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Original article

Shorter duration of antibiotic treatment for acute bacteraemic cholangitis with successful biliary drainage: a retrospective cohort study

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ABSTRACT

Objectives: To assess the effectiveness of short duration antimicrobial therapy for acute cholangitis with bacteraemia.

Methods: We conducted a retrospective cohort study of patients with acute bacteraemic cholangitis with successful biliary duct drainage at a single centre in Japan. We compared short-course antimicrobial therapy (SCT, ≤7 days) and long-course therapy (LCT, ≥8 days), with a primary outcome of 30-day mortality. We constructed logistic regression models for mortality and a composite outcome, including mortality, recurrence, recrudescence, new bacteraemia, liver abscess or other complications related to cholangitis. We also developed a propensity score for SCT with inverse probability weighting for both the primary outcome and the composite outcome.

Results: We identified 263 patients in our cohort; 86 (32.7%) patients received SCT and the remaining 177 (67.3%) received LCT. The median durations of SCT and LCT were 6 days (range 2–7 days) and 12 days (range 8–46 days), respectively. The 30-day mortalities of SCT and LCT were 4.7% (4/85) and 5.7% (10/176), respectively (p 1.00). Logistic regression analysis showed that the odds ratio of SCT for 30-day mortality and the composite outcome were 1.07 (95% CI 0.25–4.52, p 0.93) and 1.08 (95% CI 0.48–2.45, p 0.85), respectively. Propensity score analyses for both 30-day mortality and the composite outcome did not demonstrate a difference between SCT and LCT (p 0.65 and p 0.95, respectively).

Conclusions: SCT with a median duration of 6 days did not have worse outcomes than LCT with a median duration of 12 days. Shortening the duration of antimicrobial therapy may be a reasonable option when treating acute bacteraemic cholangitis following successful biliary drainage. **A. Doi, Clin Microbiol Infect 2018;24:1184**

Introduction

Acute cholangitis is a common disorder, which places a substantial burden on patients and the acute care system [1–4]. Antimicrobial therapy with appropriate biliary drainage is considered the standard of care in managing acute cholangitis, with or without bacteraemia [4,5]. However, the optimal duration of antimicrobial therapy remains unknown. Seven to 10 days of antimicrobial therapy is common for the treatment of acute cholangitis [5] and many infectious disease specialists recommend a longer duration of treatment, such as 14 days, when bacteraemia is present [6]. More recently, some authors have suggested that antimicrobial treatment with a shorter duration could cure acute cholangitis, provided that biliary drainage was successful [7]. However, few studies have investigated the optimal duration of antimicrobials, particularly when complicated by bacteraemia.

To determine the optimal duration of antimicrobial treatment of acute bacteraemic cholangitis with successful biliary drainage, we conducted a retrospective comparative study to evaluate the effectiveness of antimicrobial treatment with short duration.

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Materials and methods

Settings and participants

We conducted a single-centre, historical cohort study from January 2012 to February 2017 at Kobe City Medical Centre General Hospital in Kobe, Japan, an acute tertiary-care hospital with 700 beds. The study protocol was approved by the ethics committee of the hospital.

We included all patients who were hospitalized for acute bacteraemic cholangitis or who developed acute bacteraemic cholangitis during hospitalization, with successful biliary drainage by procedures such as endoscopic retrograde cholangiopancreatography. Acute bacteraemic cholangitis was defined by clinical diagnosis of treating physicians with positive blood cultures.

Patients' characteristics

We identified patients according to them having an International Classification of Diseases, 10th revision code for 'cholangitis' and a positive blood culture in the hospital during the study period. We then reviewed their clinical charts to evaluate their characteristics. For some missing data, the patients were contacted by telephone to determine these data. Patients under 16 years of age were excluded. Variables recorded at study entry included the following: age, sex, the location of patients at the time of onset of infection (community-acquired or hospital-acquired), new-onset or recurrence, pre-infection medical co-morbidities, anatomical abnormalities of the bile duct due to stenting or diseases, drug use, including corticosteroids, other immunosuppressants and chemotherapy, and use of medical devices. We also recorded vital signs, duration of fever and other symptoms, laboratory data, imaging study results, culture results, susceptibility results, and the specific antimicrobials used for treatment. We measured time from admission to biliary drainage, or from onset of symptoms to drainage for nosocomial infections. We also estimated whether covering, appropriate empirical treatment was provided or not, based on the CLSI breakpoint [8]. Those antimicrobials for which the breakpoint was not determined by CLSI for a given organism were not included in the analysis. Scores of the Tokyo Guideline Grade [9] and quick Sepsis-related Organ Failure Assessment (qSOFA) [10] were also derived from the medical charts to assess the severity of cholangitis.

Study outcomes

We compared short-course antimicrobial therapy (SCT), which was defined as a total duration of antimicrobials for $\leq$7 days, with long-course therapy (LCT), in which patients were provided antimicrobials for $\geq$8 days, for acute bacteraemic cholangitis. When antibiotics were changed from intravenous to oral, we included the days of oral antibiotics in addition to the days of intravenous antibiotic use in 'the duration' until they were completely discontinued.

The primary outcome was mortality up to 30 days after initiating antibiotic treatment. Secondary outcomes included recurrence, which was defined as recurrence of symptoms after complete cure of the disease within 3 months after the onset; recrudescence, which was defined as symptoms worsening again before cure of the disease; new bacteraemia or liver abscess within 3 months and other complications that occurred as a consequence of cholangitis. Because of the relatively small number of patients with those outcomes, a composite outcome was constructed defined as the occurrence of any of the primary or secondary outcomes.

Microbiological studies

Two sets of blood cultures (Bactec Plus Aerobic and Anaerobic; BD Biosciences, Frankland Lakes, NJ, USA) were taken from all patients suspected of having cholangitis. Blood samples were processed in BACTEC-FX and identification and antimicrobial susceptibility testing for Gram-negative bacilli, *Staphylococcus* sp. and *Enterococcus* sp. were performed using commercially available panels, Microscan from the Walkaway automated system (Beckman Coulter, Brea, CA, USA). Identification of *Streptococcus* sp. was performed by standard biochemical testing and susceptibility with commercially available panels (Beckman Coulter). Identification of anaerobes was performed by standard biochemical testing and antibiotic susceptibility with the disc diffusion method, judged based on the category of *Enterobacteriaceae* in the M-100, S-22 version of CLSI [8]. For all bacteria cultured, CLSI recommendations and criteria were used to define susceptibility to antimicrobial agents [8].

Statistical analysis

To analyse categorical variables, we used the chi-squared test or Fisher's exact test when appropriate. For continuous variables, we used the Shapiro–Wilk normality test to check whether the parametric model was appropriate. We then used the Student's *t*-test or Wilcoxon rank-sum test when appropriate. We constructed a logistic regression model for the primary outcome and the composite outcome to estimate the odds ratio (OR) of SCT compared with LCT, adjusting for variables that were likely to be useful but not likely to be related to each other, with or without a low p value. For a sensitivity analysis, we developed a propensity score for SCT and estimated ORs with inverse probability weighting methods, using variables likely to influence the outcomes, for both the primary outcome (i.e. 30-day mortality) and the composite outcome. For analyses, we used STATA version 14.2 for Macintosh (StataCorp, College Station, TX, USA).

Results

We identified 263 cases of culture-confirmed acute bacteraemic cholangitis. The characteristics of the patients are shown in Table 1.

The mean age of the patients was 77 years (range 31–102 years). Eighty-six (32.7%) patients received SCT and the remaining 177 (67.3%) received LCT. The median durations of SCT and LCT antimicrobial therapy were 6 days (range 2–7 days) and 12 days (range 8–46 days), respectively (Fig. 1). All patients received intravenous antimicrobials but some were switched to oral antimicrobials later. The SCT group received less oral antimicrobials than the LCT group (9/86 (10.5%) and 87/177 (49.5%), respectively, $p < 0.001$). Nine patients in the SCT group received a median duration of 3 days of oral antimicrobials (range 2–5 days), and 87 patients receiving LCT had a median duration of 7 days of oral antimicrobials (range 1–35 days). Endoscopic retrograde cholangiopancreatography was performed in most patients (85/86 (98.8%) and 171/177 (96.6%) for SCT and LCT, respectively, p 0.43). Co-morbidities in both groups were largely similar. Medical treatments that might have affected the immune systems of the patients were similar between SCT and LCT, including use of glucocorticoids, other immunosuppressive agents and on-going chemotherapy (Table 1). The median qSOFA scores for SCT and LCT were 0 (range 0–3) and 1 (range 0–3), respectively (p 0.02). The median Tokyo Guideline Grade of SCT and LCT was 1 (range 1–3) and 2 (range 1–3), respectively (p 0.02). The white blood cell counts and C-reactive protein levels tended to be higher in the LCT group than the SCT group (p 0.04 and p 0.15, respectively). The most common causative organisms found in

Table 1
Comparison of clinical characteristics of the patients between short-course and long-course antibiotics

	Treatment duration ≤7 days n = 86 (%)	Treatment duration ≥8 days n = 177 (%)	p value
Age, years (mean, range)	78.3 (45–102)	76.7 (31–102)	0.36
Female sex	36/86 (41.9)	64/177 (36.2)	0.45
Nosocomial onset	8/86 (9.3)	24/177 (13.6)	0.41
Not first onset	25/86 (29.1)	41/177 (23.2)	0.40
Gallstone or sludge present	61/86 (70.9)	124/177 (70.1)	0.85
Co-morbidities			
Congenital biliary diseases	1/86 (1.2)	1/177 (0.1)	0.55
Diabetes mellitus	31/86 (36.0)	60/177 (33.9)	0.84
Congestive heart failure	17/86 (19.8)	29/177 (16.4)	0.61
Chronic kidney disease[a]	18/86 (20.1)	51/177 (28.9)	0.22
Cerebrovascular accident	14/86 (16.3)	33/177 (18.6)	0.77
Liver cirrhosis	6/86 (7.0)	15/177 (8.5)	0.85
Chronic lung diseases	16/86 (18.6)	29/177 (16.4)	0.78
Haematological malignancies[b]	2/86 (2.3)	3/177 (1.7)	0.66
Solid organ malignancies[b]	33/86 (38.4)	80/177 (45.2)	0.36
Susceptibility to biliary duct obstruction			
Mass lesions (abscesses or tumours) in liver	3/86 (3.5)	16/177 (9.0)	0.13
Anatomical abnormalities in the biliary tract	26/86 (30.2)	55/177 (31.1)	1.00
Existing stent in the biliary tract	21/86 (24.4)	43/177 (24.3)	1.00
Treatment affecting immunity of the patients			
Use of glucocorticoids	2/86 (2.3)	4/177 (2.3)	1.00
Use of other immunosuppressive agents	3/86 (3.5)	2/177 (1.1)	0.33
Use of chemotherapy	6/86 (7.0)	9/177 (5.1)	0.74
Causative organisms			
Gram-positive	11/86 (12.8)	47/177 (26.6)	0.01
Gram-negative	75/86 (87.2)	157/177 (88.7)	0.88
Anaerobes	6/86 (7.0)	6/177 (3.4)	0.32
Polymicrobials	12/86 (14.0)	44/177 (24.9)	0.04
ID consultation	8/86 (9.3)	59/177 (33.3)	<0.001
Empirical antimicrobials covering the causative organisms	75/78 (96.2)	136/157 (86.6)	0.02
Time to drainage (hours)	13.3 (0.5–90)	20.9 (0.5–289)	0.03
qSOFA score (median, range)	0 (0–3)	1 (0–3)	0.02
Tokyo Guideline Grade (median, range)	1 (1–3)	2 (1–3)	0.02
WBC at diagnosis (/mm^3, mean, range)	10 370 (1100–25 500)	11 880 (700–41 200)	0.04
CRP at diagnosis (mg/dL, mean, range)	6.75 (0.09–26.73)	9.50 (0.02–35.11)	0.15
Total bilirubin at diagnosis (mg/dL, mean, range)	3.0 (0.5–8.9)	3.7 (0.3–26.4)	0.18
Body temperature (°C, mean, range)	38.0 (35.6–41.0)	38.0 (35.3–40.9)	0.70
Duration of antibiotics days (median, range)	6 (2–7)	12 (8–46)	

Abbreviations: CRP, C-reactive protein; ID, infectious diseases expert; LCT, long-course therapy; qSOFA, Sepsis-related Organ Failure Assessment; SCT, short-course therapy; WBC, white blood cells.
We were able to obtain all data on continuous variables except for qSOFA, where there were two missing points of data in the LCT group.
[a] Defined as having creatinine levels >1.5 mg/dL.
[b] Defined as malignancies without cure under chemotherapy or those that were diagnosed within 1 year.

blood cultures were Gram-negative bacteria (75/86 (87.2%) in SCT group and 157/177 (88.7%) in LCT group, p 0.88). However, more Gram-positive organisms were found in the LCT group (47/177 (26.6%) versus 11/86 (12.8%), p 0.02). LCT also had more patients with polymicrobial bacteria (12/86 (14.0%) versus 44/177 (24.9%), p 0.04). Empirical antibiotic treatment was more frequently covering in the SCT group (75/78 (96.2%) versus 136/157 (86.6%), p 0.02). Frequently identified organisms and initial antimicrobials are listed in the Supplementary material (Tables S1 and S2). There were more infectious diseases expert consultations in the LCT group (8/86 (9.3%) versus 59/177 (33.3%), p 0.001).

We were able to determine the primary outcome in 261 (99.2%) patients. The 30-day mortality rates of SCT and LCT were 4.7% (4/85) and 5.7% (10/176), respectively (OR 0.82, 95% CI 0.18–2.95, p 0.74). There were two deaths in those who received antimicrobial therapy for a very short period (≤4 days, 10.5%), and there was one death in those who received it for a very long period (≥21 days, 6.3%). Univariate analyses for other secondary outcomes also did not show any statistical differences between the two groups (Table 2).

A logistic regression analysis using variables (empirical antimicrobials covering the causative organisms, qSOFA score, time to drainage, polymicrobial infections, Gram-positive organisms identified) for the primary outcome and the composite outcome showed that the ORs for SCT were 1.07 (95% CI 0.25–4.52, p 0.93), and 1.08 (95% CI 0.48–2.45, p 0.85), respectively (Table 2).

The result of the propensity score analysis using inverse probability weighting with variables association for SCT consisting of detection of Gram-positive organisms, presence of polymicrobial infections, presence of infectious diseases consultation, empirical antimicrobials covering the causative organisms, qSOFA score, time to drainage, liver mass and white blood cell count, showed no significant difference in both 30-day mortality and the composite outcome (p 0.65 and p 0.95, respectively, Table 2). The details were provided in Supplementary Tables (Tables S3, S4 and S5).

Discussion

Our results suggest that antimicrobial SCT with a median duration of 6 days did not lead to worse clinical outcomes in acute bacteraemic cholangitis compared with LCT with a median duration of 12 days. Our findings are supported by logistic regression analysis and propensity score analysis using inverse probability weighting for both the primary outcome (30-day mortality) and the composite outcome.

There is scarce clinical evidence regarding the duration of treatment for acute cholangitis. In an observational study, Van Lent et al. proposed that a short duration of therapy (≤3 days) appeared

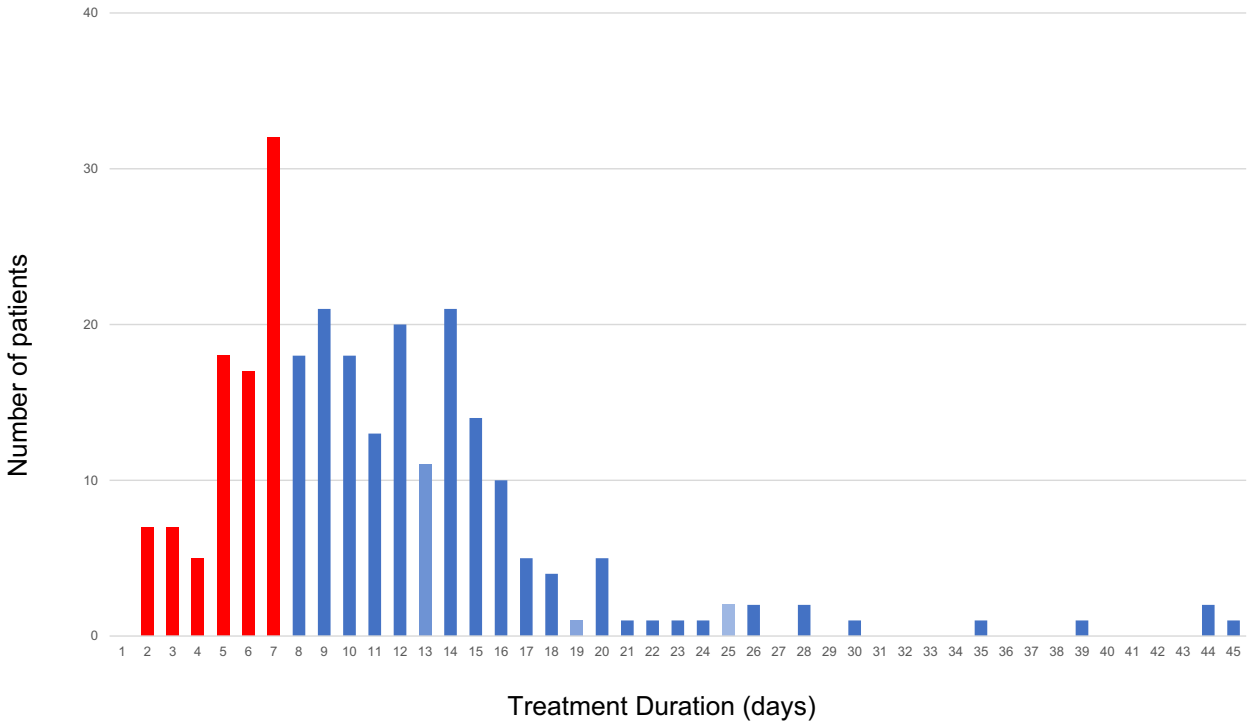

Fig. 1. Antimicrobial treatment duration of the study patients. Red bars, the patients on short-course therapy (SCT) and blue bars, the patients on long-course therapy (LCT).

Table 2
Results of primary and secondary outcomes between short-course therapy and long-course therapy

Characteristics	Number of outcomes. SCT vs LCT (%)	Univariate analysis			Logistic regression analysis			Propensity score analysis (IPW)		
		OR	95% CI	p value	OR	95% CI	p value	ATE	95% CI	p value
Mortality	4/85 vs 10/176 (4.7 vs 5.7)	0.82	0.18–2.95	1.00	1.07	0.25–4.52	0.93	0.02	−0.05 to 0.08	0.65
Recrudescence	3/77 vs 6/153 (3.9 vs 3.9)	0.99	0.26–3.87	1.00						
Recurrence	5/77 vs 12/151 (6.5 vs 7.9)	0.82	0.30–2.24	0.69						
Bacteraemia	4/72 vs 12/132 (5.6 vs 9.1)	0.61	0.20–1.83	0.43						
Composite outcome	14/86 vs 27/177 (16.3 vs 15.3)	1.07	0.59–2.29	1.93	1.08	0.48–2.45	0.85	−0.002	−0.09 to 0.09	0.95

Abbreviations: ATE, average treatment effect; IPW, inverse probability weighting; LCT, long-course therapy; OR, odds ratio; SCT, short-course therapy.

sufficient when adequate drainage was achieved [7]. However, their study was a descriptive case series without proper statistical analyses and only 26.7% of the patients had accompanying bacteraemia. Dooley et al. recommended 7–10 days of treatment [5], although their recommendation also was not based on clinical evidence. Kogure et al. proposed a fever-based approach, where antimicrobial agents were discontinued after defervescence for 2 days after successful endoscopic drainage [11]. However, this relatively small study was a case series comprising only 18 patients, with no control group for comparison. Another study compared shorter duration versus longer duration of antimicrobial therapy for acute cholangitis with Gram-negative bacteraemia [12]. This study, however, is a 'before and after' study to compare different periods with room for various biases. Gomi et al. recommended in the Tokyo Guideline a duration of 4–7 days after source control for non-bacteraemic cholangitis, and recommended a minimum of 2 weeks duration in association with bacteraemia, especially when caused by Gram-positive cocci, provided that anatomical problems were resolved upon the presence of residual stones or obstructions of the bile duct [6]. In fact, infectious diseases specialists tend to recommend a relatively long duration of antimicrobial therapy for bacteraemic cholangitis, reflected in the statistically significant tendency for those patients on LCT to have an infectious diseases consultation found in our study. However, this recommendation was based on the guideline for the management of complicated intra-abdominal infection, which does not specifically recommend treatment for acute cholangitis [13]. In addition, the recommendations were not based on relevant clinical evidence.

Recently, a randomized controlled trial studying treatment duration for appropriately drained intra-abdominal infections compared outcomes 4–5 days after drainage with a conventional duration of up to 10 days [14]. The short treatment duration did not have worse outcomes such as the occurrence of recurrent intra-abdominal infection or mortality. However, only 10.8% of the participants had acute cholangitis and only a few had concurrent bacteraemia [14]. Likewise, short courses of antimicrobial therapy of 6–10 days had similar outcomes compared with longer courses for *Enterobacteriaceae* bacteraemia [15]. Our findings were more specific to those who have acute bacteraemic cholangitis, for which many experts have considered longer treatment necessary. Therefore, our findings are quite novel.

In terms of antimicrobial stewardship, reducing the length of antibiotic courses may be effective in reducing antibiotic resistance through the proposed mechanism that shorter courses of

antibiotics reduce the selective pressure on the bacterial flora, and this might prevent the emergence of resistance [16,17]. In fact, shortening the antibiotic duration may reduce the burden of morbidity and mortality related to selection of antimicrobial-resistant pathogens [18], *Clostridium difficile* infections [19] and other adverse events, including allergies and organ toxicity, in addition to healthcare costs.

Animal studies have demonstrated that biliary drainage is imperative for antimicrobial agents to reach the infected areas [5,20]. Successful treatment of acute cholangitis might depend mainly on drainage of the biliary tract and antimicrobial therapy might only have an adjunctive role, even in the presence of bacteraemia.

There are several limitations in our study. This is a single-centre, retrospective study and the results may not be applicable to patients in different settings. The qSOFA and Tokyo Guideline severity scores of those patients on LCT were worse than for those on SCT, and fewer patients in the LCT group were treated initially by empirical antimicrobials than those in the SCT group. In addition, more Gram-positive organisms were involved in those in the LCT group, and the group had more patients with polymicrobial infections. These issues might have confounded our findings, although our sensitivity analyses with adjustments for those factors led to the same conclusions. Still, there is a possibility that the patients in the LCT group had different characteristics, of which we were unaware, that led to longer treatment duration by clinicians. Further prospective studies are necessary to overcome this potential room for bias. We are also aware that the LCT group might have inherent bias for survival; i.e. those who received LCT lived long enough to be enrolled in LCT [21]. However, this kind of survival bias provides a longer opportunity window for death to the SCT group, so it pushes towards disadvantageous results for SCT.

The reason our cohort had less mortality than in previous reports of bacteraemic cholangitis remains unknown, but may be due to differences in co-morbidity or skills in procedures [22], or due to our inclusion criteria, which excluded cases with unsuccessful biliary drainage. A recent study demonstrated factors associated with mortality in bacteraemic cholangitis, such as inadequate initial antibiotic therapy or biliary obstruction by hepatobiliary malignancy, similar to our findings [23]. Our study did not aim to demonstrate the effectiveness of shorter antimicrobial therapy for those cholangitis patients with risk factors. Further studies are needed to find the optimal duration of antimicrobial therapy when those factors are present.

In conclusion, our study suggests that acute bacteraemic cholangitis with appropriate biliary drainage can be treated with a shorter duration of antimicrobials than conventionally recommended. Further prospective, randomized trials are needed to better clarify our findings regarding the optimal duration for treatment of acute bacteraemic cholangitis [24].

Transparency declaration

Dr Iwata reports grants from Pfizer Inc. and Torii Corp. outside the submitted work. All other authors have no conflicts of interest.

Contribution to authorship

DA drafted the study design; TM and KI reviewed the final study protocol and all authors prepared the final study protocol. DA and KI conducted data analyses and TM supervised them. All participated in the final manuscript preparation, and agreed with the latest manuscript.

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Ethics approval

The study protocol was approved by the ethics committee of the hospital.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.cmi.2018.01.021.

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