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Non-operative treatment of acute appendicitis in children: clinical efficacy of amoxicillin-clavulanic acid in a retrospective single-centre study

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ABSTRACT

Background The success rate of non-operative treatment (NOT) of acute uncomplicated appendicitis (AUA) in children varies from 65% to 95%. There are no recommendations on the appropriate antibiotic therapy.

Objective To determine the clinical efficacy of amoxicillin-clavulanic acid for NOT of AUA in children.

Methods Design: Cross-sectional study in a single medical centre. Settings: Emergency department and Paediatric Visceral Surgery department of the Children Hospital in Toulouse, France. Patients: Patients 5–15 years old who were diagnosed with appendicitis, (1) With abdominal pain and a first episode of acute appendicitis, (2) With no radiological or ultrasound evidence of appendicolith, appendiceal perforation, pelvic abscess nor peritonitis, and (3) With non-septic general aspect, were included. Interventions: NOT consisted of hospital admission. The antibiotic treatment was a combination of amoxicillin and clavulanic acid (80 mg/kg/day of amoxicillin): intravenous regimen during 48 hours followed by oral route during 7 days. Main outcome measure: Success rate of amoxicillin-clavulanic acid NOT in children with AUA at 2 years.

Results The initial success rate of amoxicillin-clavulanic acid NOT in children with AUA was 100% (104/104 patients). The success rate at 2 years was 85.6% (89/104) at discharge. None of the 15 patients who underwent surgery after recurrence of appendicitis presented with peritonitis, appendiceal perforation nor pelvic abscess.

Conclusion Narrowed antibiotic therapy with amoxicillin and clavulanic acid seems to be an alternative to surgery in children with AUA. It is necessary to wait for the results of ongoing studies to confirm these results.

INTRODUCTION

Acute appendicitis in children and adults is generally treated surgically. In cases of acute uncomplicated appendicitis (AUA), surgery is subject to perioperative complications in 5%–15% of cases, with severe complications in 1%–7% of patients.^{1–5} After retrieval of the anatomopathological results from the removed appendix, the mean rate of so-called ‘negative’ appendectomy, that is, removal of healthy appendices, is 1%–40%.^{6–10} These

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ The success rate of this non-operative treatment (NOT) for acute uncomplicated appendicitis (AUA) in children varies from 65% to 95%.
- ⇒ There are no recommendations on the appropriate antibiotic therapy and the modalities of use.

WHAT THIS STUDY ADDS

- ⇒ The initial success rate of amoxicillin-clavulanic acid NOT for AUA in children was 100% (104/104 patients).
- ⇒ The success rate at 2 years was 85.6% (89/104) at discharge.
- ⇒ None of the 15 patients who underwent surgery after recurrence of appendicitis presented with peritonitis, appendiceal perforation nor pelvic abscess.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ NOT with a narrowed antibiotic therapy using amoxicillin-clavulanic acid appears to be an effective alternative to surgical intervention for AUA in children regarding local bacteriological epidemiology

observations have led surgeons to rethink their approach. Historically, medical treatment was first attempted when surgery proved impossible—in pregnant women, soldiers or submariners.¹¹ Since these patients reacted favourably to antibiotic treatment, the idea of generalising this non-surgical approach started to be considered. The success rate of this non-operative treatment (NOT) for AUA in children varies from 65% to 95%.^{3 5 12–15} There are no recommendations on the appropriate antibiotic therapy and the modalities of use. A meta-analysis published in 2017 detailed the care provision in 10 studies and the various antibiotic therapies administered. All these centres prescribed broad-spectrum antibiotic treatments (piperacillin-tazobactam, cefmetazole, sulbactam-ornidazole, meropenem, ciprofloxacin-gentamicin-metronidazole,

flomoxef, cefoperazone). Only one centre used amoxicillin-clavulanic acid but associated with gentamicin for 48 hours minimum.^{3 5 13–24}

At the Children Hospital of Toulouse, the treatment protocol for AUA in children, implemented in 2014, advises antibiotic therapy by amoxicillin/clavulanic acid with 80 mg/kg/day of amoxicillin through the intravenous route for 48 hours, followed by oral amoxicillin/clavulanic acid with 80 mg/kg/day of amoxicillin for 7 days.²⁵ The choice of antibiotic is guided by the local bacterial epidemiology.²⁶ In case of allergy to penicillin, the treatment is cefuroxime+metronidazole (2 days intravenous then oral relay by the same molecules).

We hypothesised that the 2-year success rate of NOT with amoxicillin/clavulanic acid of AUA in children would be over 80%.

The aim of our study was to assess the success rate 2 years after NOT with amoxicillin/clavulanic acid in cases of AUA in children. Clinical data on children that failed NOT were compared with those that were successfully managed conservatively.

MATERIAL AND METHODS

We conducted a retrospective, single-centre study. Children aged 5–15 years hospitalised between 1 January 2018 and 31 December 2018 at the Children Hospital of Toulouse for AUA and treated with intravenous and then oral amoxicillin-acid clavulanic were included. Medical files were selected by cross-referencing the associated International Classification of Diseases, 10th Revision diagnostic codes (K35.3, K35.8, K38.1). Appendicitis was suspected when patients presented to the Emergency Room with a typical history of abdominal pain initially in the epigastric area and migrating to the right lower quadrant. On clinical suspicion of appendicitis, radiological evaluation using either abdominal ultrasonography (performed by a paediatric radiology specialist) or CT was performed. The radiographic diagnosis of uncomplicated appendicitis was pragmatic and based on the radiologist's global impression, as is done in routine practice. Subsequently, findings were recorded with standardised methods. Diagnosis of appendicitis was confirmed when a dilated appendix with a diameter greater than 6 mm with non-compressibility, localised free fluid, increased echogenicity of periappendiceal fat. Across all age groups, the optimal appendiceal diameter threshold is 7 mm for the diagnosis of paediatric appendicitis.²⁷ Inclusion criteria included all the following: (1) Imaging-confirmed uncomplicated appendicitis by ultrasound or CT: increase in the calibre of the appendix, measured at more than 6 mm in diameter with non-compressibility, localised free fluid, increased echogenicity of periappendiceal fat; (2) Age 5–15 years; (3) Non-septic clinical aspect (good general condition, normal haemodynamic status, normal diuresis); (4) Intravenous and oral antibiotic regimen by amoxicillin-clavulanic acid; (5) Parental good understanding of the monitoring instructions.

Exclusion criteria included any of the following: (1) Ultrasound or CT scan showing one or several stercoliths, an abscess, appendicular mass or generalised peritonitis; (2) Primary or secondary immune deficiency; (3) Parental refusal of research protocol; (4) Impossibility of home follow-up after discharge from hospital; (5) Allergy to penicillin. Those criteria were defined taking in consideration the known risk factors for recurrent or complicated appendicitis.^{11 28} Children under 5 years old tend to have less reliable signs and symptoms and present at later stages as evidenced by a higher frequency of perforation.²⁹

The surgeon decides for each patient the management strategy according to criteria before enrolment.

The data were collected from the patients' medical digitised or paper files. After anonymisation, the data were entered in an Excel sheet. Collected data were: patient characteristics (age, gender and body weight); initial clinical evaluation (body temperature, pulse rate, respiration rate, blood pressure, abdominal pain using the Visual Analogue Pain Scale and nausea or vomiting). The evolution of these data over the first 3 days of treatment was examined. Radiological data and data from the initial biological workup were collected (C reactive protein (CRP), leucocytes including polymorphonuclear neutrophils and platelets). Details of the initial antibiotic therapy and subsequent oral antibiotic medication (including medication type, dosage and duration), the follow-up ultrasound and CRP at the follow-up consultation were collected.

The initial success criteria for NOT is resolution of abdominal pain and hospital discharge without appendectomy. Criteria for discharge were no fever for 24 hours, tolerating a diet, ambulatory, non-opioid analgesic requirements.

Statistical analysis

The qualitative variables were expressed as frequencies and percentages. The quantitative variables, which were not normally distributed, were described using median, and IQR. For the comparison between the groups (success group and failure group), the tests were conducted with a significance threshold of $p < 0.05$. The percentages were tested with the χ^2 test or Fisher's test depending on the number of patients, and the medians with a Mann-Whitney test and by logistic regression. Multivariate analysis was performed using a logistic regression model. The analyses were conducted using SAS software, V.9.4 (SAS Institute).

Patient and public involvement

According to French law on ethics, patients were informed that their codified data would be used for the study and for publication. Their non-opposition to the use of the data and to publication was collected. Patients were not involved in the design this study. The results of the study will be disseminated to study participants by a letter addressed by post.

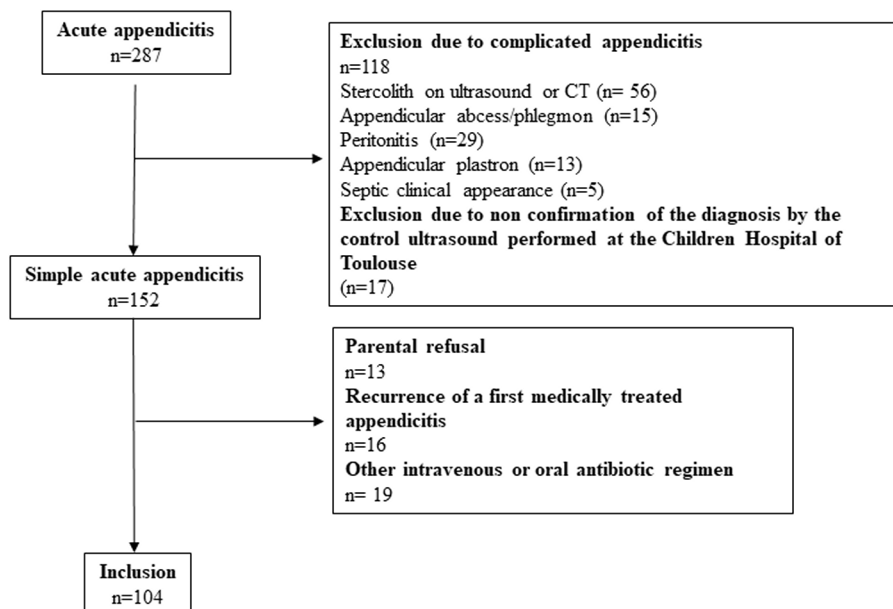


Figure 1 Study flow of non-operative management for paediatric uncomplicated appendicitis.

Ethics statement

According to French law on ethics, patients were informed that their codified data will be used for the study. According to the French ethic and regulatory law (public health code) retrospective studies based on the exploitation of usual care data should not be submitted to an ethics committee but they have to be declared or covered by reference methodology of the French National Commission for Informatics and Liberties (CNIL).

Collection and computer processing of personal and medical data were implemented to analyse the results of the research. Toulouse University Hospital signed a commitment of compliance to the reference methodology MR-004 of the French CNIL. After evaluation and validation by the data protection officer and according to the General Data Protection Regulation (Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016), this study completed all the criteria, was registered in the register of data study of the Toulouse University Hospital (RnIPH number 2021–67) and was covered by MR-004 (CNIL number: 2206 723 v 0).

RESULTS

From 1 January 2018 to 31 December 2018, 287 children aged 5–15 years were hospitalised at the Children Hospital of Toulouse for acute appendicitis. A total of 104 patients were included (figure 1).

The study population comprised 104 patients (62% boys). The median age was 10 years (IQR: 8–11). The median for symptoms evolution was 1 day (IQR: 1–2). Fever was present initially in 30% of cases (n=31/104). Abdominal pain was present in 99% of cases (n=103/104). The median score of the pain assessment scale on arrival was 4 (IQR: 0–5). Nausea or vomiting were reported

in 38% of cases (n=40/104). On day 2 after admission, 4.8% of the patients were feverish (n=5/103) and on day 3 after admission, 1.9% of the patients were feverish (n=2/103). The maximum temperature ranged from 37°C to 39.6°C with a median of 37.5°C. On the second day of hospitalisation, 39% of patients reported abdominal pain (n=40/103) and 9.7% still reported abdominal pain on the third day (N=10/103). On the third day, 8% of patients reported abdominal pain (n=8/103). Of the patients, 2.9% presented with nausea or vomiting on the second day (n=3/103) and none did so on the third day.

The diameter of the appendix ranged from 6 mm to 13 mm with a mean of 7.6 mm on ultrasound (n=101) and 9 mm^{8–13} on CT scan (n=3). A periappendiceal fat infiltration was described in 88% of cases, and minimal periappendiceal effusion in 22% of cases.

The median value of the initial CRP was 11.3 mg/L (IQR: 3–24), leucocytes 11.3 G/L (IQR: 8.7–14.7), polymorphonuclear neutrophils 8.6 G/L (IQR: 5.3–12) and platelets count 269 G/L (IQR: 233–309).

The median dosage of intravenous amoxicillin was 81.2 mg/kg/day (IQR: 71–95). The dosage of amoxicillin was available for all patients and 55% of these patients received at least 80 mg/kg/day (n=57/104). The duration of intravenous antibiotic therapy was 2 days for all patients with a total of 6 injections.

All patients were switched to oral antibiotic (amoxicillin/clavulanic acid). The median dosage of oral amoxicillin was 80 mg/kg/day (IQR: 73–94), prescribed for a median duration of 7 days (IQR: 7–7). The initial success rate (resolution of abdominal pain and hospital discharge without appendectomy) was 100%. The median length of hospital stay was 3 days (IQR: 3–4).

A follow-up consultation was conducted for 102 patients, in a mean time span of 2 weeks after discharge

from hospital. The follow-up CRP was ≤ 5 mg/L in 97% of cases (80/82 patients). The follow-up ultrasound was pathological (diameter > 6 mm, infiltration, effusion) in 9% (n=9) of the 100 patients for whom data were available. Ultrasound monitoring has been implemented because it was a new service protocol but patient management has not changed even if the ultrasound was pathological (diameter > 6 mm, infiltration, effusion) for 9 patients at 15 days of follow-up. No significant link was identified between having a pathological abdominal ultrasound at day 15 and recurrence of appendicitis.

In our population, 14.4% patients had surgery (15/104) following a recurrence of the appendicitis in the 2 years after the antibiotic therapy. The median time for surgical treatment was at 82 days after the first day of the initial hospitalisation (IQR: 55–233). None of the patients who underwent an operation because of a recurrence presented with complicated appendicitis. There were no cases of abscess, peritonitis nor plastron in the 15 patients who were operated on in our study. All the anatomopathological results concluded to the diagnosis of appendicitis.

There was no significant difference in the comparison between the success and failure groups in terms of the medical treatment for: age of patients, pain scale at day 0 and day 2 of the treatment, maximum temperature, time gap to onset of symptoms, CRP, leucocytes, polymorphonuclear neutrophils count, platelet count, intravenous and oral routes for amoxicillin/clavulanic acid, the duration of the IV and oral treatments and the duration of hospitalisation (table 1). In a multivariate analysis, a significant difference was found between the two groups for the diameter of the appendix on the ultrasound with a median of 7 mm (IQR: 7–9) in the success group versus 8 mm (IQR: 7.2–9.5) in the failure group (OR=1.4; 95% CI 1.0 to 1.8, p=0.02). The presence of an effusion (OR 3.9; 95% CI 1.3 to 12.6, p=0.02), a pathological

ultrasound at the follow-up visit (OR 6.7; 95% CI 2.1 to 21.9; p=0.002) and the duration of symptoms (1 day vs 2 days) (OR 1.3; 95% CI 1.0 to 1.8, p=0.01) were factors associated with treatment failure.

The quantitative variables, whose distribution was asymmetrical, were described using median, and IQR. For the comparison between the groups (success group and failure group), the tests were conducted with a significance threshold of p<0.05. The percentages were tested with the χ^2 test or Fisher's test depending on the number of patients, and the medians with a Mann-Whitney test and by logistic regression. Multivariate analysis was performed using a logistic regression model.

DISCUSSION

Our results confirm the efficacy of antibiotic therapy by amoxicillin/clavulanic acid for NOT of AUA, with a success rate at 2 years of 85% in our series of 104 patients.

Our study population is similar to those described in previous studies in terms of age and gender.^{13–15} Our inclusion criteria are also the same as those used in current recommended practice to define uncomplicated acute appendicitis.^{15 28} Over-reliance on an appendiceal diameter greater than 6 mm, often the only finding, continues to be the most common cause of false-positive interpretations. Telesmanich *et al* found a mean appendiceal diameter of 6.7 mm in those without appendicitis, suggesting that the customary upper normal limit of 6 mm is too sensitive.³⁰ Kim *et al* found a strong correlation with a negative exam when periappendiceal fat inflammation is absent or minimal.⁶ We emphasised the importance of identifying secondary US findings of appendicitis, especially periappendiceal fat thickening with increased echogenicity, in our standardised reporting template and the education of staff and residents in an effort to reduce false-positive interpretations. According to the

Table 1 Characteristics of included patients

Patient characteristics	Total, n=104	Successful NOT at 2 years, n=89	Failed NOT at 2 years, n=15	P value
Median age, years (IQR)	10 (8–11)	9 (8–11)	10 (8–11)	0.12
Median duration of symptoms, days (IQR)	1 (1–2)	1 (1–2)	2 (1–3)	0.046
Median weight, kg (IQR)	32 (26–41)	32 (26–41)	32 (27–36)	1
Median maximal body temperature, °C (IQR)	37.5 (37.2–37.9)	37.5 (37.2–37.8)	37.3 (37.2–37.9)	0.1
Median neutrophils, cell/ μ L (IQR)	8.6 (5.3–12)	8.6 (5.3–11.5)	10.3 (4.2–15.7)	0.56
Median CRP, mg/L (IQR)	11.3 (3.4–24.3)	10 (3–21.4)	21 (14.4–30)	0.09
Median ultrasound appendix diameter, mm (IQR)	7.6 (7–9)	7 (7–9)	8 (7.2–9.5)	0.02
Median EPA at day 0 of hospitalisation, n (IQR)	4 (0–5)	3 (0–5)	4 (3–7)	0.19
Median intravenous antibiotic duration, days (IQR)	2 (2)	2 (2–2)	2 (2)	1
Median oral antibiotic duration, days (IQR)	7 (7–7)	7 (7–7)	7 (7–7)	0.2
Median length of hospital stay, days (IQR)	3 (3–4)	3 (3–4)	3 (3–4)	0.94

The parameters measured and reported relate to the initial admission with appendicitis, not total during the follow-up period. CRP, C reactive protein; EPA, electronic pain assessment; NOT, non-operative treatment.

2020 update of the WSES (World Society of Emergency Surgery) Jerusalem guidelines, in paediatric patients with suspected acute appendicitis, we suggest against making a diagnosis based on clinical scores alone.³¹

The acceptance of our protocol by the parents was good, with a low number of refusals for the NOT (n=13). The recurrences observed were all cases of simple appendicitis. The patients and their families were well informed about the signs that should lead to re-admission to hospital. This global care package that associates follow-up and therapeutic education with the initial treatment makes it possible to prevent complications and cases of appendiceal peritonitis or severe sepsis. A well-explained and closely monitored medicinal treatment thus appears to be a safe option with minimal risk for the patients.

Beta-lactam/beta-lactamase inhibitor combinations have an *in vitro* activity against Gram-positive, Gram-negative and anaerobe organisms. Amoxicillin/clavulanate is still an option in mild community-acquired intra-abdominal infections (IAIs). In adults, the empirical antibiotic regimens for non-critically ill patients with community-acquired IAIs as advised by the 2017 WSES guidelines are the following: amoxicillin/clavulanate 1.2–2.2g 6 hourly or ceftriazone 2g 24 hourly + metronidazole 500mg 6 hourly or cefotaxime 2g 8 hourly + metronidazole 500mg 6 hourly. In patients with beta-lactam allergy: ciprofloxacin 400mg 8 hourly + metronidazole 500mg 6 hourly or moxifloxacin 400 24 hourly. In patients at risk for infection with community-acquired ESBL (extended spectrum betalactamases)-producing Enterobacteriaceae: ertapenem 1g 24 hourly or tigecycline 100mg initial dose, then 50mg 12 hourly.³²

The antibiotic therapy by amoxicillin/clavulanic acid used in our study is a first-line therapy frequently used in paediatrics. This choice of antibiotic therapy was guided by the encouraging local bacterial epidemiological data. The bacteriological data between 2015 and 2019 show that 80% of the strains of *Escherichia coli* identified in peritoneal liquid (n=296) are sensitive to the combination of amoxicillin and clavulanic acid, and that 93% of the *Klebsiella spp* (n=29) are sensitive to this combination. All of the anaerobic bacteria strains were sensitive to amoxicillin/clavulanic acid.²⁶ The choice of this antibiotic therapy, which does not target *Pseudomonas aeruginosa* (which is the main reason for the use of piperacillin-tazobactam in other studies), is implied by the fact that this microbe is considered more of a bystander than a pathogen agent in this condition.^{3,5,13–24} Combatting antibiotic resistance remains a major challenge. This therapeutic choice appears reasonable in terms of respecting the bacterial ecology in non-severe forms of appendicitis. The chosen dosage of 80 mg/kg/day of amoxicillin facilitates the transition to the oral route since this corresponds to the dosage of the available drinkable suspension. Additionally, this dosage is appropriate in terms of the pharmacokinetics and pharmacodynamics for the site infected and the pathogens suspected. Compared with

the other studies that used antibiotics with a broader spectrum (piperacillin-tazobactam, cefmetazole, meropenem, ciprofloxacin-gentamicin-metronidazole), the originality of our study lies in the choice of an antibiotic with a narrower spectrum.¹⁸ Our success rate of 85% for NOT was the same as described by the meta-analysis published in 2017 (82%).¹⁸ However, the antibiotic regimens described in the 10 studies included in this meta-analysis were all of a broader spectrum. Using amoxicillin-clavulanic acid and gentamicin for initial treatment in acute simple paediatric appendicitis, Gorter *et al* reported a short-term efficacy of 92% at the 8 weeks follow-up. Only 25 children were included in this study.²²

More recently, a paediatric study (children aged 7–17 years) reported a success rate at 1year in the ‘non-surgical care’ group of 67.1% (95% CI 61.5% to 72.31%) for the 284 children who completed the follow-up procedure.¹² The antibiotic administered in this study was a piperacillin-tazobactam combination but the median intravenous treatment duration was only 1 day. In adults, a study published in 2011 studied the non-inferiority of amoxicillin/clavulanic acid treatment over that of surgery in acute appendicitis in adults. This trial concluded an absence of non-inferiority with a significantly higher rate of peritonitis in the 30 days following discharge from hospital in the non-operated patients treated by antibiotics.³³

Our study was retrospective and covered a single medical centre, with no control group. Current data on NOT for appendicitis are insufficient to allow us to establish therapeutic recommendations. Multicentre, randomised and prospective trials are underway: the APPY (Appendectomy versus non-operative treatment for acute uncomplicated appendicitis in children) Trial which plans to include 978 patients,²⁸ the CONTRACT (Conservative treatment for uncomplicated appendicitis in children) Study in Great Britain³⁴ and the APAC (Initial non-operative management of uncomplicated appendicitis in children) Study.³⁵ These multicentre studies including a large number of patients will make more substantial conclusions on antibiotic therapy for acute appendicitis in children. We should note that in two of these three trials, the decision as to which antibiotics to administer is left to the discretion of the doctor caring for the patient.

Conclusion

NOT with a narrowed antibiotic therapy using amoxicillin-clavulanic acid appears to be an effective alternative to surgical intervention for AUA in children with regard to local bacteriological epidemiology. Narrowed antibiotic therapy by amoxicillin/clavulanic acid presents satisfactory results and limits the risk of developing antibiotic resistance compared with antibiotics with a broader spectrum. Our results also lead us to conclude that this treatment does not induce a risk of aggravation or complications for the patients. These results should be confirmed by larger studies.

Contributors CP, OA, CM, IC and CB contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript. LR, CL, DD aided in interpreting the results and worked on the manuscript. All authors discussed the results and commented on the manuscript. CB is acting as guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the University Hospital of Toulouse review board (RnIPH number 2021-67). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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