Friday 453

Detection of *C. difficile* in a Pediatric Population using a Multiplex Stool Panel

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abstract

Background: *C difficile* (CD) is an important agent of nosocomial and community acquired gastroenteritis (GE). However, detection in young children (<3 years of age) may represent asymptomatic colonization and the American Academy of Pediatrics suggests routine testing in this age group is not recommended (1). The impact of inclusion of CD on multiplex molecular GE panels versus testing in a more selective manner is not well characterized. In this study, the results of use of panels in comparison to standard of care (SOC), analyte specific testing for CD were examined.

Methods This was a multicenter trial at 5 US children's hospitals. Children <18 years presenting to the Emergency Department (ED) or Urgent Care with acute GE had clinical and epidemiologic data collected at baseline and day 7-10. During the pre-intervention period (PRE), SOC tests for GE pathogens were performed at the provider's discretion; the FilmArray® Gastrointestinal (GI) Panel was performed for a subset of enrolled patients but the results were not reported. During the post-intervention period (POST), clinicians were educated and the GI Panel was performed on all enrolled patients in real time and all results reported except CD on those <1 year. Data were analyzed for the detection of CD to see the prevalence, clinical relevance, and treatment during the 2 periods.

Results: A total of 1157 patients were enrolled (571 PRE, 586 POST) with stool samples tested by FilmArray GI Panel on 375 (66%) PRE and 586 (100%) POST with 43 (11.5%) and 94 (16%) positive for CD respectively. CD was ordered as SOC and positive in 2/27 (7 %) PRE and 6/30 (20 %) POST. Among the 137 CD positives by GI Panel, 49 (36%) were sole detections and 98 (72%) were in children <3 years. Co-detections were seen in 88 (64%) samples, with norovirus, Enteropathogenic *E.coli* (EPEC), and adenovirus the 3 most common targets. An alternate etiology for GE (excluding EPEC and Enteroaggregative *E.coli*) was detected in 66 of 98 (67%) of those <3 years of age versus 15 of 39 (38%; odds ratio 3.3; p<0.01) >3 years. Treatment for CD was given to no patients in the PRE and 6 in POST, 4 of whom had risk factors for CD.

Conclusion: CD is commonly detected in pediatric patients, especially in those < 3 years, often in the context of co-infection with other GE pathogens. In the ED setting, standard CD testing is uncommon for children evaluated for GE. Education and careful consideration of CD results from multiplex panels is needed to prevent misattribution or mistreatment of GE illness, particularly in young children.

background

- Diarrheal illnesses are common in pediatric populations, but an infectious etiology is not always ascertained.
- The FilmArray Gastrointestinal Panel (GI) is a rapid (~ 1 hr), highly multiplexed test that detects 22 targets including bacteria (*Campylobacter* spp., *P. shigelloides*, *Salmonella* spp., *Shigella*/EIEC, *Vibrio* spp., *Vibrio cholerae*, *Y. enterocolitica),* enteropathogenic *E. coli* (enteroaggregative *E. coli*, enteropathogenic *E. coli*, enterotoxigenic *E. coli*), Shiga-like toxin-producing *E. coli*, viruses (astrovirus, norovirus GI/GII, rotavirus A, and sapovirus), parasites (*Cryptosporidium* spp., *Cyclospora cayetanensis*, *Entamoeba histolytica, Giardia lamblia*) and *C. difficle* toxin genes (CD) from stool.
- CD carriage is common in young children, and the American Academy of Pediatrics advises that it is prudent to avoid routine testing for *C. difficile* in children younger than 1 year. Testing for *C. difficile* can be considered in children 1 to 3 years of age with diarrhea (>3 loose stools/24hr), but testing for other causes of diarrhea, particularly viral, is recommended first.(1)
- The impact of inclusion of CD on multiplex molecular GE panels versus testing in a more selective manner is not well characterized.
- In this study, the results of use of panels in comparison to standard of care (SOC), analyte specific testing for CD were examined.

methods

- This was a multicenter, prospective, step wedge trial at 5 US children's hospitals. Children <18 years presenting with acute GE with symptoms (>24 hr but < 14 days) had clinical and epidemiologic data collected at baseline and day 7-10.
- During the **pre-intervention** period (PRE), SOC tests for GI pathogens were performed at the provider's discretion; the FilmArray GI Panel (BioFire Dx, SLC, UT) was performed for a subset of enrolled patients but results were **not reported**.
- During the **post-intervention** period (POST), the FilmArray GI Panel was performed on all enrolled patients in real time and all results **reported, except CD on those <1 year**.
- Education of the clinical staff occurred prior to the beginning of the POST to explain the testing and the interpretation of results.
- Data were analyzed for the detection of CD to see the prevalence, clinical relevance, and treatment during the 2 periods.

results

Figure 1: Study Population - 1157 patients were enrolled (571 PRE, 586 POST)

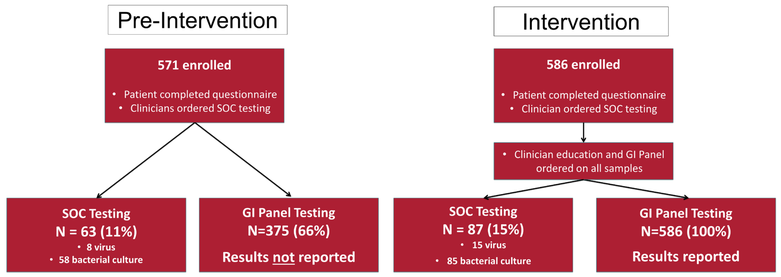


Table 1. C difficile Positivity with Standard of Care (SOC) versus the FilmArray GI Panel Testing

	Standard of Care		FilmArray GI Panel	
Age	# CD pos/ #tested	% Positive	# CD pos/ #tested	% Positive
Pre-Intervention[a]				
<12 m	1/2	50%	22/86	26%
1-2 yr	0/1	0%	10/69	14%
2-3 yr	0/2	0%	2/38	9%
>3 yr	1/23	4%	9/182	5%
Pre total	2/28	7%	43/375	11%
Intervention				
<12 m post	0/1	0%	36/138 [b]	26%
1-2 yr post	1/2	50%	21/108	19%
2-3 yr	0/2	0%	7/59	12%
>3 yr post	5/25	20%	30/281	11%
Post total	6/30	20%	94/586	16%
Combined total	**8/58**	**14%**	**137/961**	**14%**

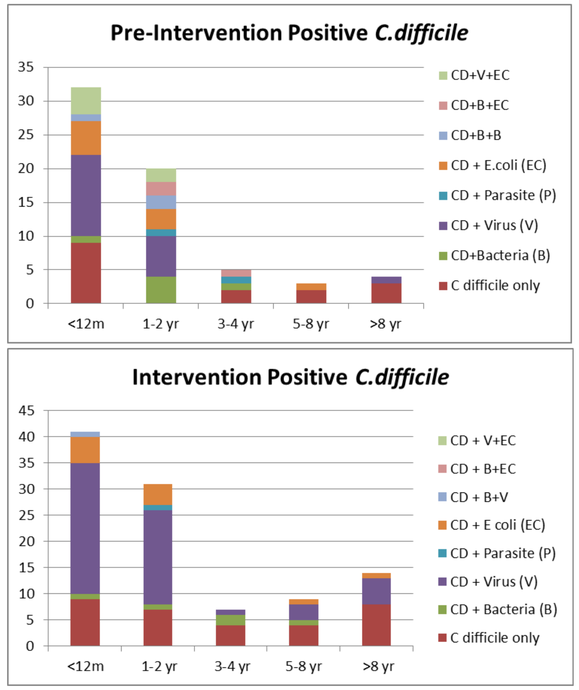
[a] FilmArray results were not released in the Pre-Intervention phase
[b] CD results in those <12m were not released to the physician in the Intervention phase.

Table 2. Characteristics of Patients based CD testing with the FilmArray GI Panel

	Pre-Intervention			Intervention		
	CD Pos # (%)	CD Neg # (%)	p value[a]	CD Pos # (%)	CD Neg # (%)	p value[a]
No. patients	**43**	**332**		**94**	**492**	
Symptoms						
>3 stools/24 hrs	20 (47)	221 (67)	0.0099	58 (22)	310 (63)	<0.001
Stool, loose	27 (63)	245 (74)	0.13	79 (84)	398(81)	0.49
Fever	22 (51)	189 (57)	0.56	50 (53)	240 (49)	0.48
Vomiting/Nausea	36 (84)	225 (77)	0.30	70 (74)	387 (79)	0.29
Prior Antibiotic Exposure	**10 (23)**	**33 (10)**	**0.012**	**20 (21)**	**74 (15)**	**0.15**
Antibiotics for CD given						
Vancomycin	0	2		2	0	
Metronidazole	0	7		6	2	
Other	0	1		1	0	
Complete full course of treatment[b]	**0**	**3**		**4**	**0**	
Presence of a Potential Pathogen other than CD	**24/43 (56)**	NA		**57/94 (61)**	NA	

[a]"N-1" Chi-squared test
[b] Full course treatment = 7-10 days (vancomycin, metronidazole, fidaxomicin, or nidizoxanide)

Figure 2: Co- Detections with the FilmArray GI panel by Patient Age



- Co-detections were seen in 88/137(64%) CD positive samples (Pre-Intervention + Intervention), with norovirus, Enteropathogenic *E.coli* (EPEC), and adenovirus the 3 most common targets.

Table 3: *C. difficile* Positive with an Alternate Pathogen detected with the FilmArray GI Panel that could Explain GE

CD Positive (Pre-intervention and Intervention)	Alternate Pathogen* # (%)	
<3 yrs, CD + N=98	**66 (67%)**	**p = 0.0035**
>3 yrs, CD + N=39	**15 (38%)**	**OR =3.3 (95 % CI: 1.5-7.3)**

*Excludes EPEC and EAEC due to uncertain clinical significance
p value (2 tailed, Fisher exact): Odds Ratio (OR)

conclusions

- CD is commonly detected in pediatric stool samples, often seen in the context of co-infection with other GE pathogens especially those <3 years of age. This finding is consistent with the known carriage of CD in young children.
- Careful consideration of CD results from multiplex panels is needed to prevent misattribution or mistreatment of GE illness, particularly in young children.
- Selective reporting and prior education can prevent misattributing CD as causative agent:
  - CD results suppression in those <1 yr of age prevented possible misdiagnosis.
  - Consideration of other possible pathogens, particularly in those <3 years of age is important.
- Education provided in the Intervention appeared to be effective in preventing treatment of CD in those unlikely to have disease as evidences by no treatment given to any patients 1-3 yrs of age in the POST period in this study.
- Detection of CD in those >3 yrs of age did not lead to treatment in the majority of cases.

References: [1]Schutze et al Pediatrics. 2013. 131: 196-200.