Reviewer's report

Title: Variations in rates of nosocomial infection among Canadian neonatal intensive care units may be practice-related

Version: 2 Date: 5 February 2005

Reviewer: Gabriel Escobar

Reviewer's report:

General

In an era in which the majority of newborns entering the neonatal intensive care unit (NICU) survive, emphasis has shifted to the prevention of morbidity. In this respect, nosocomial infections remain one of the most challenging problems facing neonatologists. Although not always fatal, it is clear to anyone practicing in the NICU that they cause considerable morbidity and that, at least for some babies, prolong length of stay considerably.

While it is clear that certain factors - e.g., prolonged ventilator dependence, use of deep catheters, hyperalimentation, and repeated exposure to systemic antibiotics - must somehow play a role, the challenge has been (and remains) to "tease out" the relative contributions of these factors. It also seems intuitively obvious that different NICU practices (e.g., how and how often one "breaks into" a central line hook-up) must play a role, but, again, establishing quantitatively that this or that unit has a "best practice" remains elusive, a sort of Holy Grail of outcomes research.

In this paper, a team from a network that maintains one of the most sophisticated NICU databases in the world has tackled this important issue. They provide some important findings, namely: 1) documenting that rates of nosocomial infection (NI) vary across centers, even after controlling for a number of risk factors; 2) demonstrating that the epidemiology of these infections is not uniform among VLBW and HBW infants (data on HBW NIs are rare); and 3) demonstrating that outcomes among infants with NI also vary - for example, among VLBW infants, mortality does not appear to be increased, whereas the same is not true for HBW infants.

There are a number of problems with this paper, however, that detract considerably from its ability to permit strong inferences from their results.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. Framing the data analysis in a robust theoretical construct

In this paper, the authors have basically limited themselves to the manipulation of available data using a traditional approach (bivariate analyses followed by multivariate analyses). However, given the fact that a number of possible causal pathways for NI exist, an approach that permits the selection of variables to be driven by available software (stepwise regression) truly begs the question.

For example, one can go through the list of their variables (Table 3) and postulate a series of possible pathways, e.g., --
Decreasing GA -> increasing SNAP-II -> increasing need for assisted ventilation -> delay in feeding -> increasing need for parenteral nutrition if increasing likelihood of NI

However, simply bundling variables into a multivariate model does not provide much insight. For example, use of a central venous line is not significant for VLBW babies; this is hardly surprising given that assisted ventilation (a predictor for central line use) and parenteral nutrition (also a predictor for central line use) are also in the model. If one puts in a series of inter-related variables into a regression model, it is hardly surprising that some of them will pan out and that some will not.

2. Justify the use of the denominator (all NICU admissions)

The primary denominator employed for this study is all NICU admissions. This is problematic because many admissions to the NICU are brief. This leads to censoring in two ways: 1) some healthy babies are in the NICU so briefly that they do not really get a chance to develop NI; and 2) some babies, who would have developed NI had they survived, die early. A related issue is that there are some babies admitted to an NICU who experience very limited exposure to risk factors for NI (e.g., a 34 week infant with Pierre Robin syndrome that responds to positioning but requires a 3 week stay simply to gain weight without IVs or assisted ventilation).

Again, this highlights the problem of the lack of a theoretical construct. A more robust strategy would be to identify those patients who are at significant risk for NI based on what is known of the biology of NI. Thus, instead of employing “all NICU admissions,” it might be better to restrict the analysis to “all NICU admissions at major risk for NI.” For example, such a group might consist of all babies with SNAP > 9 OR assisted ventilation OR use of a central line. Risk-adjusted comparisons among such a group would provide far more meaningful information (e.g., given a central line, what really appears to be associated with NI is the fact that lipids were/were not used).

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. When reporting data from logistic regression models, it is important to report the overall explanatory power of the model as well as its model fit (c-statistic + Hosmer-Lemeshow p-value).

2. Some centers appear to have very few babies, as is evidenced by their extraordinarily wide confidence intervals. The authors should report center numbers & rates; a sensitivity analysis excluding such centers would be worth reporting, as it might decrease the apparent variation (and demonstrate that a specific practice, such as leaving a central line in for more than 2 weeks, accounts for much of the apparent variation).

3. It seems odd to include Group B streptococcus among the infections in the older infants. This is not usually considered a nosocomial infection and may be distorting the results.

4. Prior to running their model, the authors should run a correlation matrix and make a rational decision (as opposed to letting the stepdown do it) as to which variable to include (for example, I suspect that central line use and hyperalimentation use have a correlation coefficient approaching 1).

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Discretionary Revisions (which the author can choose to ignore)

In the results section, there is an odd sentence: The median onset of the first infection from day of admission was 19 +/- 26(SD) what is the SD about? Medians do not have standard deviations. Or are they referring to median across centers?
Figure 2: The title seems odd. Another sample figure title.

**What next?:** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions.

**Level of interest:** An article whose findings are important to those with closely related research interests.

**Quality of written English:** Acceptable.

**Statistical review:** No.

**Declaration of competing interests:**

I declare that I have no competing interests.