2012

Reply to Herigon and Newland

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Reviewed work(s):
Source: *Infection Control and Hospital Epidemiology*, Vol. 33, No. 2 (February 2012), pp. 208-210
Published by: The University of Chicago Press on behalf of The Society for Healthcare Epidemiology of America
Stable URL: http://www.jstor.org/stable/10.1086/663961
Accessed: 03/03/2012 15:24

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Infect Control Hosp Epidemiol 2012;33(2):207-208

 0899-823X/2012/3302-0019$15.00. DOI: 10.1086/663963

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2. Abraha I, Montedori A. Modified intention to treat reporting in randomised controlled trials: systematic review. *BMJ* 2010;340: c2697.

Reply to Herigon and Newland

To the Editor—We appreciate the interest of Herigon and Newland[1] in our trial of *Staphylococcus aureus* decolonization measures in patients with community-associated skin and soft-tissue infections.[2] These authors raise an important issue in the reporting of randomized controlled trials that has been a source of much debate and has received considerable attention: handling missing outcomes in intention-to-treat (ITT) analyses.

The lack of a clear definition for the term "intention to treat" has resulted in inconsistencies in the reporting of clinical trials.[3,4] The *Cochrane Handbook for Systematic Reviews of Interventions*[5] describes 3 principles of ITT analysis, although the application of all criteria is not clearly agreed upon: (1) analyzing participants in their randomized intervention group, regardless of whether the assigned intervention actually occurred (which is generally accepted); (2) measuring outcome data for all participants (which is nearly impossible); and (3) analyzing all randomized participants (which may involve imputing data for participants with missing outcomes). Some trials use other analytic methods, including "per-protocol" analysis, which includes only participants who were known to comply with the allocated intervention and who completed the trial, and "treatment-received" or "as-treated" analysis, in which participants, regardless of their randomization assignment, are analyzed by the intervention that was performed.[5]

As earlier CONSORT (Consolidated Standards of Reporting Trials) guidelines[6] recommended the use of ITT analysis when analyzing randomized trial data, the term "modified ITT analysis" is now being utilized with increasing frequency to reflect missing outcome data or protocol deviations.[7] As Herigon and Newland (and others) point out, the meaning of the term "modified ITT" is not uniformly applied.[5,7] Indeed, a more accurate definition of the analyses performed in our trial is "available case analysis," in which only participants with outcome data available at longitudinal study visits were included and participants were analyzed in the arm to which they were assigned, regardless of compliance with the assigned regimen.[5,7] Of note, the revised CONSORT 2010 statement requests that trial reports include whether the analysis was conducted by retaining participants in their originally assigned groups, replacing the prior guidance to report whether an "intention-to-treat" analysis was conducted.[8]

As no consensus exists for handling missing data in ITT analyses, clinical trial experts recommend designing and conducting studies in a manner that minimizes losses to follow-up.[3,4] Our patient population had a high prevalence of predictors of attrition reported in prior studies;[9] 10% of our study participants reported not having a permanent home, and 15% and 51% reported having no health insurance or public health insurance, respectively. Strategies to maximize retention included a 2-staged enrollment process, flexible scheduling, cash remuneration for time and travel, and obtaining multiple phone numbers and contact information for people close to participants.[9]

Missing data in clinical trials is largely inevitable. However, the interpretation of missing outcome values is controversial and can be addressed in several ways. One method is to impute values for the missing data, assuming that all participants lost to follow-up experienced the event or did not experience the event.[5] Herigon and Newland examined our data with one extreme assumption: that all participants lost to follow-up remained colonized with *S. aureus.* Analyzing the data with the opposite assumption, in which all participants with missing data were eradicated of *S. aureus* colonization, supports our original findings determined by available case analysis (Table 1). However, as suggested by Herigon and Newland, imputation of missing values with either the best or the worst case value results in biased results and is often too extreme.[10] Another method for imputation of missing values is "last observation carried forward" (LOCF). Of note, a patient's colonization status after any intervention is confounded by multiple factors (eg, exposure to other colonized household members, interval antibiotics), and spontaneous decolonization without intervention may occur in up to 50% of participants.[11] In addition, colonization was a requirement for study enrollment. Thus, we believe that the LOCF method would introduce additional bias into our study (Table 1). Ultimately, statistical techniques cannot adequately compensate for missing values.[5] The missing data in our study are considered "missing completely at random" (MCAR), and the available case analysis approach is a valid interpretation of outcomes data if the MCAR assumption is met.[5,10] Logistic regression analysis, including demographic and epidemiologic factors, was performed to detect significant differences between patients with and without missing longitudinal data.

TABLE 1. Eradication of *Staphylococcus aureus* Carriage

	Hygiene education only			Education and mupirocin			Education, mupirocin, and chlorhexidine			Education, mupirocin, and bleach baths		
	Available case analysis	ITT eradication imputed	LOCF	Available case analysis	ITT eradication imputed	LOCF	Available case analysis	ITT eradication imputed	LOCF	Available case analysis	ITT eradication imputed	LOCF
1 month after intervention												
Proportion (%)	24/64 (38)	35/75 (47)	24/75 (32)	35/62 (56)	48/75 (64)	35/75 (47)	35/64 (55)	46/75 (61)	35/75 (47)	34/54 (63)	55/75 (73)	34/75 (45)
P value	...	...	...	.030	.033	.066	.050	.071	.066	.006	.001	.094
RR	...	...	...	1.51	1.37	1.38	1.46	1.31	1.46	1.68	1.57	1.42
95% CI	...	...	...	1.02–2.12	1.02–1.84	0.96–1.97	0.99–2.15	0.97–1.78	0.97–2.20	1.15–2.44	1.19–2.07	0.94–2.14
4 months after intervention												
Proportion (%)	31/64 (48)	42/75 (56)	32/75 (43)	32/57 (56)	50/75 (67)	35/75 (47)	31/57 (54)	49/75 (65)	37/75 (49)	36/51 (71)	60/75 (80)	38/75 (51)
P value	...	...	...	.400	.180	.622	.510	.242	.413	.020	.002	.326
RR	...	...	...	1.16	1.19	1.10	1.12	1.17	1.16	1.46	1.43	1.18
95% CI	...	...	...	0.82–1.63	0.92–1.54	0.77–1.56	0.79–1.58	0.90–1.51	0.82–1.64	1.07–1.98	1.13–1.80	0.84–1.68

NOTE. Data are proportion (%) of participants in whom *S. aureus* carriage was eradicated. The hygiene-education-only (control) group was used as the comparator group to determine relative risk (RR) and *P* values. *P* values represent comparisons between the intervention group and the control group. "Available case analysis" represents the original analysis performed for the randomized clinical trial.[2] "ITT eradication imputed" represents an analysis in which patients lost to follow-up were assumed to be eradicated of *S. aureus* carriage. "LOCF" represents an analysis in which colonization status at the prior time point was imputed for missing data at the subsequent longitudinal samplings. ITT, intention to treat; LOCF, last observation carried forward; CI, confidence interval.

At 1 month after the intervention, age was a significant predictor of attrition, with older individuals being more likely to remain in the study; however, this association did not persist at 4 months (data not shown).

Interestingly, participants randomized to the control group (receiving only personal and household hygiene education) had the highest retention. This was an open trial, and patients were aware of the 4 potential randomization arms. Other investigators have observed the phenomenon in which study retention was higher if the perceived benefits of the study outweighed the burdens and risks of the intervention or the condition being treated.[9,12] As participants in the intervention arms received decolonization measures at enrollment, they may not have perceived added benefit in returning for follow-up visits for colonization culturing and survey completion. In contrast, participants in the control arm may have been hopeful that they would eventually receive decolonization measures if they continued in the study, although this was never suggested to them.

We believe that the data generated by this trial provide evidence for a regimen already prescribed by many practitioners and, as many questions remain, serve as a foundation for future trials.

ACKNOWLEDGMENTS

Financial support. S.A.F. and B.C.C. have received salary support from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and the NIH Roadmap for Medical Research (UL1 RR024992 and KL2 RR024994); B.C.C. has received grant support from Pfizer. The contents of this letter are solely the responsibility of the authors and do not necessarily represent the official view of the NCRR or the NIH.

Potential conflicts of interest. B.C.C. reports receiving research support from, serving as a consultant for, and being on the speakers' bureau of Pfizer. All other authors report no conflicts of interest relevant to this article. All authors submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and the conflicts that the editors consider relevant to this article are disclosed here.

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Infect Control Hosp Epidemiol 2012;33(2):208-210
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