ORIGINAL CONTRIBUTION

Postoperative Outcomes of Patients With Nonperforated Gangrenous Appendicitis: A National Multicenter Prospective Cohort Analysis

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BACKGROUND: Controversy exists regarding the use of postoperative antibiotics for nonperforated gangrenous appendicitis.

OBJECTIVE: The aim of this study was to evaluate the rate of postoperative infectious complications and the effect of postoperative antibiotic use among patients with nonperforated gangrenous appendicitis.

DESIGN: This was a prospective cohort study conducted during 2 months.

SETTINGS: A national multicenter observational study was conducted in 62 Dutch hospitals.

PATIENTS: All of the consecutive patients who had surgery for suspected acute appendicitis were included. Patients were excluded if no appendectomy was performed or appendectomy was performed for pathology other than acute appendicitis.

MAIN OUTCOMES MEASURES: Type of appendicitis was categorized as phlegmonous, gangrenous, or perforated. The primary end point was the rate of infectious complications (intra-abdominal abscess and surgical site infection) within 30 days after appendectomy. Univariable and multivariable logistic regression analyses were performed to identify predictors of infectious complications.

RESULTS: A total of 1863 patients were included: 1321 (70.9%) with phlegmonous appendicitis, 181 (9.7%) with gangrenous appendicitis, and 361 (19.4%) with perforated appendicitis. Infectious complications were more frequent in patients with gangrenous versus phlegmonous appendicitis (7.2% vs 3.8%; $p = 0.03$). This association was no longer statistically significant in multivariable analysis (OR = 1.09 (95% CI, 0.49–2.44)). There was no significant difference in infectious complications between ≤24 hours (n = 57) of postoperative antibiotics compared with >24 hours (n = 124; 3.6% vs 8.9%; $p = 0.35$) in patients with gangrenous appendicitis.

LIMITATIONS: Possible interobserver variability in the intraoperative classification of appendicitis was a study limitation.

CONCLUSIONS: Patients with nonperforated gangrenous appendicitis are at higher risk of infectious complications than patients with phlegmonous appendicitis, yet gangrenous disease is not an independent risk factor. Postoperative antibiotic use over 24 hours was not associated with decreased infectious complications. See **Video Abstract** at http://links.lww.com/DCR/A1000.

Funding/Support: None reported.

Financial Disclosure: Drs de Wijkerslooth and van den Boom were supported by a grant from ZonMW (The Netherlands Organization for Health Research and Development; project No. 848015008).

Drs de Wijkerslooth and de Jonge shared first authorship for this article.

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Dis Colon Rectum 2019; 62: 1363–1370
DOI: 10.1097/DCR.0000000000001466

RESULTADOS POSTOPERATORIOS DE PACIENTES CON APENDICITIS GANGRENOSA NO PERFORADA: UN ANÁLISIS DE COHORTE PROSPECTIVO MULTICÉNTRICO NACIONAL

ANTECEDENTES: Existe controversia sobre el uso de antibióticos postoperatorios para la apendicitis gangrenosa no perforada.

OBJETIVO: El objetivo de este estudio fue evaluar la tasa de complicaciones infecciosas postoperatorias y el efecto del uso de antibióticos postoperatorios en pacientes con apendicitis gangrenosa no perforada.

DISEÑO: Estudio de cohorte prospectivo realizado durante dos meses.

LUGAR: Estudio observacional multicéntrico nacional en 62 hospitales holandeses.

PACIENTES: Todos los pacientes consecutivos sometidos a cirugía por sospecha de apendicitis aguda. Los pacientes fueron excluidos si no se realizó una apendicectomía o si se realizó una apendicectomía para otra patología que no fuera la apendicitis aguda.

PRINCIPALES MEDIDAS DE RESULTADOS: El tipo de apendicitis se clasificó como flegmonosa, gangrenosa o perforada. El criterio de valoración primario fue la tasa de complicaciones infecciosas (absceso intraabdominal e infección en el sitio quirúrgico) dentro de los 30 días posteriores a la apendicectomía. Se realizaron análisis de regresión logística univariables y multivariables para identificar predictores de complicaciones infecciosas.

RESULTADOS: Se incluyeron un total de 1863 pacientes: 1321 (70,9%) con apendicitis flegmonosa, 181 (9,7%) con apendicitis gangrenosa y 361 (19,4%) con apendicitis perforada. Las complicaciones infecciosas fueron más frecuentes en pacientes con apendicitis gangrenosa frente a flegmonosa (7,2% frente a 3,8%, p = 0,03). Esta asociación ya no fue estadísticamente significativa en el análisis multivariable (OR 1,09; IC del 95%: 0,49 a 2,44). No hubo diferencias significativas en las complicaciones infecciosas entre ≤ 24 h ($n = 57$) de los antibióticos postoperatorios en comparación con> 24 h ($n = 124$) (3,6% vs. 8,9%, p = 0,35) en pacientes con apendicitis gangrenosa.

LIMITACIONES: Posible variabilidad interobservador en la clasificación intraoperatoria de la apendicitis.

CONCLUSIÓN: Los pacientes con apendicitis gangrenosa no perforada tienen un mayor riesgo de complicaciones infecciosas que los pacientes con apendicitis flegmonosa, aunque la enfermedad gangrenosa no es un factor de riesgo independiente. El uso de antibióticos postoperatorios durante 24 horas no se asoció con una disminución de las complicaciones infecciosas. Vea el Resumen del Video en http://links.lww.com/DCR/A1000.

KEY WORDS: Appendectomy; Appendicitis; Classification; Postoperative complications.

The treatment of gangrenous nonperforated appendicitis is controversial.[1,2] Routine administration of postoperative antibiotics to reduce the rate of infectious complications remains a topic of debate. Most guidelines lack clear recommendations on gangrenous appendicitis (GA; *gangrenous* implies *nonperforated gangrenous* unless specified otherwise).[3–7] The guideline by the Surgical Infection Society, however, recommends to limit the postoperative use of antibiotics to 24 hours.[8] Although the authors state that this is based on level 1A evidence,[8] adherence to the guideline is poor. Many surgeons consider GA as a complex appendicitis similar to a perforated appendicitis or appendicitis with abscess and/or purulent peritonitis. For these patients, antibiotic prophylaxis is usually given for 3 to 5 postoperative days.[7,9,10] On the contrary, others do not prescribe any postoperative antibiotic treatment or just a short course (24 or 48 h).[9,10] It has been reported in the literature that standardization of practice leads to improved surgical outcomes for appendicitis and several other indications.[11–16] Therefore, it is key to address this variation in medical care and to develop a standardized strategy for this type of appendicitis. To our knowledge, previous literature focused on a population of both phlegmonous appendicitis (PA) and GA,[17,18] and little is known with respect to merely the latter. Therefore, we aimed to evaluate postoperative outcomes for gangrenous appendicitis exclusively. The primary aim of this study was to compare the rate of postoperative infectious complications between patients with GA and PA. Secondly, the effect of postoperative antibiotic use on the rate of infectious complications was studied.

PATIENTS AND METHODS

Study Design, Setting, and Participants

In 2014, data from all of the consecutive patients who had surgery for suspected acute appendicitis (AA) in 62 Dutch hospitals were prospectively collected during a predefined 2-month study period (June and July). The study protocol was reviewed and approved by the medical ethics committee in the Academic Medical Center in Amsterdam. Owing to the observational, noninterventional study design, the informed consent requirement was waived. One or 2 surgical residents per participating hospital were responsible for the data registration. Additional details on the study design can be found in previous publications from this cohort.[19,20] For this analysis, patients who had an appendectomy (open or laparoscopic) for AA were selected from the database. Both adult and pediatric patients were included.

Collected Data

Baseline patient characteristics (ie, sex, age, and ASA classification) were registered, as well as several preoperative, intra-

operative, and postoperative variables, including temperature, white blood cell (WBC) count, and C-reactive protein (CRP) at presentation; time between onset and operation (hours); preoperative antibiotic prophylaxis (yes or no); type of appendicitis; extent of peritonitis (none, local, or diffuse); type (laparoscopic or open) and duration of surgery (in minutes); duration of postoperative antibiotic treatment (intravenous and oral); overall 30-day postoperative complications; intra-abdominal abscess (IAA); surgical site infection (SSI); length of hospitalization (days from operation); readmission; percutaneous drainage; reoperation; and 30-day mortality.

Outcome Measures

The main outcomes in this study were type of appendicitis, duration of postoperative antibiotic use, and rate of infectious complications (including IAA and SSI) within 30 days after appendectomy. The type of appendicitis was classified as phlegmonous, gangrenous, or perforated based on the operative report. *Gangrenous appendicitis* was defined as appendicitis with signs of necrosis or gangrene without mention of macroscopic perforation. *Duration of postoperative antibiotic* use was recorded as the total duration of intravenous and oral antibiotics together, in postoperative days. IAA was defined as a fluid collection in the abdomen, diagnosed postoperatively by cross-sectional imaging and necessitating treatment (antibiotics treatment or (radiological or surgical) drainage). SSI was recorded only if this resulted in restart or prolongation of antibiotic treatment or surgical drainage of the wound (under local or generalized anesthesia). Secondary outcomes were length of hospital stay (LOS) and the rate of overall complications, readmission, percutaneous drainage, and/or reoperation (all within 30 d after appendectomy).

Statistical Analysis

In univariable analysis, outcomes were compared between gangrenous and other types of appendicitis. The independent samples Student *t* test and Mann–Whitney test were used in case of continuous variables, and the χ^2 and Fisher exact test were used in case of categorical variables, as appropriate. To evaluate the effect of duration of postoperative antibiotic treatment on the infectious complication rate, groups of different duration were compared with the same statistical tests as described for the primary end point. Furthermore, logistic regression analysis was performed to compare outcomes in multivariable analysis. A 2-sided $p < 0.05$ was considered significant. All of the data analysis was performed in SPSS version 21 (IBM Corp, Armonk, NY). This article was written using the Strengthening the Reporting of Observational Studies in Epidemiology statement checklist.[21]

RESULTS

In June and July 2014, 1975 patients had surgery for suspected AA. The details of these patients have been described in previous reports.[19,20] After exclusion of 112 patients (Fig. 1), 1863 remained eligible for analysis. The median age was 29 years (interquartile range (IQR), 16–47), and 514 (27.6%) were under the age of 18 years. Fifty-three percent (980/1863) were male. Type of appendicitis was scored as phlegmonous in 1321 (70.9%), gangrenous in 181 (9.7%), and perforated in 361 patients (19.4%). In total, there were 237 postoperative complications (12.7%), and 137 (7.4%) were infectious complications. The rate of infectious complications was 20.5% in patients with perforated appendicitis versus 7.2% in patients with GA and 3.8% in patients with PA ($p < 0.001$). Patients with perforated disease were excluded from additional analyses.

PA Versus GA

Significant differences in baseline and perioperative characteristics were observed between patients with GA and PA. Patients with GA had a higher median (IQR) age (40 (19–56) vs 27 y (16–42); $p < 0.001$) and had higher WBC count and CRP levels at presentation (Table 1). Postoperative antibiotics were administered significantly more often to patients

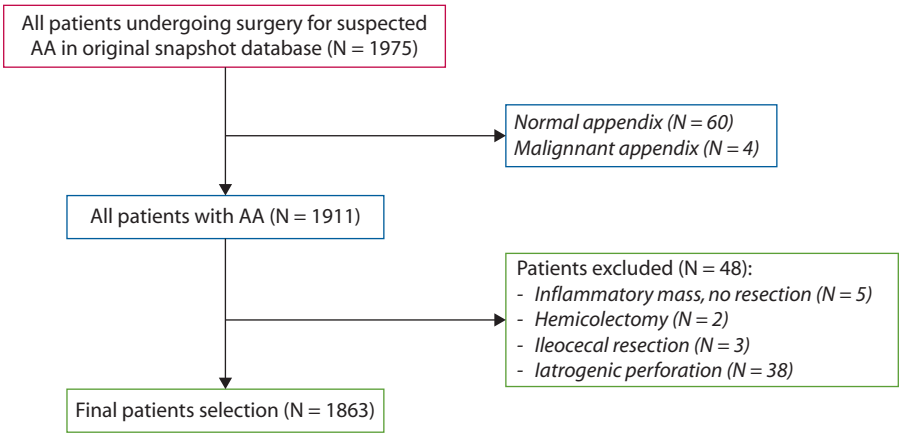

FIGURE 1. Patients included in present analysis. AA = acute appendicitis.

TABLE 1. Baseline and perioperative characteristics of the study population (N = 1502)

Variable	*GA (n = 181)*	*PA (n = 1321)*	*p*
Age, median (IQR), y	40 (19–56)	27 (16–42)	<0.001
Sex, male, n (%)	103 (56.9)	687 (52)	0.216
ASA, n (%)			0.076 (f)
I–II	173 (95.6)	1292 (97.8)	
III–IV	8 (4.4)	29 (2.2)	
Temperature, mean (SD), °C	37.6 (0.8)	37.3 (0.7)	<0.001
WBC, mean (SD), 10^9/L	15 (4.7)	13.7 (4.6)	<0.001
CRP, median (IQR), mg/L	64 (26–124)	24 (9–54)	<0.001
Time to surgery, median (IQR), h	6.5 (4–14)	6.5 (4–13)	0.331
Preoperative AB prophylaxis, n (%)	175 (96.7)	1260 (95.4)	0.426
Type of surgery, n (%)			0.954
Laparoscopic	133 (73.5)	968 (73.3)	
Open	48 (26.5)[a]	353 (26.7)[b]	
Degree of peritonitis, n (%)			<0.001
None	102 (56.4)	1216 (92.1)	
Localized	67 (37)	91 (6.9)	
Diffuse	12 (6.6)	14 (1.1)	
Duration of surgery, median (IQR), min	44 (32–56)	38 (30–50)	<0.001
Postoperative AB use, n (%)	135 (74.6)	128 (9.7)	<0.001
Duration postoperative AB use, n (%)			<0.001
None	46 (25.4)	1192 (90.2)	
24 h	11 (6.1)	33 (2.5))	
2–3 d	37 (20.4)	28 (2.1)	
4–5 d	64 (35.4)	48 (3.7)	
>5 d	23 (12.7)	19 (1.4)	

PA = phlegmonous appendicitis; GA = gangrenous appendicitis; IQR = interquartile range; f = Fisher exact test; WBC = white blood cell count; CRP = C-reactive protein; AB, antibiotics.
[a]A total of 7 gangrenous appendicitis patients (3.8%) had laparoscopy converted to open surgery.
[b]A total of 15 phlegmonous appendicitis patients (1.1%) had laparoscopy converted to open surgery.

with GA versus those with PA (74.6% vs 9.7%; $p < 0.001$). The rate of infectious complications was significantly higher among patients with GA compared with PA (7.2% vs 3.8%; $p = 0.033$), as were the rates of IAA and complications overall (Table 2). In addition, median (IQR) LOS was 3 days (2–5 d) for GA compared with 2 days (1–2 d) for PA ($p < 0.001$).

Risk Factors for Infectious Complications

In univariable analysis, risk factors for the development of an infectious complication in patients with GA and PA included increasing age, elevated temperature at presentation, higher level of WBCs at presentation, presence of localized or diffuse peritonitis (versus none), and gangrenous disease (versus phlegmonous). In multivariable logistic regression analysis, only age, WBC count, and duration of surgery showed a statistically significant association with infectious complications (Table 3).

TABLE 2. Univariable outcome analysis (N = 1502)

Variable	*GA (n = 181)*	*PA (n = 1321)*	*p*
LOS, median (IQR), d	3 (2–5)	2 (1–2)	<0.001
Any complication, n (%)	31 (17.1)	101 (7.6)	<0.001
Infectious complication, n (%)	13 (7.2)	50 (3.8)[a]	0.033
IAA	11 (6.1)	23 (1.7)	0.001
SSI	2 (1.1)	32 (2.4)	0.421 (f)
Readmission, n (%)	11 (6.1)	56 (4.2)	0.261
Reintervention, n (%)	6 (3.3)[b]	20 (1.5)[c]	0.117 (f)
Percutaneous drainage	4 (2.2)	15 (1.1)	0.273 (f)
Reoperation	4 (2.2)	14 (1.1)	0.260
Mortality, n (%)	1 (0.6)	1 (0.08)	0.227

LOS = length of stay; PA = phlegmonous appendicitis; GA = gangrenous appendicitis; IAA = intra-abdominal abscess; SSI = surgical site infection; f = Fisher exact test.
[a]Five patients experienced IAA and SSI.
[b]Two patients underwent drainage and reoperation.
[c]Nine patients underwent drainage and reoperation.

Postoperative Antibiotics for GA

Among 181 patients with GA, postoperative antibiotic use was limited to ≤24 hours in 57 patients (31.5%) and given >24 hours in 124 patients (68.5%). Patients with extended antibiotic use were older (median age = 44 (IQR, 24–59 y) vs 31 y (IQR, 13–59 y); $p = 0.006$), had higher median CRP levels at presentation (78 (IQR, 29–144 mg/L) vs 46 mg/L (IQR, 17–86 mg/L); $p = 0.003$), and more frequently showed local or diffuse peritonitis during surgery (14% vs 57.3%; $p < 0.001$). Infectious complications occurred more often among patients with extended antibiotic use, but the difference was not statistically significant (3.5% vs 8.9%; $p = 0.233$; Table 4). The median LOS was prolonged by the extended antibiotic use (4 (IQR, 3–6) vs 2 d (IQR, 1–2); $p < 0.001$).

DISCUSSION

This prospective cohort study demonstrated that patients with nonperforated GA are at higher risk of postoperative

TABLE 3. Multivariable outcome analysis, n=1502

	Univariable analysis			*Multivariable analysis*		
Variable	*OR*	*95% CI*	*p*	*OR*	*95% CI*	*p*
Age, y	1.01	1.00–1.03	0.04	1.02	1.00–1.03	0.046
Temperature, ˚C	1.51	1.08–2.10	0.015	1.32	0.91–1.91	0.146
WBC, 10^9/L	1.06	1.01–1.12	0.016	1.07	1.00–1.13	0.038
CRP, mg/L	1.00	0.99–1.01	0.100	1.00	0.99–1.00	0.470
Peritonitis (vs none)	1.93	1.03–3.62	0.042	1.28	0.55–2.94	0.567
GA (vs PA)	1.97	1.05–3.69	0.036	0.88	0.37–2.10	0.768
Open procedure (vs laparoscopic)	1.50	0.88–2.55	0.135	1.68	0.89–3.14	0.107
Duration of surgery, min	1.02	1.01–1.03	0.006	1.02	1.01–1.04	0.004
Postoperative AB use (vs none)	2.29	1.32–3.95	0.003	1.55	0.65–3.69	0.318

WBC = white blood cell count; CRP = C-reactive protein; GA = gangrenous appendicitis; PA = phlegmonous appendicitis; AB, antibiotic.

infectious complications than patients with PA. However, having GA (versus PA) was not identified as an independent risk factor for developing infectious complications. Postoperative antibiotic use longer than 24 hours after appendectomy was not associated with a decreased rate of infectious complications but did correlate with a longer length of stay.

Patients with GA were shown to differ from patients with PA on various levels. They are older, they have higher CRP and WBC levels at arrival to the hospital, and they present with localized or diffuse peritonitis in the abdomen more often than patients with PA. The rate of intra-abdominal abscess was >3 times as high in patients with GA compared with patients with PA. This confirms in a multicenter prospective setting what was previously reported by Romano et al[22] in their retrospective single-center study including 372 patients. In this study, age, WBC count, and duration of surgery were identified as independent risk factors for infectious complications, whereas a gangrenous type of appendicitis was not. A previous study on nonperforated appendicitis (n = 728) by Coakley et al[17] identified open surgery and GA (both the surgical and histopathologic assessments) as risk factors. Only patients with a histopathologic confirmation of nonperforated appendicitis were included in their study, and the rate of infectious complications observed was 8.4% (61/728). In contrast, the rate in this study was 4.2%, 63 infectious complications among 1502 patients, whereas inclusion was solely based on the intraoperative classification appendicitis. Open surgery showed a slight trend toward significance, which might reflect a type II error here. Had the study population or the infectious complication rate been larger, a significant association with infectious complications might have arisen.

TABLE 4. Postoperative antibiotics for gangrenous appendicitis (N = 181)

Variable	*≤24 h (n = 57)*	*> 24 h (n = 124)*	*p*
LOS, median (IQR), d	2 (1–2)	4 (3–6)	<0.001
Any complication, n (%)	4 (7.0)	27 (21.8)	0.014
Infectious complication, n (%)	2 (3.5)	11 (8.9)	0.233
IAA, n (%)	2 (3.5)	9 (7.3)	0.506 (f)
SSI, n (%)	–	2 (1.6)	1.0 (f)
Readmission, n (%)	4 (7.0)	7 (5.6)	0.743 (f)
Reintervention, n (%)	1 (1.8)	5 (4)	0.667 (f)
Percutaneous drainage, n (%)	1 (1.8)	3 (2.4)	1.0 (f)
Reoperation, n (%)	1 (1.8)	3 (2.4)	1.0 (f)
Mortality, n (%)	–	1 (0.8)	1.0 (f)

LOS = length of stay; IQR = interquartile range; IAA = intra-abdominal abscess; SSI = surgical site infection.

As expected, the majority of patients with GA received antibiotics postoperatively, whereas 25% were not given any antibiotics after appendectomy. If the surgeon chose to prescribe postoperative antibiotic treatment, this lasted >24 hours in 92% of the patients. This did not decrease the infectious complications rate when comparing patients with 24 hours of postoperative antibiotics versus none. However, LOS was longer in patients with extended antibiotic use: the median LOS was doubled compared with patients who received a maximum of 24 hours of treatment. This finding is consistent with the results from a small cohort study (n = 58) by Emil et al.[1] They reported an almost 50% reduction in LOS without an increase in complications for patients with GA given 2 postoperative doses of antibiotics instead of the conventional longer treatment duration based on clinical criteria.[1] This further supports the recommended duration of 24 hours of postoperative antibiotics in the Surgical Infection Society/Infectious Diseases Society of America guideline, currently based on only 1 study on nonperforated appendicitis by Mui et al.[18] In this randomized controlled trial, prolonged antibiotic use was associated with an increase of complications related to antibiotic treatment without a reduction of infectious complications. This is in line with a recent single-center (n = 1007) study by Nordin et al[23] as well. The authors reported outcomes before and after a protocol change toward classifying GA as simple appendicitis and omitting postoperative antibiotics.[23] A significant decrease in hospitalization and antibiotic use was observed for patients with gangrenous disease (n = 69), without an increase in complications.

In clinical practice and research, PA is usually classified as simple appendicitis, whereas GA and perforated appendicitis are most often categorized together as complex appendicitis. This study emphasizes that these 3 types of appendicitis have different risks of infectious complications: 3.8%, 7.2%, and 20.5%. This implies that GA should perhaps be considered a separate entity, instead of being categorized together with either PA or perforated appendicitis. GA was more often accompanied by localized or diffuse pus than PA (37% vs 7%). Although the degree of peritonitis was not proven to be an independent risk factor for infectious complications in the present analysis, it is likely that this does play a role to some extent. Previous studies have reported a correlation between peritonitis and postoperative complications.[24,25] Therefore, apart from the aspect of the appendix, the degree of peritonitis should perhaps also be part of the classification system.[26] Surgeons are already familiar with using this in their decision regarding whether to prescribe postoperative antibiotics.[9,10] The optimum classification of appendicitis that correlates well with clinical outcomes has yet to be developed.[27,28] This may help the standardization of practice in the future.

Strengths and Limitations

The strengths of the present study are the prospective nature, national study participation, and the large number of patients included. Nonetheless, some important limitations need to be mentioned. First of all, patient inclusion in this study was based on the intraoperative classification of appendicitis by surgeons. This surgical classification is known to be more predictive of postoperative outcomes than the histopathologic classification,[29] but it is also associated with interobserver variability, and its reliability may therefore be questioned.[10,30] This concerns the distinction between perforated and nonperforated appendicitis, as well as assessment of gangrenous discoloration. Moreover, (assessment of) the extent of necrosis may vary: an appendix could show phlegmonous inflammation for the greater part with necrosis at the tip. This may be differently classified and treated depending on the surgeon operating, which may in turn have influenced results. Second, concerning the analysis of postoperative antibiotic use, one may argue that some bias may be present, because patients at higher risk of complications may have been prescribed more antibiotics than the more fit patients.

Despite its limitations, this study shows that patients with nonperforated GA differ from patients with PA in baseline characteristics and risk of postoperative infectious complications. Nonperforated GA should be considered its own distinctive entity, separate from phlegmonous (simple) and perforated (complex) appendicitis. Future research should focus on a universal and reliable classification system for appendicitis and a standardization of postoperative antimicrobial policy.

ACKNOWLEDGMENTS

The Snapshot Appendicitis Collaborative Study Group members, who provided study patients and collected data, included G.J.D. van Acker, M.D., Ph.D. (Medical Center Haaglanden, Den Haag), B. Akkermans, M.D. (Bronovo Hospital, Den Haag), G.J.M. Akkersdijk, M.D., Ph.D. (Spaarne Hospital, Hoofddorp), G.D. Algie, M.D. (M.C. Groep Zuiderzee, Lelystad), J.H. Allema, M.D., Ph.D. (Haga-Juliana Children's Hospital, Den Haag), C.S. Andeweg, M.D., Ph.D. (St. Jansdal Hospital, Harderwijk), N. Appeldorn (Ropcke-Zweers Hospital, Hardenberg), J.G. van Baal, M.D., Ph.D. (Ziekenhuisgroep Twente, Almelo), C.M. den Bakker, M.D. (Kennemer Gasthuis, Haarlem), S.A.L. Bartels, M.D., Ph.D. (Albert Schweitzer Hospital, Dordrecht), C. van den Berg, M.D. (Diaconessenhuis, Leiden), B. Boekestijn (Groene Hart Hospital, Gouda), F.C. den Boer, M.D., Ph.D. (Zaans Medical Center, Zaandam), D. Boerma, M.D., Ph.D. (St. Antonius Hospital, Nieuwegein), A.L. van den Boom, M.D. (Reinier de Graaf Groep, Delft), M.C. Boute, M.D. (Westfriesgasthuis, Hoorn), S.A.W. Bouwense, M.D. (Canisius-Wilhelmina Hospital, Nijmegen), J. Bransen, M.D. (Catharina Hospital, Eindhoven), F.A. van Brussel, M.D. (Spaarne Hospital, Hoofddorp), O.R.C. Busch, M.D., Ph.D. (Academic Medical Center, Amsterdam), S.M.M. de Castro, M.D., Ph.D. (Sint Lucas Andreas Hospital, Amsterdam), H.A. Cense, M.D., Ph.D. (Rode Kruis Hospital, Beverwijk), C. Croese, M.D. (Medical Center Haaglanden, Den Haag), T. van Dalen, M.D., Ph.D. (Diakonessenhuis, Utrecht), I. Dawson, M.D., Ph.D. (IJsselland Hospital, Capelle aan Den IJssel), E. van Dessel, M.D. (ZorgSaam Zeeuws-Vlaanderen, Terneuzen), R. Dettmers, M.D. (Rijnland Hospital, Leiderdorp), N. Dhar, M.D. (BovenIJ Hospital, Amsterdam), F.Y.M. Dohmen (St Jans Gasthuis, Weert), K.W. van Dongen, M.D., Ph.D. (Diaconessenhuis, Leiden), P. van Duijvendijk, M.D., Ph.D. (Gelre Hospital, Apeldoorn), R.R. Dulfer, M.D. (Sint Franciscus Gasthuis, Rotterdam), B.J. Dwars, M.D., Ph.D. (Slotervaart Hospital, Amsterdam), J.P. Eerenberg, M.D., Ph.D. (Tergooi Hospital, Hilversum), M. van der Elst, M.D., Ph.D. (Reinier de Graaf Groep, Delft), E.D. van den Ende, M.D., Ph.D. (Ropcke-Zweers Hospital, Hardenberg), L.M.M. Fassaert, M.D. (Orbis Medical Center, Sittard), J.T. Fikkers, M.D. (Haga Hospital, Den Haag), J.W. Foppen (St Jansdal Hospital, Harderwijk), E. J.B. Furnee, M.D., Ph.D. (Diakonessenhuis, Utrecht), F.P. Garssen, M.D. (Amstelland Hospital, Amstelveen), M.F. Gerhards, M.D., Ph.D. (Onze Lieve Vrouwe Gasthuis, Amsterdam), H. van Goor, M.D., Ph.D. (Radboud University Medical Center, Nijmegen), R.R. Gorter, M.D. (Emma Children's Hospital–Academic Medical Center/Free University Medical Center, Amsterdam and Rode Kruis Hospital, Beverwijk), J.S. de Graaf, M.D., Ph.D. (Medical Center Leeuwarden, Leeuwarden), L.J. Graat, M.D. (Elisabeth-TweeSteden Hospital, Tilburg), J. Groote, M.D. (Wilhelmina Hospital, Assen), A.C. van der Ham, M.D., Ph.D. (Sint Franciscus Gasthuis, Rotterdam), J.F. Hamming, M.D., Ph.D. (Leids University Med-

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