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**TITLE: Performance of stool cultures before and after a 3-day hospitalization: fewer cultures, better for patients and for money**

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## **Abstract**

We evaluated retrospectively the yield of stool culture (SC) depending on the length of hospitalization, and we characterized the patients missed by the 3-day rejection rule. SC detects bacterial enteric pathogens (*Campylobacter* spp., *Salmonella enterica*, *Yersinia* spp., *Shigella* spp.). During this 5-year study period, 13,039 SCs were requested, and 376 were positive (2.9%). The yield of SC dropped from 11.7% before 3 days of hospitalization to 0.7% after 3 days in children and 4.3% to 0.3% in adults. Finally, only 13 clinically relevant cases (0.2% of SC prescribed after 3 days) were undiagnosed by strict application of the 3-day rule. In conclusion, rejection of SC prescribed after 3 days of hospitalization allows to reduce workload by 37.8% for children and 65.7% for adults, representing a cost of €12,500 (\$16,250) per year in our hospital.

## Introduction

Stool culture (SC) are prescribed to detect bacterial enteric pathogens (*Campylobacter* spp., *Salmonella enterica*, *Yersinia enterocolitica*, *Shigella* spp.), which are frequently community-acquired. Therefore, the yield of SC is low in hospitalized patients (2.6-6.1%) (Fan et al., 1993)(Rohner et al., 1997), especially after 3 days of hospitalization (0.5%) (Bauer et al., 2001). Thus, some laboratories reject SC submitted after 3 days of hospitalisation (“3-day rule”), considering *Clostridium difficile* is the major microorganism responsible for nosocomial bacterial diarrhoea (Versalovic, 2011).

In 2001, a European study group (Bauer et al., 2001) modified this 3-day rejection rule to propose exceptions for high risk patients in adult population (neutropenic, HIV-positive, or age > 65 years with comorbidities). These guidelines were validated in Freiburg Hospital (Germany): the global yield of stool culture was 1.0% on 3416 samples, and 82.5% of the SC were sent after 3 days of hospitalization. This particular population may not be representative of all European laboratories. In Lisbon (Portugal) the global yield of SC was 9% on 853 samples and 64.6% of the stool cultures were sent after 3 days of hospitalisation (Hanscheid et al., 2002). The guidelines validated for adults by Bauer et al. were later extended to children in 2007 (Seyler et al., 2007). In this paediatric population from Oxford, the global yield of SC was 1.9% on 5262 samples, and 29% of the stool cultures were sent after 3 days of hospitalization.

The first objective of this study is to evaluate retrospectively in Lille University Hospital (France) the yield of SC depending on the length of hospitalization, and to characterize the patients missed by the 3-day rejection rule. It seems necessary to evaluate the application of rejection criteria separately on children (age < 16 years old), because the

epidemiology of infectious diarrhoea differs markedly between adults and children (Pfeiffer et al., 2012). The second aim is to evaluate the potential savings for the laboratory.

## **Material and Methods**

Stool cultures requested from January 2007 to December 2011 in Lille University Hospital were included retrospectively in this study. Follow-up cultures after a positive result were excluded. For *Campylobacter* spp. detection, all specimens were streaked onto Karmali medium (bioMérieux, Marcy l'Etoile, France) without microfiltration and incubated at 37°C in a microaerophilic atmosphere (85% nitrogen, 10% carbon dioxide, 5% oxygen) for 48 hours. To detect *Salmonella enterica* and *Shigella* spp., all specimen were streaked onto Hektoen medium (bioMérieux, Marcy l'Etoile, France) and incubated at 37°C in air for 24 hours. To enhance the recovery of *Salmonella enterica*, we used a Selenite F broth (bioMérieux, Marcy l'Etoile, France), which was subcultured onto Hektoen after 18 hours of incubation at 37°C. *Yersinia enterocolitica* were detected using Schiemann-CIN medium (bioMérieux, Marcy l'Etoile, France) after an incubation of 24 hours at 28°C in air.

To identify bacterial enteric pathogens, we used conventional biochemical techniques from January 2007 to September 2009. For *Salmonella enterica* and *Shigella* spp., suspicious colonies on Hektoen were screened for urease activity and streaked onto Kligler agar. Depending on the results of these tests, we continued with VITEK 2 GN (bioMérieux, Marcy l'Etoile, France) or with *Shigella* antisera (Bio-Rad, Marnes la Coquette, France). *Campylobacter* spp. were identified by API Campy (bioMérieux, Marcy l'Etoile, France), and *Yersinia enterocolitica* using the VITEK 2 GN. From October 2009 to December 2011, we used MALDI-TOF mass spectrometry (Microflex; Bruker Daltonics, Wissembourg, France).

*Shigella* strains were still identified by seroagglutination since MALDI-TOF cannot identify this specific bacterial genus.

We estimated the average stool culture would cost 7.98€ for our laboratory. This global cost can be decomposed into culture media (1.53€), automated specimen inoculation (1.04€), bacterial identification (0.41€) and technical personnel (5.00€).

Statistical analysis was performed with SPSS 20.0. Mann-Whitney test was used to compare the length of hospitalization for children versus adults. Chi-squared test was used to compare the yield of SC, and this analysis was also stratified by hospitalization length. *P*-values of less than 0.05 were considered to indicate a statistically significant difference.

## Results

During this 5-year study period, 13,039 SC were requested, corresponding to 10,635 patients (including 2,238 children). 376 were positive (2.9%): 239 SC for *Campylobacter* spp. (63.6% of the positive stool cultures), 111 for *Salmonella enterica* (29.5%), 18 for *Shigella* spp. (4.8%), and 8 for *Yersinia enterocolitica* (2.1%).

The global yield of SC was higher for children (7.6%) than for adults (1.7%) ( $p<0.001$ ) (Table 1). Only 37.8% of SC were prescribed after 3 days of hospitalization for children compared to 65.7% for adults ( $p<0.001$ ). As the yield of SC falls sharply when the length of hospitalization increases, we performed a stratified analysis based on 4 categories of hospitalization length (Figure 1). At Day 0, the yield of SC was 18.8% for children and 7.9% for adults ( $p<0.001$ ). After Day 3, no significant difference was found between the yield of SC in children (0.7%) versus adults (0.3%) ( $p=0.09$ ).

Strict application of the 3 day-rule rejection criteria would have led to miss 7 cases of bacterial enteric pathogens for children (3.5% of all positive SC) and 23 cases for adults (13.0% of all positive SC) (Table 2). Among these 30 missed cases, 4 were asymptomatic carriers, 4 had non-diarrheal manifestations of enteric infection (SC prescribed after bacteraemia or abscess due to enteric pathogens), and 9 were hospitalized patients with a community acquired diarrhoea at Day 0 but the first SC was prescribed after more than 3 days of hospitalization. Only 13 of the 30 positive SC prescribed after 3 days of hospitalization would have been relevant (4 children and 9 adults), representing 0.2% of all the SC prescribed for nosocomial diarrhoea.

Patients suffering from nosocomial diarrhoea often received chemotherapy during the preceding weeks (7 of the 13 clinically relevant cases) but only 2 of them had severe

neutropenia (absolute neutrophil count  $< 0.5 \times 10^9/L$ ). Four patients had haematological malignancies, 2 had solid tumours and 1 was treated with methotrexate for Crohn's disease.

The yield of SC was higher during warmer months: 4.0% from May to September (with a maximum of 5.0% in July) against 2.0% from October to April (with a minimum of 1.7% in February). The number of SC prescribed per month remained stable, regardless of the season (mean = 217, standard deviation =18).

Using the 3-day rule, 7,830 SC would have been rejected (60.0% of all the SC received). The potential savings for the laboratory would have been about 12,500€ per year (culture media 2,400€, automated specimen inoculation 1,630€, bacterial identification 640€ and technical personnel 7,830€).

## Discussion

Even if the yield of SC prescribed after 3 days of hospitalization was low (0.7% for children and 0.3% for adults), 13 clinically relevant cases would have been missed by the strict application of the 3-day rule (4 children and 9 adults). Among these 9 adult cases of nosocomial diarrhoea undiagnosed, only 2 would have been detected by the application of Bauer guidelines (1 had age > 65 years associated with comorbidities, and 1 had severe neutropenia).

Interestingly, we found that 7 patients out the 13 clinically relevant cases of nosocomial diarrhoea received chemotherapy. Asymptomatic colonization with enteropathogenic bacteria can lead to invasive disease triggered by cancer chemotherapy, as previously reported for *Salmonella* (Delaloye et al., 2004), probably due to mucositis and immunosuppression. In our study, 4 patients developed nosocomial *Campylobacter* diarrhoea (2 *C. coli*, 2 *C. jejuni*) and 3 developed *Salmonella enterica* diarrhoea after receiving chemotherapy.

After 3 days of hospitalization, there was no significant difference between the yield of SC in children compared to adults. Although children seem particularly susceptible to develop community-acquired diarrhoea, that does not justify the research of enteropathogenic bacteria after 3 days of hospitalization. Globally, SC did not add much value to the diagnosis of nosocomial diarrhoea, except for patients under cancer chemotherapy.

The higher number of positive SC cases detected in warm months (May to September) can be explained by the epidemiology of *Campylobacter* and *Salmonella* infections (representing 93% of our positive cases). Indeed, the increase of ambient temperature is known to be associated with *Campylobacter* (Nichols et al., 2012) or *Salmonella* (Ravel et al., 2010) infections. However, the number of SC prescribed per month remained stable during

the year. This may be explained by the winter seasonality of viral gastroenteritis (Mounts et al., 2000), contrasting with the summer seasonality of most bacterial enteric infections. Physicians prescribe SC in case of diarrhoea, not knowing if the aetiological agent is a bacteria, a parasite or a virus.

The introduction of rejection criteria for SC can potentially delay the diagnosis of nosocomial outbreaks due to bacterial enteric pathogens (Bruins et al., 2003). These outbreaks are very rare nowadays, thanks to higher standards of hygiene. Actually, no cluster of nosocomial cases has been identified during the 5 years covered by this study.

In conclusion, rejection of SC prescribed after 3 days of hospitalization allows to reduce workload by 37.8% for children and 65.7% for adults, representing cost-savings of 12,500€ (16,250 \$) per year. Few cases of clinically relevant enteric infections are missed, but even the exception criteria proposed by Bauer et al. do not identify all of these cases. Patients under cancer chemotherapy seem particularly at risk to develop nosocomial diarrhoea caused by enteropathogenic bacteria. Overall, this study highlights the importance of communication between clinical microbiologists and physicians before the prescription of SC for patients suffering from nosocomial diarrhoea.

### **Conflict of interest statement**

None declared.

### **Funding sources**

None.

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## Tables and Figures legends

**Table 1.** Characteristics of the study population (children versus adults)

**Table 2.** Epidemiology of the bacterial enteric pathogens detected after 3 days of hospitalization

*C.: Campylobacter, S.: Salmonella, Y.: Yersinia*

**Figure 1.** Stool culture yield stratified on the length of hospitalization (children versus adults)

\*:  $p < 0.001$ , NS: non significant

**Table 1.** Characteristics of the study population (children versus adults)

Stool Culture (SC)	Children		Adults		<i>P</i> -value
	Positive	Negative	Positive	Negative	
Total Number of SC (%)	199 (7.6%)	2,431 (92.4%)	177 (1.7%)	10,232 (98.3%)	<0.001
SC sent before 3 days (%)	192 (11.7%)	1,443 (88.3%)	154 (4.3%)	3,420 (95.7%)	<0.001
SC sent after 3 days (%)	7 (0.7%)	988 (99.3%)	23 (0.3%)	6,812 (99.7%)	0.09
Median length of hospitalization (days)	0	2	1	8	<0.001
Age (mean years ± standard deviation)	4.84 (± 4.62)	3.44 (± 4.86)	43.89 (±20.49)	60.07 (± 18.95)	
Sex Ratio	1,26	1,21	1,36	1,14	0.22

**Table 2.** Epidemiology of the bacterial enteric pathogens detected after 3 days of hospitalization

<b>Epidemiology</b>	<b>n (%)</b>	<b>Bacterial species</b>
<b>Children</b>		
Community acquired diarrhoea	1 (14%)	1 <i>C. jejuni</i>
Nosocomial diarrhoea (with chemotherapy)	2 (29%)	1 <i>C. coli</i> , 1 <i>S. enterica</i>
Nosocomial diarrhoea (without chemotherapy)	2 (29%)	1 <i>C. coli</i> , 1 <i>S. enterica</i>
Non-diarrheal manifestation of enteric infection	1 (14%)	1 <i>S. enterica</i>
Asymptomatic carrier	1 (14%)	1 <i>C. jejuni</i>
Total	7 (100%)	2 <i>C. jejuni</i> , 2 <i>C. coli</i> , 3 <i>S. enterica</i>
<b>Adults</b>		
Community acquired diarrhoea	8 (35%)	1 <i>C. jejuni</i> , 5 <i>C. coli</i> , 2 <i>S. enterica</i>
Nosocomial diarrhoea (with chemotherapy)	5 (22%)	2 <i>C. jejuni</i> , 1 <i>C. coli</i> , 2 <i>S. enterica</i>
Nosocomial diarrhoea (without chemotherapy)	4 (17%)	2 <i>C. jejuni</i> , 1 <i>S. enterica</i> , 1 <i>Y. enterocolitica</i>
Non-diarrheal manifestation of enteric infection	3 (13%)	3 <i>S. enterica</i>
Asymptomatic carrier	3 (13%)	1 <i>C. jejuni</i> , 1 <i>C. coli</i> , 1 <i>S. enterica</i>
Total	23 (100%)	6 <i>C. jejuni</i> , 7 <i>C. coli</i> , 9 <i>S. enterica</i> , 1 <i>Y. enterocolitica</i>

*C.*: *Campylobacter*, *S.*: *Salmonella*, *Y.*: *Yersinia*