Methenamine for the Prevention of Recurrent UTIs:

A Desirability of Outcomes Ranking (DOOR) analysis for the Alternative to Prophylactic Antibiotics for the Treatment of Recurrent Urinary Tract Infections in Women Trial

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Background:

- Low dose daily antibiotic prophylaxis is frequently utilized as a preventative strategy for recurrent UTIs. This strategy raises concerns for increased antibiotic use and antimicrobial resistance, highlighting the need for effective non-antibiotic approaches.
- The Alternative to Prophylactic Antibiotics for the Treatment of Recurrent Urinary Tract Infections in Women (ALTAR) trial demonstrated that twice daily methenamine hippurate was non-inferior to daily low dose antibiotics for the prevention of recurrent UTIs.[1]
- Non-inferiority trials are frequently misrepresented or misinterpreted by patients and clinicians.[2,3] Non-inferiority trials also do not address which treatment approach is preferred.[2,3]
- The Desirability of Outcomes Ranking (DOOR) and Response Adjusted for Duration of Antibiotic Risk (RADAR) superiority methodology has been used as a secondary outcome in selected non-inferiority studies to incorporate antibiotic exposure and clinical outcomes to assess for clinical superiority.[4-6]

Aim:

To apply DOOR/RADAR methodology to the ALTAR trial to evaluate for clinical superiority of methenamine hippurate as compared to antibiotic prophylaxis for the prevention of recurrent UTIs

Methods:

- The first step for DOOR analysis is to create categories that rank clinical outcomes using the data supplement of the ALTAR trial.
- Categories were created by comparing the clinical outcome of the number of UTIs observed during the study period for both the antibiotic prophylaxis group and methenamine group.
- Next, participants were assigned a ranking combining both the clinical outcome of number of UTIs in the study period as well as antibiotic use, with the principle that a better ranking is achieved in the group with less antibiotic use as long as the same clinical outcome of number of UTIs is achieved.
- Thus, the group with no UTIs in the methenamine group represents the most desirable clinical outcome, while the group with six episodes of UTIs in the antibiotic prophylaxis group the least.
- Finally, the Mann-Whitney U test was used to compare outcomes between these groups.

	Methenamine Group (n=103)	Antibiotic Prophylaxis Group (n = 102)
No Episodes of UTI	44 (43%) *	55 (54%)
1 Episode of UTI	27 (26%)	21 (21%)
2 Episodes of UTI	7 (7%)	15 (15%)
3 Episodes of UTI	10 (10%)	7 (7%)
4 Episodes of UTI	7 (7%)	2 (2%)
5 Episodes of UTI	6 (6%)	2 (2%)
6 Episodes of UTI	2 (2%)	0 (0%) **

Table 1: Number of UTIs by Treatment Group. Number of UTIs observed during study period between groups receiving methenamine hippurate as compared to antibiotic prophylaxis. The most desirable outcome (*) and the least desirable outcome (**) are as designated above.

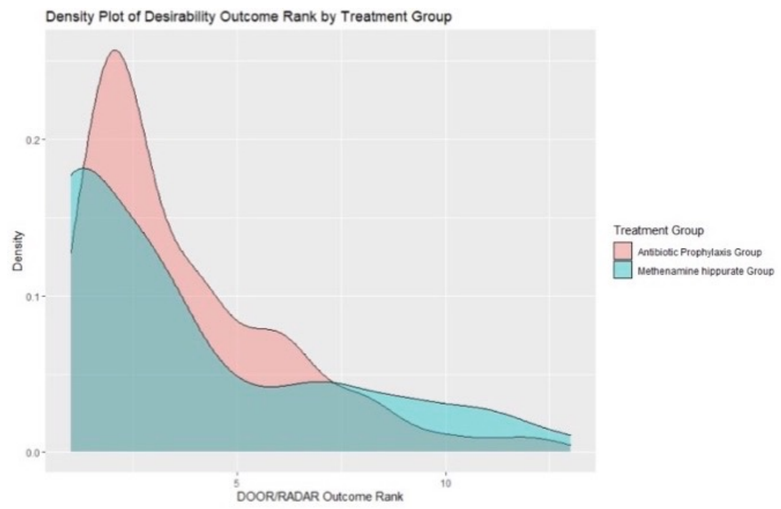

Figure 1: Density Plot of Desirability of Outcome Rank by Treatment Group. The density of DOOR/RADAR outcomes of methenamine hippurate as compared to antibiotic prophylaxis group.

Results:

- The ALTAR study included 205 patients over a 12 month treatment period to measure the incidence of symptomatic, antibiotic-treated UTIs.
- 102 patients received low dose antibiotics with either nitrofurantoin, trimethoprim, or cephalexin daily.
- 103 patients received twice daily methenamine hippurate.
- As per DOOR/RADAR analysis, the methenamine and antibiotic prophylaxis groups were divided into categories based on the number of UTIs observed during the study period with ranking based on combined clinical outcome and antibiotic use as displayed in Table 1. The density plot of the DOOR/RADAR outcomes are displayed in Figure 1.
- Using the Mann-Whitney U test, the probability of a better DOOR score (i.e. more desirable outcome) for a randomly selected patient from the methenamine group compared to the antibiotic group was 58% (p-value 0.045)

Conclusions:

- Applying the DOOR/RADAR analysis to the data from the ALTAR trial provides evidence to suggest that there is a higher probability for a more desirable outcome in women who receive methenamine hippurate as compared to prophylactic antibiotics for the prevention of UTIs.
- A limitation of this DOOR/RADAR analysis is that the severity of each UTI episode or adverse events are not incorporated in the analysis, as which treatment group these events occurred in cannot be discerned with the available data. Incorporating this information to future analyses would be meaningful and represents important clinical information for patients and providers.

References:

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