC might involve the use of bioactive substances with known anti-infective properties. LF is a mammalian milk glycoprotein involved in innate immune host defenses and can reduce the incidence of late-onset sepsis in VLBW infants [47] and of NEC in animal models.[48] The bovine isoform is nearly homologous to the human one. LF targets all pathogens, has bifidogenic properties, and enhances maturation of the nascent gut.[49] In a recent trial, bovine LF produced a 65% decrease in late-onset sepsis and a significant decrease in NEC of any stage of severity.[50]

Moreover, LF seems to have a strong candidacidal activity and might have a role also specifically for fungal infection prevention.[51,52] In fact, a randomized controlled trial enrolling 472 neonates demonstrated a reduction in the risk of invasive fungal infection for LF-treated infants (relative risk between 3.8 and 11, with a number needed to treat between 14 and 17.5).[53] As no adverse effects or treatment intolerances have been reported to date, the role of LF in the management of infections and NEC in NICU looks very promising and worthy of future, larger-sized trials to confirm these findings.

The Special Case of VAP

VAP represents a particular challenge because it affects most critically ill patients needing mechanical ventilation for their respiratory failure, including preterm neonates. VAP is responsible for a vicious cycle because it leads to a longer duration of ventilation, and as the additional days of ventilation is inversely related to the birth weight,[54,55] this may obviously affect the insurgence of bronchopulmonary dysplasia and sepsis. Conversely, a previous episode of sepsis is a significant risk factor for VAP occurrence in preterm babies.[56] It is not surprising that VAP represents a significant risk factor for death in ELBW babies (OR: 3.4; 95% CI: 1.20 to 12.31).[56] The risk for VAP is significantly higher below 28 weeks' gestation,[56] thus smaller babies are at greater risk for concurrent complications. Despite its importance and the fact that VAP is among the commonest nosocomial infections in pediatric critical care units in Europe and North-America,[57,58] few data are available about its occurrence in NICUs, and a certain degree of variability in VAP definitions in the different studies exists. Thus no clear strategy for its prevention is currently available.

Preventative proposed interventions include early extubation strategies and switching to noninvasive respiratory support, the reduction of transfers of the babies outside the NICU, and frequent changes of the ventilator circuits; however, more data are needed to properly evaluate the efficacy of each intervention.[59,60]

Very recently, two intriguing new approaches have been proposed. Ryan et al used an ultraviolet germicidal irradiation in the heating ventilation and air-conditioning system of their NICU and observed a significantly reduced tracheal microbial colonization and VAP (from 74 to 39%; $p = 0.04$; relative risk: 1.89; number needed to treat 2.85).[61] Christensen et al proposed the use of a low sodium saline solution for airway care and bronchoalveolar lavage in intubated neonates. This solution should decrease the incidence of VAP by reducing the damage to the innate antimicrobial system of airways subjected to serial lavages (as happens in long-term ventilated neonates). These authors observed a reduction in VAP incidence from 4.2/1,000 episodes in the control group to 1.6 VAPs/1,000 ventilator days in the treatment arm ($p = 0.04$) and also a lower incidence of chronic lung disease ($p < 0.001$).[62]

Even though these findings are preliminary and produced by trials that may not be free from biases, they look promising in identifying new lines of research to prevent VAP and concurrent complications including neonatal sepsis.

Disclosures

Authors P.M. and E.A.J. collaborate in the framework of several EU-funded and endorsed projects in the area of antifungal safety and treatment in neonates. They represent in these projects the TINN European collaborative group. E.A.J. and P.M. are, respectively, coordinator and work package leader of the FP7 European Project Treat Infections in Neonates (TINN). P.M. and D.F. are, respectively, Chairman and Advisor of the Scientific Committee of the Foundation "Crescere Insieme al S. Anna-ONLUS."

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