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The BioWipe: A Non-invasive Method to Detect Intestinal Carriage of Multi-Drug Resistant Gram-negative Bacteria

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Colonization precedes infection and facilitates spread of several clinically important multi-drug resistant organisms (MDRO). Reliable detection of carriage is important to improve our understanding of risk factors and spread of MDRO. Bacterial culture of stool samples obtained from peri-rectal swabs or whole stool is often used for this purpose.(1) The previously described BioWipe method is a non-invasive stool collection method that resembles the use of toilet paper, and can be self-administered.(2) The BioWipe consists of a 100×160 mm square of soft, absorbent synthetic fiber material attached to a plastic backing layer (Fisher Scientific, USA). It is used prior to using toilet paper after a bowel movement. The wipe with collected stool sample is placed onto the surface of an absorbent pad (3M™ Petroleum Sorbent Pads, Fisher Scientific, USA) containing modified Cary Blair transport media. The two parts are then folded together and placed inside a plastic bag. Prior

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Competing Interests

Dr. Bonomo reports grants from Allecra, Entasis, Merck, Roche, Wockhardt, Shionogi, and Achaogen, outside the submitted work. Dr. van Duin has served as a consultant for Allergan, Achaogen, Qpex, Shionogi, Tetraphase, Sanofi-Pasteur, T2 Biosystems, NeuMedicine, Roche, MedImmune, Astellas, Merck, and Pfizer.

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to use, both components are treated with ultraviolet light irradiation in a biological safety cabinet for 30 minutes. After sample collection, the BioWipe is eluted with 20 mL mix of Phosphate Buffer Saline solution (PBS, pH=7.2) and 0.1% Tween 80 (vol/vol) directly in its original bag in a biosafety cabinet, until the stool sample is completely eluted. The resulting suspended stool sample is used for further processing.

Here, we collected samples from 27 patients who were admitted to North Carolina Jaycee Burn Center, a real-world setting with high levels of antibacterial resistance.(3) The study was approved by the Institutional Review Board with a waiver of informed consent as it was considered minimal risk. A total of 27 BioWipe samples were paired with whole stool samples collected immediately prior to use of the BioWipe.

BioWipe samples and whole stool samples were processed similarly to compare yield of bacterial growth. Prior to processing, 100 mg of whole stool was suspended in 5 mL of PBS. To detect cefotaxime-resistant and carbapenem-resistant Gram-negative bacteria, MacConkey agar plates supplemented with 1 mg/L of cefotaxime and mSuperCarba (Chromagar, Springfield, NJ) agar plates were used. For both BioWipe and whole stool samples, 100 µl aliquots of various dilutions were plated in duplicate, and incubated at 37°C for 24 ± 3 hours. Selected colonies were streaked onto a new plate of the same selective media. Five colonies were selected from each type of selective media plate. The plates were incubated for 24±3 hours at 37°C. Purified colonies were transferred into Tryptic Soy Broth (TSB) non-selective media and incubated for 24 ±3 hours at 37°C. Matrix-assisted laser desorption/ionization-time-of-flight (MALDI-TOF) mass spectrometry was used for species identification.

Overall, concordance between cultures from whole stool and BioWipe samples was seen in 18/27 (66%) paired samples. In 9/27 (33%) paired samples, cultures from neither the whole stool nor the BioWipe sample resulted in growth of any Gram-negative bacteria. In 9/27 (33%) paired samples, the same bacteria were recovered from both sample types; *Pseudomonas aeruginosa* (n=6), *Klebsiella pneumoniae* (n=1), *Escherichia coli* (n=1), and *Enterobacter bugandensis* (n=1). In three of these nine positive paired samples, additional bacteria were recovered from the BioWipe sample that were not recovered from the whole stool sample; *Stenotrophomonas maltophilia* (n=1), *K. pneumoniae* (n=1), and *Achromobacter* spp., *Pseudomonas* spp. with *S. maltophilia* (n=1). In 6/27 (22%), bacteria were only isolated from cultures from the BioWipe sample; *Pseudomonas spp.* (n=4), *Klebsiella aerogenes* (n=1), and *P. aeruginosa* with *Enterobacter cloacae* (n=1). A possible explanation for this discrepancy is that Gram-negative MDRO found only as part of the skin microbiome and not in the intestinal microbiome may be detected by the BioWipe. Skin carriage of Gram-negative MDRO is common in burn patients.(4) In 3/27 (11%), bacteria were only isolated from cultures from the whole stool sample; *P. aeruginosa* (n=1), *E. coli* (n=1), and *E. cloacae* (n=1).

There are important limitations to our study. First, as this was a clinical study using actual patient samples, we were limited in the number of patient samples that we could obtain. While we have a smaller number of samples, the use of stool samples with clinically relevant numbers of Gram-negative MDRO provides more relevant information as compared

to artificial experiments with spiked samples. Second, we studied a specific population of patients and results may not be generalizable to others. The burn population was chosen for their known high likelihood of carriage of Gram-negative MDRO, but further studies on other at-risk populations such as oncologic patients will be important.

In summary, previously reported data combined with the data reported here support the use of the BioWipe for the research detection of Gram-negative MDRO intestinal carriage.

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Ethical Approval

This study was approved by the Institutional Review Board of the University of North Carolina Hospitals (IRB19–0700).

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