

# Antibiotic associated diarrhea: incidence, risk factors and treatment

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## INTRODUCTION

Antibiotic-associated diarrhea (AAD) is a common adverse effect of antibiotic (AB) treatment. Symptoms range from mild and self-limiting to severe diarrhea, particularly in case of a *Clostridium difficile* infection. The overall incidence of AAD, including the mild to moderate diarrhea without clinical diagnostic evaluation, is not well established.

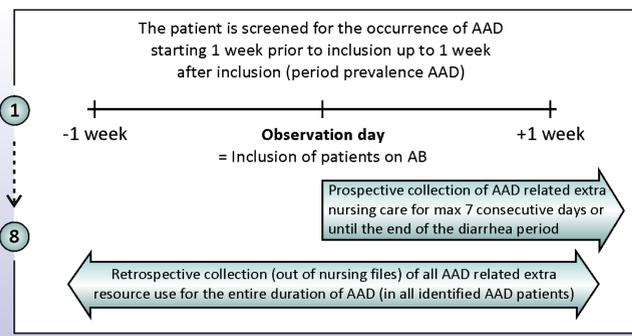
## AIMS

This study aimed to measure the occurrence of AAD in hospitalized patients in the northern part of Belgium, to investigate associated risk factors and to document AAD associated diagnostic investigations, contamination control and treatment.

## METHODS

### Selection of patients

- all adult patients hospitalized at an internal medicine ward of 4 Belgian participating hospitals were screened for AB use at the observation day
- 8 observation days with time delay of 10-14 days between each observation day
- patients receiving AB on the observation day were included in the study and screened for signs and symptoms of AAD using a period prevalence methodology.



### Data collection

- Clinical data were collected for all AB users
- In case of diarrhea, start and stop dates were noted together with associated diagnostic procedures (laboratory tests, endoscopy, etc.), contamination control and diarrhea treatment (IV hydration, medication).
- AAD related investigations and treatment were collected for the entire duration of AAD.
- Additionally, a checklist of extra nursing care for patients with diarrhea was completed by the treating nurses from the day of inclusion up to a maximum of seven consecutive days or until the end of the diarrhea period.

## RESULTS

In the 19 participating wards of internal medicine, a total of 2543 hospitalized patients were screened and in 743 patients AB use was registered at the observation days, revealing a **point prevalence of AB use of 29.2%**.

In 98 of the 743 included AB users, signs and symptoms of diarrhea were noted (13.2%). Diarrhea developed after the start of AB treatment in 71 of them, giving a **period prevalence of AAD of 9.6%**, including 4 with confirmed *Clostridium difficile* infection.

**Table 1: Description of the population.**

	Total sample of AB users n=743	Comparison between nonAAD and AAD patients		
		nonAAD n=672	AAD n=71	p value of difference
<b>Demographic characteristics</b>				
Age (yrs) mean (range)	67.7 (16-99)	67.3 (18.1)	71.9 (16.8)	0.040
Gender % male	51.5%			
<b>Clinical characteristics</b>				
Transfer from other ward	16.5%	16.4%	16.9%	0.917
ADL score (6-24) mean (SD)	12.3 (5.7)	12.0 (5.6)	14.2 (5.8)	0.002
Disorientation score (2-8) mean (SD)	2.9 (1.7)	2.9 (1.6)	3.5 (1.9)	0.001
<b>Risk factors for diarrhea</b>				
Inflammatory bowel disease	7.3%	7.4%	5.6%	0.577
Proton pump inhibitors	54.6%	53.1%	69.0%	0.011
Chemotherapy	6.2%	6.0%	8.5%	0.406
Radiotherapy	2.0%	1.8%	4.2%	0.165
Tube feeding	3.9%	3.6%	7.0%	0.151
Endoscopic procedures	15.9%	14.9%	25.4%	0.022
Abdominal surgery	3.1%	2.8%	5.6%	0.194
Diabetes	26.6%	25.7%	35.2%	0.086
COPD	25.4%	25.7%	22.5%	0.555
HIV	1.2%	1.2%	1.4%	0.873
Transplantation	3.0%	3.0%	2.8%	0.940
Decubitus	0.4%	0.1%	2.8%	0.001
Laxatives	15.8%	16.4%	10.9%	0.260
Risk score (sum of factors) mean (SD)	1.5 (1.1)	1.5 (1.1)	1.9 (1.1)	0.001
<b>Antibiotic use before diarrhea</b>				
More than one antibiotic prescribed	19.2%	18.0%	31.0%	0.008
<b>Type of antibiotics*</b>				
Penicillins	63.1%	62.9%	64.8%	0.760
Quinolones	22.2%	21.6%	28.2%	0.204
Cephalosporins	11.8%	12.1%	9.9%	0.586
Macrolides	8.1%	8.2%	7.0%	0.737
Aminoglycosides	3.4%	3.6%	1.4%	0.336
Sulfonamides	1.7%	1.8%	1.4%	0.818
Other ab	7.3%	7.0%	9.9%	0.376

\*Type of antibiotics > 100% due to double and triple use

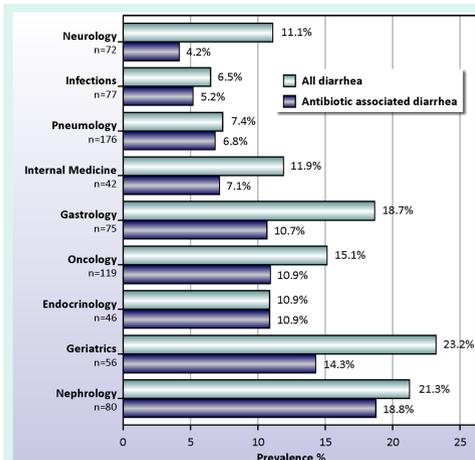


Figure 1: AAD according to the ward of admission

AAD started between 1 and 16 days after AB start (median 5) and had a duration of 2 to 41 days (median 4). AAD was significantly associated with higher age and the use of double AB and proton pump inhibitors. AAD patients had extra laboratory investigations (79%), received extra pharmacological treatment (42%) and 10 of them were isolated (14%). AAD related extra nursing time amounted to 51 minutes per day for the treatment of diarrhea.

**Table 2: Risk factors associated with the development of AAD.**

Associated factors	Univariate	Multivariate
	OR (95% CI)	OR (95% CI)*
Age > 70y	2.22 (1.30-3.77)	2.41 (1.39-4.18)
More than one AB	2.05 (1.19-3.51)	2.27 (1.30-3.98)
ADL score (6-24)	1.07 (1.02-1.11)	
Disorientation score (2-8)	1.23 (1.09-1.39)	
Risk score (sum of risk factors)	1.42 (1.14-1.75)	
Proton pump inhibitors	1.97 (1.16-3.32)	1.98 (1.15-3.43)
Endoscopic procedures	1.94 (1.09-3.45)	
Diabetes	1.57 (0.94-2.63)	
Decubitus	19.45 (1.74-217.24)	32.11 (2.82-366.13)
University Hospital	1.70 (1.03-2.80)	
Nephrology ward	2.50 (1.34-4.67)	2.34 (1.23-4.47)

\*Nagelkerke Rsquare= 0.103

**Table 3: AAD related outcome and actions.**

AAD related investigations n=71	
Standard bacteriological investigations (n)	27
Specific for clostridium (n)	66
Other bacteriological investigations (n)	6
Additional investigations (endoscopy)	1
AAD related treatment n=71	
Patient isolation in single room (n)	10
Pharmacological treatment (n)	
- Probiotics (enterol)	9
- Anti-diarrheal (loperamide)	9
- Antibiotics	1
- Antiparasitics (flagyl)	3
IV hydration (n)	12
AAD related nursing care	
Extra daily nursing care time median (range)	51.3 (5-154)

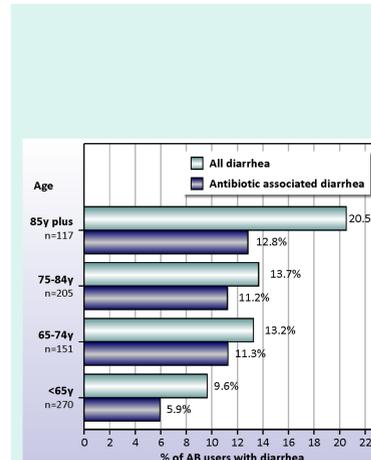


Figure 2: AAD according to age categories

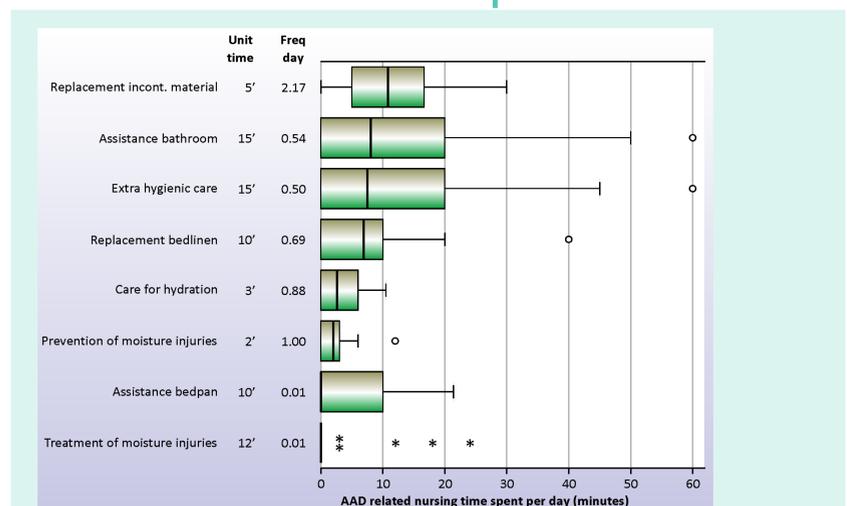


Figure 3: Extra nursing care related to the treatment of patients with antibiotic-associated diarrhea (AAD) expressed as total time spent per action per day. Frequency and estimation of nursing time spent to each action was based on observations in 26 AAD positive patients spread over 94 AAD days. Unit time=estimated time (in minutes) needed to perform this action. Freq day=median frequency of the action performed per patient and per day

## DISCUSSION

### Strengths and Limitations

- One of the first studies that focused on the overall prevalence of AAD (including uncomplicated cases)
- Slight underestimation of the real prevalence of AAD due to several reasons
- Extra nursing care only measured in patients with clear diarrhea

### Prevalence of AB use and AAD

- Point prevalence of AB use of 29,2% in internal medicine wards previously also found in the ESAC study (29,8%)
- Period prevalence of AAD comparable with calculated prevalence from controls of review of 14 RCTs (14,6% - Hempel et al, 2012)

### Prevention of AAD

- Meta-analyses on the prevention of AAD revealed that preventive treatments such as probiotics and especially *Saccharomyces boulardii* halved the risk of AAD development. A cost-effectiveness analysis is highly recommended.

## AKNOWLEDGEMENTS

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## CONCLUSION

**In this observational study, with one third of hospitalized patients receiving AB, an AAD period prevalence of 9.6% in AB users was found. AAD caused extra investigations and treatment and an estimated extra nursing care of almost one hour per day. Preventive action, including the reconsideration of a more generalized use of probiotics, is highly recommended to reduce the prevalence of AAD and associated health care costs**