

BMJ Open Treating Parents to Reduce NICU Transmission of *Staphylococcus aureus* (TREAT PARENTS) trial: protocol of a multisite randomised, double-blind, placebo-controlled trial

Aaron M Milstone,^{1,2} Danielle W Koontz,¹ Annie Voskertchian,¹ Victor O Popoola,¹ Kathleen Harrelson,¹ Tracy Ross,³ Susan W Aucott,⁴ Maureen M Gilmore,⁴ Karen C Carroll,³ Elizabeth Colantuoni⁵

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For numbered affiliations see end of article.

Correspondence to
Dr Aaron M Milstone;
amilsto1@jhmi.edu

ABSTRACT

Introduction: More than 33 000 healthcare-associated infections occur in neonatal intensive care units (NICUs) each year in the USA. Parents, rather than healthcare workers, may be a reservoir from which neonates acquire *Staphylococcus aureus* (*S. aureus*) colonisation in the NICU. This study looks to measure the effect of treating parents with short course intranasal mupirocin and topical chlorhexidine antiseptics on acquisition of *S. aureus* colonisation and infection in neonates.

Methods and analysis: The TREAT PARENTS trial (Treating Parents to Reduce Neonatal Transmission of *S. aureus*) is a multicentre randomised, masked, placebo-controlled trial. Shortly after a neonate is admitted to the NICU, parents will be tested for *S. aureus* colonisation. If either parent screens positive for *S. aureus*, then both parents as a pair will be enrolled and randomised to one of the two possible masked treatment arms. Arm 1 will include assignment to intranasal 2% mupirocin plus topical antiseptics with chlorhexidine gluconate impregnated cloths for 5 days. Arm 2 will include assignment to placebo ointment and placebo cloths for skin antiseptics for 5 days.

The primary outcome will be neonatal acquisition of an *S. aureus* strain that is concordant to the parental baseline *S. aureus* strain as determined by periodic surveillance cultures or a culture collected during routine clinical care that grows *S. aureus*. Secondary outcomes will include neonatal acquisition of *S. aureus*, neonatal *S. aureus* infection, eradication of *S. aureus* colonisation in parents, natural history of *S. aureus* colonisation in parents receiving placebo, adverse reactions to treatment, feasibility of intervention, and attitudes and behaviour in consented parents. Four hundred neonate-parent pairs will be enrolled.

Ethics and dissemination: The study was approved by Johns Hopkins University IRB in June 2014 (IRB number 00092982). Protocol V.7 was approved in November 2014. Findings will be published in peer-reviewed journals.

Trial registration number: NCT02223520.

Strengths and limitations of this study

- This will be the first study to measure the effectiveness of treating parents as a strategy to reduce the spread of *Staphylococcus aureus* in the neonatal intensive care unit.
- Methodological strengths include: two study sites, masked intervention with placebo control, masked assessment of outcome, and intent to treat analysis plan.
- Study units have intensive *S. aureus* infection control programmes and a low incidence of *S. aureus* disease, so the primary outcome is *S. aureus* acquisition, not *S. aureus* infection.

INTRODUCTION

More than 33 000 healthcare-associated infections (HAIs) occur in neonatal intensive care units (NICUs) each year in the USA.¹ HAIs are estimated to result in \$28–\$45 billion in healthcare costs annually.² In addition to the short-term costs of HAIs, neonatal infections contribute to neurological disabilities and poor growth outcomes.^{3–4} *Staphylococcus aureus* (*S. aureus*) is the second most common pathogen causing HAIs in neonates.⁵ A study of very low birthweight infants in 20 US NICUs found that 3.7% develop bloodstream or central nervous system *S. aureus* infections with an attributable mortality approaching 20%.⁶ Despite aggressive measures to prevent *S. aureus* infections in neonates, the burden of *S. aureus* disease remains high in this population.^{7,8}

Up to 40% of neonates acquire *S. aureus* in the first 2 months of life.^{9,10} Vertical transmission of *S. aureus* is rare, but postnatal transmission from the mother to healthy infants is common in the first few months of

life.^{9 11} Although healthcare workers have been implicated as a source of spreading *S. aureus* in NICUs, they are often not the source for transmission of *S. aureus* in NICUs. Parents, rather than healthcare workers, may be a key reservoir from which neonates acquire *S. aureus* colonisation in the NICU.^{12–19} This paradigm is consistent with a changing NICU environment where skin-to-skin contact between parents and neonates is encouraged and may promote *S. aureus* transmission, while at the same time, common hospital infection prevention measures have reduced healthcare worker transmission of *S. aureus*. This protocol describes the TREAT PARENTS trial (**T**reating **P**arents to **R**educe **N**eonatal **T**ransmission of *S. aureus*), a randomised, masked, placebo-controlled trial that will measure the effect of treating parents with short course intranasal mupirocin and topical chlorhexidine antiseptics on acquisition of *S. aureus* colonisation and infection in neonates (ClinicalTrials.gov NCT02223520). Rather than a patient-directed approach (screening and treating *S. aureus* colonised neonates) which has limitations in the neonatal population,^{20 21} the TREAT PARENT trial tests a parent-directed approach that may eliminate or delay a neonate's exposure to *S. aureus*. Similar to treating pregnant mothers with group B *Streptococcus* during labour and delivery to prevent disease in newborn infants, this study will engage parents in preventing *S. aureus* infections in their neonates. The findings of the proposed study could provide a new tool for HAI prevention in the NICU.

Primary objective

1. To compare the effect of treating parents with short course intranasal mupirocin and topical chlorhexidine bathing or placebo on acquisition of *S. aureus* colonisation in neonates.

Secondary objectives

1. To compare the relatedness of *S. aureus* strains colonising parents and *S. aureus* strains acquired by their neonates in the NICU.
2. To compare the effect of treating parents with short course intranasal mupirocin and topical chlorhexidine bathing or placebo on *S. aureus* infections in neonates.
3. To determine the efficacy of short-course intranasal mupirocin and topical chlorhexidine bathing to eradicate *S. aureus* colonisation in parents.

METHODS AND ANALYSIS

Study design

The TREAT PARENTS trial is a placebo-controlled, double-masked, randomised clinical trial.

Study population and setting

Neonates admitted to the Johns Hopkins Hospital (JHH) NICU and the Johns Hopkins Bayview Medical

Center NICU and their parents or legal guardians will be screened for eligibility. We will define parents as the biological mother and the father. In the event that one of the parents is not available or does not visit the child in the NICU, we will ask the available parent to identify a primary visitor of the child in the NICU as a second study participant. The JHH NICU is a 45-bed NICU in a quaternary care centre that admits approximately 700 neonates per year. The Johns Hopkins Bayview Medical Center (Bayview) NICU is a 25-bed, level III unit with approximately 375 admissions per year.

Inclusion criteria

1. Neonate has never had a prior clinical or surveillance culture grow *S. aureus*
2. Neonate was transferred from another hospital or admitted from home and had admission screening cultures for *S. aureus* colonisation that were negative
3. Parent(s) is(are) able to visit the child at the bedside
4. Parent(s) test positive for *S. aureus* at screening
5. Neonate has anticipated stay longer than 5 days in the NICU
6. Parent(s) is(are) willing to be randomised
7. No documented or reported allergies to any agent used in either treatment regimen
8. Able to perform written informed consent.

Exclusion criteria

1. Allergies to any agent used in either treatment regimen
2. Neonate has had a prior clinical or surveillance culture grow *S. aureus*
3. Neonate admitted to NICU from home and is greater than 7 days of age
4. Neonate admitted to NICU from another hospital and is greater than 7 days of age
5. Neonate is a ward of the State
6. Not able to provide written informed consent.

Recruitment of patients

We will pre-screen neonates for eligibility. A member of the study team will approach all eligible parents at the bedside and request participation. After recruitment and informed consent, parents will undergo pre-randomisation screening to determine if the parents are colonised with *S. aureus*. Parent screening cultures will be performed by trained study team members using standardised methodology by obtaining a swab from the anterior nares, throat, groin and peri-anal area. These samples will be analysed in the Johns Hopkins Microbiology Laboratory according to Clinical and Laboratory Standards Institute guidelines.

Randomisation and allocation concealment

If either parent screens positive for *S. aureus*, then both parents as a pair will be eligible for randomisation to one of the two possible masked treatment arms (figure 1). The neonate–parent “pair” will be the unit of randomisation and each parent will be allocated to the

same group if both consent. Since couples can re-expose each other after treatment (especially in households), both parents will be treated even if only one parent is colonised with *S. aureus*. Stratified permuted-block randomisation will be performed using R statistical software to achieve balanced allocation of participants within study site and within strata of birth weight (\geq or <1500 g). Use of varying block sizes (4, 6 and 8) will decrease the risk of imbalance. Neonates of multiple gestations and their parents will be randomised as a single family unit. Investigators and participants will be masked to treatment assignment. A pharmacist will dispense treatment in pre-sealed opaque packaging to preserve the concealment of treatment. Additionally, the treating clinicians of the neonates will be masked to treatment assignment. In the event of a medical emergency where knowledge of the participant's blinded treatment is critical to their medical management, the blind may be broken by the investigator after consultation with the Data Safety Monitoring Board (DSMB).

Intervention

Participants will be randomly assigned to one of two arms.

1. **Treatment:** Intranasal mupirocin twice daily for 5 days plus topical antiseptics with chlorhexidine gluconate impregnated cloths daily for 5 days.
2. **Placebo:** placebo intranasal ointment (petrolatum) twice daily for 5 days and placebo cloths (not chlorhexidine gluconate impregnated) for skin antiseptics daily for 5 days.

Participant timeline

Parent evaluation time points

All participants will begin the 5-day treatment course at randomisation. The study team members will contact study participants during the treatment period to promote compliance. After completion of the treatment period, residual treatment will be retrieved and returned to pharmacy for compliance measurements. Participant self-reported adverse events will be recorded by the study team. Parent(s) will be re-tested for colonisation at 2-week intervals from randomisation for the first 8 weeks and then every 4 weeks until discharge. The final visit and testing will be performed at the time of a neonate's discharge from the NICU or at the time the child is identified to have acquired *S. aureus*. Data will be obtained via interviews and from the electronic medical record and directly entered into REDCap (a secure web application for building and managing online databases). To promote participant retention, remuneration will be provided when participants reach pre-specified milestones.

Neonate evaluation time points

After randomisation of parents, the neonate will undergo baseline testing to determine baseline *S. aureus* colonisation status. This testing will occur on study day 1, the same day that parents begin treatment. Screening cultures will be performed by obtaining a swab from the

anterior nares, umbilicus, groin and peri-anal area. Those neonates who test positive for *S. aureus* colonisation at the time of randomisation will not be included in the primary outcome analysis. After baseline testing, repeat testing will be performed every 7 days. The final visit and testing will be performed at the time of a neonate's discharge from the NICU. Results of cultures collected as part of routine patient care (eg, blood cultures, respiratory cultures, wound cultures, surveillance cultures) will also be available to identify *S. aureus* acquisition in neonates (table 1).

OUTCOMES

Primary end point

Primary outcome is neonatal acquisition of an *S. aureus* strain that is concordant to the parental *S. aureus* strain as determined by periodic surveillance cultures or cultures collected during routine clinical care.

Acquisition will be defined as meeting two criteria:

1. A neonate who had baseline surveillance cultures that were negative for *S. aureus*;
2. A neonate who has a subsequent surveillance culture or culture collected during routine clinical care that grows *S. aureus*.

Concordant strains must meet the following criteria:

1. Strains that are related using pulsed-field gel electrophoresis analysis. Isolates will be considered related if their patterns have ≤ 3 band differences. Isolates with >3 band differences will be considered epidemiologically different strain types. Alternative typing methods may be used to further discriminate highly prevalent strains.
2. The same strain from the initial parent screening is identified from the neonate.

Secondary end points

1. Neonatal acquisition of *S. aureus* as determined by periodic surveillance cultures or a culture collected during routine clinical care that grows *S. aureus*
2. Neonatal *S. aureus* infection as determined by cultures collected during routine clinical care
3. Eradication of *S. aureus* colonisation in parents following treatment
4. Natural history of *S. aureus* colonisation in parents receiving placebo
5. Adverse reactions to treatment
6. Feasibility of intervention in this population as applied
7. Attitudes and behaviour in all consented parents.

STATISTICAL ANALYSIS PLAN

Sample size and power calculations

The assumed Placebo group concordant colonisation rate is 10% and power calculations are conservatively based on the unadjusted Cox proportional hazards model where the primary covariate is the treatment group indicator. Given that we expect 10% of the

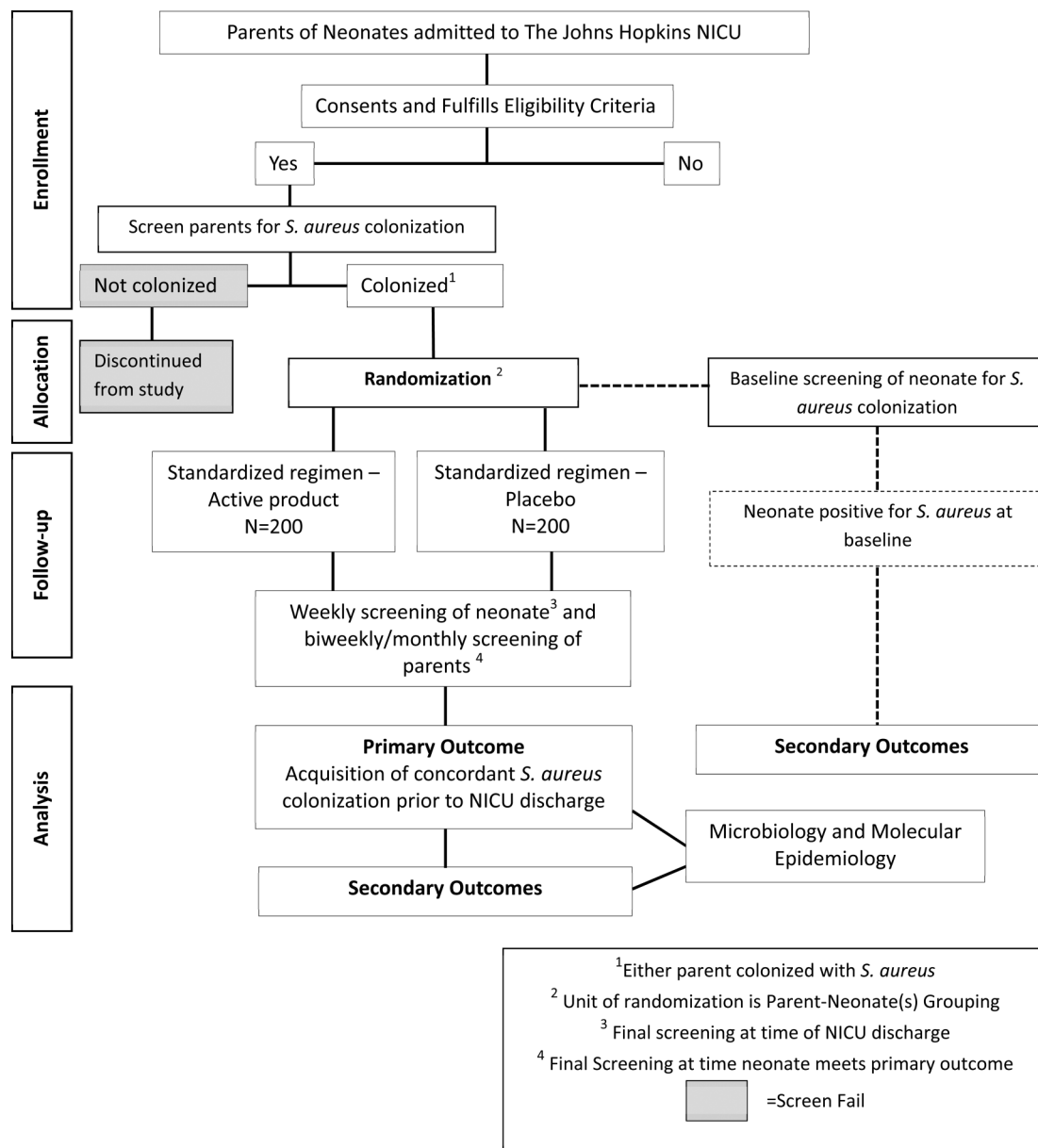


Figure 1 Overview of study design (NICU, neonatal intensive care unit).

parent–neonate pairs will be non-singleton births, we assessed the conservative power of the trial assuming that the outcomes from the non-singleton neonates are completely dependent. On the basis of the above assumptions, a total sample size of 400 neonates will provide 80% or 90% power to detect a reduction in the hazard of concordant colonisation of roughly 60% or 65%, respectively. The total sample size of 400 neonates will provide power of at least 85% to detect an absolute difference in the rate of concordant colonisation comparing the Treatment group (2%) to the Placebo group (10%). Some neonates may test positive at baseline for *S. aureus* colonisation after randomisation and will not be eligible for primary outcome analysis, so the actual enrolment will most likely exceed 400 neonates.

Interim analysis

Several interim analyses will be performed. We will perform interim analyses for both efficacy and harm after 200 and 300 neonates that are eligible for analysis have been consented, enrolled, randomised and followed for 8 weeks. After accruing the 200 and 300 neonates eligible for analysis, we will stop the trial for efficacy if the test statistic for the primary analysis (see below) falls within the O'Brien Fleming rejection region defined by $|Z_r|=2.96$ or 2.36. If the trial continues to recruit the full 400 neonates eligible for analysis, the treatment effect will be deemed statistically significant if the test statistic for the primary analysis falls within the O'Brien Fleming rejection region defined by $|Z_r|=2.01$. The O'Brien Fleming stopping rule for harm will be applied if we observe more concordant colonisations on

Table 1 Frequency of neonate and parent swab collection

	Parent only	Neonate only	Neonate Only	Neonate and parent	Neonate and parent	Neonate and parent
Time point	Screening	Randomisation	Weeks 1, 3, 5, ...	Weeks 2, 4, 6, 8, (then) 12, 16, 20, ...	Time neonate acquires <i>Staphylococcus aureus</i>	NICU discharge
Site						
Nares	X	X	X	X	X	X
Throat	X			X*	X*	X*
Umbilicus		X†	X†	X†	X†	X†
Groin	X	X	X	X	X	X
Peri-anal	X	X	X		X	X

*Parent only.

†Neonate only; the umbilicus will be tested if the neonate has an attached umbilical cord.
NICU, neonatal intensive care unit.

the treated group relative to placebo and the trial will be stopped according to the following rejection regions after accrual of 200, 300 or 400 neonates eligible for analysis; $Z_r=2.45$, 2.00 or 1.73, respectively.

In addition, an interim analysis for futility will be conducted after 200 neonates that are eligible for analysis have been consented, enrolled, randomised and followed for 8 weeks. Assuming that colonisation of the neonates occur uniformly over the study, we expect to observe 10 concordant colonisations in the Placebo group (rate of 10%) at the interim analysis. We will stop the trial if the upper bound on the 95% confidence for the concordant colonisation rate among the Placebo group at the interim analysis is <10%. Therefore, we will stop the trial for futility if the observed number of concordant colonisations in the Placebo group is ≤ 4 .

Statistical analysis

Exploratory analyses will compare baseline characteristics of the treatment groups using Student t test for continuous variables and Pearson's χ^2 test or Fisher's exact test for categorical variables. Analyses of all aims will follow the intention-to-treat principle. For the primary analysis, the parent–neonate pair will be the unit of analysis and survival analysis techniques will be used to compare the hazard of concordant colonisation comparing the Treatment and Placebo groups.²² Time will be administratively censored at 90 days after randomisation or when a neonate dies or is discharged from the NICU (except in cases where a child is transferred between the study units). To improve the precision of the estimated treatment effect, the analysis will adjust for several baseline covariates collected at the time of NICU admission that are thought to be correlated with the outcome. The baseline covariates include birth weight, an indicator for the neonate receiving breast milk, an indicator for whether the neonate was born at the participating NICU (inborn) or admitted to the NICU from home or an outside hospital (outborn). We will utilise the method developed by Lu and Tsiatis, implemented in the R package 'speff2trial', to leverage the baseline covariate information in the estimation of the treatment effect.²³ All of the selected baseline covariates

will be included in the analysis as main effects. To account for the cluster randomisation among parent–neonate dyads with multiple gestations, the SE for the treatment effect will be estimated via a bootstrap where dyads are resampled to preserve the correlation structure. If missing data should occur, data missing at random will be assumed and the principal investigator will inform, along with exploratory analyses, the relevant covariates that correlate with missingness.

Planned secondary analyses will include the following:

1. Repeat the primary analysis where time to concordant colonisation will not be censored at 90 days after randomisation; time will be defined as the time from randomisation and NICU discharge or death.
2. Define the treatment effect as the difference in the proportion of neonates acquiring concordant *S. aureus* by 4 and 8 weeks into their NICU stay comparing the treatment and control groups. The analysis will adjust for the same baseline covariates as described for the primary analysis and will be based on novel methods proposed by Rotnitzky *et al* and described in further detail in Colantuoni and Rosenblum that improve precision of estimated treatment effects incorporating prognostic baseline covariates.^{24 25}
3. Define outcome as acquisition of *S. aureus* (regardless of concordant status) using both time to acquisition and the binary indicator for any acquisition.
4. Repeating the primary analysis within strata of neonates with methicillin-resistant *Staphylococcus aureus* (MRSA) and those with methicillin-susceptible *Staphylococcus aureus* (MSSA).
5. Repeating the primary analysis within strata of neonates defined by whether or not the parent became recolonised with *S. aureus* during the study.
6. Repeat the primary analysis stratified by site of parent colonisation.
7. Perform a sensitivity analysis of the primary analysis accounting for gestational age, and also stratify by large or small size for gestational age.

Monitoring

An independent, multidisciplinary DSMB will be assembled to oversee the study. The DSMB will review

interim analyses after accrual of 200 and 300 neonates eligible for analysis. Interim analyses will be conducted for efficacy and futility. The DSMB will also review safety data and provide guidance about continuation, alternation or termination of the study on a periodic basis. The Institution for Clinical and Translational Research at Johns Hopkins will audit trial conduct periodically.

ETHICS AND DISSEMINATION

The research study team will obtain written informed consent for all participants. Consented participants will be assigned a screening number and a study identification number that will be the primary mode of identification throughout the study. All research staff will be instructed regarding the security of data and maintain the highest ethical standards in protocol adherence and data collection. During the course of the study, information collected will not be disclosed to anyone other than the study personnel. At the conclusion of the trial, only study staff will have full access to the final trial data set. Part of the informed consent will include an understanding that parents will be made aware of their *S. aureus* colonisation status. If either or both parents are colonised, parents will be informed that one or both parents are colonised, but they will not be told which parent is colonised to protect confidentiality. Also, participants will be consented to store biospecimens for future research. The study protocol and consent forms received IRB approval in June 2014. The authors commit to report data as recommend by CONSORT guidelines and findings will be published in peer-reviewed journals within 12 months of study completion and disseminated through scientific and professional conferences. Access to trial results will be provided to participants by posting results on the study website. The final trial report will link the full protocol, protocol amendments, consent form, final statistical analysis plan and laboratory methods.

PROTOCOL AMENDMENTS

All protocol changes will be submitted to the IRB and the DSMB for approval.

DISCUSSION

The TREAT PARENTS trial will test whether detection and treatment of *S. aureus* colonised parents with intranasal mupirocin and topical chlorhexidine bathing will decrease the risk of their infant acquiring *S. aureus* in the NICU, and therefore decrease infections. This study looks to shift treatment from a patient-directed approach to a parent-directed approach with the goal of eliminating or delaying a neonate's exposure to *S. aureus*. Novel strategies are needed to prevent HAIs and alleviate the billions of dollars in healthcare costs and the long-term neurological disabilities in children who survive neonatal infections. The findings of this trial could change HAI

prevention in the NICU from one that focuses on health-care workers and the environment to one that recognises and highlights parents and visitors as important sources of exposure to pathogens that contribute to HAIs.

Author affiliations

¹Department of Pediatrics, Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

²Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

³Department of Pathology, Division of Medical Microbiology, The Johns Hopkins Hospital, Baltimore, Maryland, USA

⁴Department of Pediatrics, Division of Neonatology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

⁵Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

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REFERENCES

1. Klevens RM, Edwards JR, Richards CL Jr, *et al*. Estimating health care-associated infections and deaths in U.S. hospitals, 2002. *Public Health Rep* 2007;122:160–6.
2. Scott RD. The Direct Medical Costs of Healthcare-Associated Infections in U.S. Hospitals and the Benefits of Prevention. Secondary The Direct Medical Costs of Healthcare-Associated Infections in U.S. Hospitals and the Benefits of Prevention. 2009. http://www.cdc.gov/HAI/pdfs/hai/Scott_CostPaper.pdf
3. Schlapbach LJ, Aebischer M, Adams M, *et al*. Impact of sepsis on neurodevelopmental outcome in a Swiss National Cohort of extremely premature infants. *Pediatrics* 2011;128:e348–e57.
4. Stoll BJ, Hansen NI, Adams-Chapman I, *et al*. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. *JAMA* 2004;292:2357–65.
5. Hocevar SN, Edwards JR, Horan TC, *et al*. Device-associated infections among neonatal intensive care unit patients: incidence and associated pathogens reported to the National Healthcare Safety Network, 2006–2008. *Infect Control Hosp Epidemiol* 2012;33:1200–6.
6. Shane AL, Hansen NI, Stoll BJ, *et al*. Methicillin-resistant and susceptible *Staphylococcus aureus* bacteremia and meningitis in preterm infants. *Pediatrics* 2012;129:e914–22.
7. Ericson J, Popoola VO, Smith PB, *et al*. Burden of invasive *Staphylococcus aureus* infections in hospitalized infants. *JAMA Pediatr* (in press).
8. Milstone AM, Budd A, Shepard JW, *et al*. Role of decolonization in a comprehensive strategy to reduce methicillin-resistant *Staphylococcus aureus* infections in the neonatal intensive care unit: an observational cohort study. *Infect Control Hosp Epidemiol* 2010;31:558–60.
9. Jimenez-Truque N, Tedeschi S, Saye EJ, *et al*. Relationship between maternal and neonatal *Staphylococcus aureus* colonization. *Pediatrics* 2012;129:e1252–9.

10. Leshem E, Maayan-Metzger A, Rahav G, *et al.* Transmission of *Staphylococcus aureus* from mothers to newborns. *Pediatr Infect Dis J* 2012;31:360–3.
11. Mitsuda T, Arai K, Fujita S, *et al.* Demonstration of mother-to-infant transmission of *Staphylococcus aureus* by pulsed-field gel electrophoresis. *Eur J Pediatr* 1996;155:194–9.
12. Sax H, Posfay-Barbe K, Harbarth S, *et al.* Control of a cluster of community-associated, methicillin-resistant *Staphylococcus aureus* in neonatology. *J Hosp Infect* 2006;63:93–100.
13. Al-Tawfiq JA. Father-to-infant transmission of community-acquired methicillin-resistant *Staphylococcus aureus* in a neonatal intensive care unit. *Infect Control Hosp Epidemiol* 2006;27:636–7.
14. Barbe C, Santerne B, Lemartelleur L, *et al.* Prevalence of methicillin-resistant *Staphylococcus aureus* in expressed breast milk in a neonatal intensive care unit. *J Hosp Infect* 2008;69:195–7.
15. Behari P, Englund J, Alcasid G, *et al.* Transmission of methicillin-resistant *Staphylococcus aureus* to preterm infants through breast milk. *Infect Control Hosp Epidemiol* 2004;25:778–80.
16. Gastelum DT, Dassey D, Mascola L, *et al.* Transmission of community-associated methicillin-resistant *Staphylococcus aureus* from breast milk in the neonatal intensive care unit. *Pediatr Infect Dis J* 2005;24:1122–4.
17. Pinter DM, Mandel J, Hulten KG, *et al.* Maternal-infant perinatal transmission of methicillin-resistant and methicillin-sensitive *Staphylococcus aureus*. *Am J Perinatol* 2009;26:145–51.
18. Morel AS, Wu F, Della-Latta P, *et al.* Nosocomial transmission of methicillin-resistant *Staphylococcus aureus* from a mother to her preterm quadruplet infants. *Am J Infect Control* 2002;30:170–3.
19. Conceicao T, Aires de Sousa M, Miragaia M, *et al.* *Staphylococcus aureus* reservoirs and transmission routes in a Portuguese Neonatal Intensive Care Unit: a 30-month surveillance study. *Microb Drug Resist* 2012;18:116–24.
20. Popoola VO, Budd A, Wittig SM, *et al.* Methicillin-resistant *Staphylococcus aureus* transmission and infections in a neonatal intensive care unit despite active surveillance cultures and decolonization: challenges for infection prevention. *Infect Control Hosp Epidemiol* 2014;35:412–18.
21. Popoola VO, Milstone AM. Decolonization to prevent *Staphylococcus aureus* transmission and infections in the neonatal intensive care unit. *J Perinatol* 2014;34:805–10.
22. Pocock SJ, Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. *Lancet* 2002;359:1686–9.
23. Tsiatis AA, Davidian M, Zhang M, *et al.* Covariate adjustment for two-sample treatment comparisons in randomized clinical trials: a principled yet flexible approach. *Stat Med* 2008;27:4658–77.
24. Colantuoni E, Rosenblum M. Leveraging prognostic baseline variables to gain precision in randomized trials. *Stat Med* 2015;34:2602–17.
25. Rotnitzky A, Lei Q, Sued M, *et al.* Improved double-robust estimation in missing data and causal inference models. *Biometrika* 2012;99:439–56.