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Original Article

Efficacy and safety of cefditoren pivoxil for exacerbations of chronic obstructive pulmonary disease: A prospective multicenter interventional study☆

Taiga Miyazaki [a, b, *], Kiyoyasu Fukushima [c], Kohji Hashiguchi [d], Yuichi Inoue [e], Tomo Mihara [f, 1], Toyomitsu Sawai [g], Naofumi Suyama [g, 2], Tsutomu Kobayashi [h], Akira Kondo [i], Yuichi Fukuda [j], Yosuke Harada [k, 3], Eisuke Sasaki [k], Norihito Kaku [l], Shotaro Ide [a, 4], Takahiro Takazono [a, b], Tomomi Saijo [a], Kosuke Kosai [l], Yoshitomo Morinaga [l], Shigeki Nakamura [a, 5], Kazuko Yamamoto [a], Yoshifumi Imamura [a], Koichi Izumikawa [b], Katsunori Yanagihara [l], Shigeru Kohno [a], Hiroshi Mukae [a]

[a] Department of Respiratory Medicine, Nagasaki University Hospital, Nagasaki, Japan
[b] Department of Infectious Diseases, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan
[c] Division of Respiratory Medicine, Japanese Red Cross Nagasaki Genbaku Isahaya Hospital, Isahaya, Japan
[d] Department of Respiratory Medicine, Japanese Red Cross Nagasaki Genbaku Hospital, Nagasaki, Japan
[e] Department of Respiratory Medicine, Aino Memorial Hospital, Unzen, Japan
[f] Department of Respiratory Medicine, Izumikawa Hospital, Minamishimabara, Japan
[g] Department of Respiratory Medicine, Nagasaki Harbor Medical Center, Nagasaki, Japan
[h] Department of Respiratory Medicine, Sasebo Chuo Hospital, Sasebo, Japan
[i] Department of Respiratory Medicine, JCHO Isahaya General Hospital, Isahaya, Japan
[j] Department of Respiratory Medicine, Sasebo City General Hospital, Sasebo, Japan
[k] Department of Respiratory Medicine, National Hospital Organization Ureshino Medical Center, Ureshino, Japan
[l] Department of Laboratory Medicine, Nagasaki University Hospital, Nagasaki, Japan

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ABSTRACT

Oral antibiotic therapy for patients with acute exacerbations of chronic obstructive pulmonary disease (COPD) usually involves an aminopenicillin with clavulanic acid, a macrolide, or a quinolone. To date, however, the clinical efficacy and safety of the oral cephalosporin cefditoren pivoxil has not been evaluated in Japanese patients with acute exacerbations of COPD. We conducted a prospective, multicenter, single arm, interventional study from January 2013 to March 2017 to determine the efficacy and safety of oral administration of 200 mg cefditoren pivoxil three times daily for 7 days in a cohort of 29 eligible patients from 15 hospitals. The mean age (SD) of participants was 73.1 (8.1) years and 28 had a smoking history (the mean [SD] of smoking index, 1426.7 [931.7]). The primary efficacy endpoint was clinical response (cure rate) at test of cure, which was set at 5–10 days after treatment ceased. Of the 23 patients finally analyzed, cure was achieved in 15 (65.2%), while 8 (34.8%) remained uncured. Previous experience of acute exacerbations significantly affected the cure rate: none of the three patients who had at least two prior exacerbations were cured, while 15 of the 20 patients with one or fewer prior exacerbations were cured ($p = 0.032$). The microbiological eradication rate was 88.9% at test of cure. During treatment, mild pneumonia was reported as an adverse event in one patient (3.4%) but resolved within 10 days of

Abbreviations: COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; EOT, end of treatment; $FEV_{1.0}$, forced expiratory volume in 1 s; FVC, forced vital capacity; M, mucous; P, purulent; PM, purulent-mucous; TOC, test of cure; WBC, white blood cell.

☆ All authors meet the ICMJE authorship criteria.

* Corresponding author. Department of Respiratory Medicine, Nagasaki University Hospital, Department of infectious diseases, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan.
E-mail address: taiga-m@nagasaki-u.ac.jp (T. Miyazaki).
[1] Department of Respiratory Medicine, National Hospital Organization Nagasaki Medical Center, Nagasaki, Japan.
[2] Department of Respiratory Medicine, Izumikawa Hospital, Nagasaki, Japan.
[3] Department of Respiratory Medicine, Japanese Red Cross Society Nagasaki Genbaku Hospital, Nagasaki, Japan.
[4] Department of Respiratory Medicine, Nagasaki Harbor Medical Center, Nagasaki, Japan.
[5] Department of Chemotherapy and Mycoses, National Institute of Infectious Diseases, Tokyo, Japan.

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onset. We conclude that cefditoren pivoxil represents a viable alternative for antibiotic therapy in patients with few prior exacerbations.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms and airflow limitation, presenting with breathlessness, cough, and/or sputum production [1]. In Japan in 2013, the prevalence was 4.3% among those older than 40 years, increasing to 8.7% among those older than 60 years. In 2017, data indicated that 18,523 deaths in Japan were associated with COPD [2]. This situation is compounded by the widely held assumption that many patients with COPD remain undiagnosed [3].

Despite pharmacological treatment to control symptoms, patients with COPD develop acute exacerbations that often require additional therapy [1]. Given that we know repeated acute exacerbations worsen the clinical outlook, it is important that they are prevented and treated appropriately. When considering therapy, an important factor is the fact that bacterial [4–9] or viral [10–14] infections of the respiratory tract are the main triggers of acute exacerbations. Antibiotics can significantly reduce treatment failure rates in patients hospitalized because of an exacerbation [15]. However, it should be noted that microorganisms resistant to conventional treatment are common among patients with acute exacerbations [16,17]. Furthermore, this effect is less evident among outpatients [15]. For these reasons, antibiotic use remains a subject of debate in the treatment of acute exacerbations of COPD [18,19], though it is generally agreed that their use is appropriate in the presence of purulent sputum or patients with severe illness [1].

Empirical antibiotic treatment is usually initiated with a penicillin–beta-lactamase inhibitor combination, a macrolide, or a quinolone [1,20]. Several studies have also reported the potential efficacy of cefditoren pivoxil, a cephalosporin [21,22]. However, no studies have evaluated its clinical efficacy for the treatment of acute exacerbations in Japanese patients, who are mostly older and have lower body mass indexes compared with their non-Asian peers. Causative bacteria also vary regionally. Thus, we conducted a study to evaluate the efficacy and safety of oral administration of cefditoren pivoxil in Japanese patients with acute exacerbations of COPD.

2. Patients and methods

2.1. Study design

This prospective, multicenter, single arm, interventional study was performed from January 2013 to March 2017. Specifically, we assessed the efficacy and safety of cefditoren pivoxil for the treatment of patients with acute exacerbations of COPD in 15 health care institutes. The study was registered with the UMIN-CTR (ID number UMIN000010122) on Feb 26, 2013, before the onset of patient enrollment.

2.2. Ethics

This study was approved by the review boards of each participating institute and was conducted in accordance with the ethical principles outlined in the Helsinki Declaration and Ethical Guidelines for Clinical Research set out by the Japanese Ministry of Health, Labour and Welfare. All patients were fully informed about the purpose of the study and signed a consent form before participating.

2.3. Patients

We enrolled patients of both sexes if they were aged ≥20 years and presented with a COPD exacerbation, regardless of whether they were treated as inpatients or outpatients. The participants also had to have at least one of the following factors associated with refractory severe infection: (1) age ≥65 years; (2) ≥1 year of COPD treatment; (3) ≥2 acute infectious exacerbations within the last 12 months; (4) low respiratory function in the non-infected state (e.g., requirement for oxygen inhalation therapy, percent forced expiratory volume in 1 s [%$FEV_{1.0}$] of <80%, or PaO_2 <65 mmHg [SpO_2 <92%]); (5) history of respiratory management using a mechanical ventilator; or (6) underlying diseases requiring treatment, including cardiovascular disease, diabetes, renal disease, malignant disease, and connective tissue disease. Smoking history was recorded as the smoking index, which was calculated by multiplying the number of cigarettes a patient smoked per day by the number of years he or she had smoked.

The diagnostic criteria for COPD was <70% of the ratio of $FEV_{1.0}$ to forced vital capacity (FVC) at the last examination in the preceding 12 months. Mandatory diagnostic criteria for an exacerbation of COPD were as follows: (a) new occurrence of cough and sputum, increased volume of sputum, or increased sputum purulence; and (b) increased C-reactive protein (CRP) level or peripheral leucocyte count (≥0.7 mg/dL or ≥8000/mm^3, respectively; or above the maximum reference values of the participating institutes).

The major exclusion criteria were influenza virus infection, pneumonia untreatable by oral antibiotics in the opinion of the investigator, antibiotic treatment in the past 7 days, possible need for concomitant treatment with other antibiotics or additional oral or injectable corticosteroids, and other reasons judged to render the patient as ineligible by the primary investigator (see Table S1 for full list of exclusion criteria).

2.4. Interventions

The enrolled patients received cefditoren pivoxil (100 mg) as two tablets three times daily after meals for 7 days. If the primary investigators concluded that cure was achieved by 3 days after initiation therapy (≥9 doses), they were free to stop the medication. The clinical statuses of patients were assessed on day 1 (start of treatment), day 4, day 8, and day 15, and as necessary (Table S2). The highest body temperature of the day, respiratory rate, heart rate, cough, sputum volume, sputum purulence, and laboratory test values were recorded. The grading criteria for symptoms and observations are shown in Table S3. The severity of dyspnea was assessed using the modified British Medical Research Council dyspnea scale [1]. Chest X-rays were obtained on day 1 to exclude all patients with pneumonia who were considered untreatable by oral antibiotics.

2.5. Clinical efficacy assessments

The primary efficacy endpoint of this study was the clinical cure rate at test of cure (TOC), which was 5–10 days after the end of treatment (EOT). The secondary endpoints were the response rates at EOT and at day 4 (3 days after the start of treatment) and the bacterial eradiation rates at both the TOC and the EOT. These efficacy rates (%) were calculated using a formula, ("cured" or "effective" cases)/(all cases − "indeterminate" cases) × 100, according to the below definitions for cured, effective and indeterminate, Clinical response at TOC was categorized as cured, uncured, or indeterminate according to the following rules. Cure was defined as a condition of patients in whom therapy was considered effective at EOT; who did not require any other antibiotic treatment after EOT; who had a stable body temperature, white blood cell (WBC) count, and CRP level without requiring further therapy; and who maintained improvement after the EOT or were evaluated to have no need for further therapy. Patients were categorized as uncured if they failed to meet any of the requisites for cure or if they died due to exacerbations of COPD. Finally, patients were categorized as indeterminate if they provided incomplete information about their symptoms and observations due to missing a hospital visit; if they had an increased body temperature, WBC count, and CRP that were obviously unrelated to COPD exacerbation; or if they had symptoms and/or signs of an acute COPD exacerbation that were resolved or improved during systemic antibiotic therapy for other disorders.

Early treatment response on day 4 was categorized into effective, ineffective, or indeterminate. Patients were graded as effective if their cough or sputum production (volume and purulence) was improved, at least one of their other symptoms was improved, the initial fever of ≥37 °C was resolved, and the WBC count was reduced to <8000/mm^3 and subsequently fell to within the normal range of each institute. Early treatment was considered ineffective when the treatment did not meet the criteria for effective early treatment, except for patients considered to be indeterminate because they did not provide a complete dataset (e.g., due to a missed hospital visit) or because they had other conditions that had worsened their body temperature, WBC count, and CRP level. Another secondary endpoint, treatment response at EOT, was also assessed using these three grades (effective, ineffective, and indeterminate). However, the definition of effective therapy at the EOT was modified to include patients with a normalized body temperature or a decreased CRP level as well as those who also met the other prerequisites for effectiveness.

2.6. Microbiological assessments

Microbiological assessment (i.e., isolation, identification, and counting of causative pathogens) was performed at each participating institute. Type of sputum was classified into three types based on the guidelines of Japanese Society of Chemotherapy: purulent (P), purulent-mucous (PM), and mucous (M) [23]. Sputum samples were obtained before the initiation of the study treatment and were used for bacterial cell counting when classified in Geckler's groups 4 or 5. Bacteria for which the cell count was 6–99 cells or higher (× 1000 field) were identified as causative pathogens. Next, the semiquantative analysis of the bacterial culture was performed and culture was divided into four grades: 3+ (≥10^7 cfu/mL), 2+ (10^6 cfu/mL), 1+ (10^4–10^5 cfu/mL), and ± (10^2–10^3 cfu/mL). The bacteria were subjected to an antibiotic susceptibility test. Microbiological efficacy was assessed at the EOT and TOC based on the microbiological eradication rates.

2.7. Safety and tolerability assessments

In this study, adverse events were defined as any untoward observations (including abnormal changes in laboratory tests, symptoms, or health problems) that occurred during the study, regardless of the causal relationship with cefditoren pivoxil. Adverse events were reported according to the guidelines of Japanese Society of Chemotherapy [24].

2.8. Statistical analysis

For the percentage of patients who responded to the study treatment, the 95% confidence intervals (95% CIs) for means were calculated using both the Clopper–Pearson method and normal approximation method, and the 95% CIs for microbiological eradication rates were calculated using the Clopper–Pearson method. Statistical differences in clinical laboratory values between on day 1 (baseline) and each observational day were assessed by paired *t*-tests. Clinical efficacy at TOC was analyzed by sputum subgroup (P vs. PM or M; P or PM vs. M) and history of exacerbation in the preceding 12 months (0 vs. ≥1; 0–1 vs. ≥2) using Fisher's exact test. For all analyses, a *p*-value of <0.05 was considered statistically significant.

3. Results

3.1. Patient demographic and clinical characteristics

We enrolled 29 patients in this study, of whom none met the exclusion criteria. However, six patients (20.7%) stopped their participation because of either adverse events (1 patient), concomitant disease (1 patient), or unknown reasons (4 patients). The baseline demographics of the enrolled participants are shown in Table 1. Most were elderly men (mean ± SD: 73.1 ± 8.1 years) with a high average smoking index (mean ± SD: 1426.7 ± 931.7).

3.2. Clinical and microbiological efficacy

Overall, clinical symptoms and signs improved over time (Table S4). Likewise, inflammatory markers decreased gradually, with changes in WBC counts, neutrophil counts, and CRP levels being significant on day 15 compared with baseline ($p < 0.05$ each) (Table S5).

The clinical efficacy assessment is summarized in Table 2. The overall efficacy rates at TOC, at EOT, and on day 4 were 65.2%, 75.0%, and 67.9%, respectively. Among the 24 patients assessed at TOC, 15 were cured (62.5%; 95%CI 40.6%–81.2%), 8 patients were uncured (33.3%) and one patient (4.2%) was indeterminate. Among the 25 patients assessed at EOT, therapy was considered effective in 18 (72.0%; 95%CI 50.6%–87.9%) and ineffective in 6 (24%). On day 4, the therapy was considered effective in 19 of the 29 participants (65.5%; 95%CI 45.8%–82.1%).

Patients who had two exacerbations in the preceding 12 months were significantly more likely to have clinical failure at TOC compared with patients who had one or no exacerbations ($p = 0.032$) (Table 3). However, sputum type had no significant effect on the treatment efficacy.

The causative pathogens were identified from 11 patients with the purulent and purulent-mucous sputum (Table S6). They were penicillin-susceptible *S. pneumoniae* (n = 1), penicillin-intermediate resistant *S. pneumoniae* (n = 2), methicillin-susceptible *Staphylococcus aureus* (n = 1), *Corynebacterium pseudodiphthericum* (n = 2), *Haemophilus influenzae* (n = 2), beta-

Table 1
Baseline demographics (n = 29).

	Number of patients (%)
Sex (male: female)	27 (93.1%): 2 (6.9%)
Smoking history (yes: no)	28 (96.6%):1 (3.4%)
Antibiotics administered in the past 90 days (yes: no)	8 (27.6%):21 (72.4%)
	Mean ± SD (range, median)
Age (years)	73.1 ± 8.1 (60–88, 71.0)
Body mass index (kg/m^2)	21.2 ± 4.0 (14.2–30.0, 20.5)
Weight (kg)	56.0 ± 10.5 (37.7–78.6, 57.2)
Smoking index[a]	1426.7 ± 931.7 (0–4400, 1187.5)
History of exacerbations in the past 12 months	0.5 ± 0.7 (0–2, 0)

[a] n = 24.

lactamase-negative ampicillin-resistant *H. influenzae* (n = 1), *Moraxella catarrhalis* (n = 1), *Klebsiella pneumoniae* (n = 1), and *Klebsiella oxytoca* (n = 1). Most of all were susceptible to cefditoren. The overall eradication rates at EOT and TOC were 60.0% and 88.9%, respectively (Table 4).

3.3. Safety

During therapy, the only adverse event was pneumonia. This occurred in one patient, the severity was mild, and the condition resolved with appropriate therapy after 10 days. No serious adverse events were observed in any patient.

4. Discussion

We examined the efficacy and safety of high-dose cefditoren pivoxil treatment (200 mg three times daily) in Japanese patients with acute exacerbations of COPD. Notably, we confirmed that the clinical efficacy ranged from 65.2% to 75.0% in a cohort with severe risk factors, and there were no severe adverse events. To date, the most significant causes of COPD exacerbations have been reported to be air pollution and respiratory tract infection, including infection by a virus (40%–60%) or by bacterium, such as *H. influenzae*, *S. pneumoniae*, or *M. catarrhalis* [25,26]. The causative pathogens were isolated from only 11 patients (37.9%) in this study. The most common bacteria were consistent with those reported in previous studies [25,26]. Regardless of the sputum classification, patients with a history of no more than one prior exacerbation were significantly more likely to be cured. Thus, our data support the usefulness of cefditoren pivoxil in the treatment of acute exacerbations of COPD.

A probability model of therapeutic outcomes predicted that cefditoren pivoxil was almost equally effective to levofloxacin for the treatment of acute exacerbations of COPD in patients with mild-moderate disease, but that it was less effective in patients with severe disease [27]. Recently, a direct comparative study also reported comparable efficacy between cefditoren pivoxil (200 mg twice daily for 5 days; 80% cure rate) and levofloxacin (500 mg once daily for 7 days; 75% cure rate) for the treatment of exacerbations in patients with chronic bronchitis [22]. The higher severity of COPD in the present study, with the patients typically having a causative factor for refractory severe infection, likely accounts for our lower cure rate of 65.2%.

Respiratory quinolones are broad-spectrum antibiotics with potent bactericidal activity, high bioavailability, and a high penetration rate in respiratory tissue [28]. However, their overuse must be avoided to reduce the risks of quinolone resistance development and delayed diagnosis of tuberculosis [29,30]. By contrast, cefditoren pivoxil does not have anti-tuberculosis activity; therefore, it does not have a risk to mask the onset of tuberculosis. Although it has low bioavailability [31], cefditoren pivoxil has a potent antibiotic activity against *H. influenzae*, including beta-lactamase-

Table 2
Clinical efficacy of cefditoren pivoxil.

	Evaluation	Number of patients (%) [95% confidence interval]	Efficacy rate (%)
Clinical response at TOC (Primary endpoint)	Cured	15 (62.5%) [40.6–81.2][a], [43.1–81.9][b]	65.2%
	Uncured	8 (33.3%)	
	Indeterminate	1 (4.2%)	
	Missing	5	
Treatment response at EOT (Secondary endpoint)	Effective	18 (72.0%) [50.6–87.9][a], [54.4–89.6][b]	75.0%
	Ineffective	6 (24.0%)	
	Indeterminate	1 (4.0%)	
	Missing	4	
Treatment response on Day 4 (Secondary endpoint)	Effective	19 (65.5%) [45.8–82.1][a], [48.2–82.9][b]	67.9%
	Ineffective	9 (31.0%)	
	Indeterminate	1 (3.4%)	
	Missing	0	

TOC, test of cure; EOT, end of treatment.
Efficacy rate (%) = ("cured" or "effective" cases)/(all cases − "indeterminate" cases) × 100.
[a] Clopper-Pearson method.
[b] Normal approximation method.

Table 3
Effects of the sputum type and history of COPD exacerbations on the therapeutic efficacy of cefditoren pivoxil.

		Number of patients				*p*-value[a]
		Cured	Uncured	Indeterminate	Missing	
Sputum type	M	2	3	0	0	p = 0.297
	P or PM	13	5	1	4	
	Unknown	0	0	0	1	
History of exacerbations in the past 12 months	None or once	15	5	1	5	p = 0.032
	twice	0	3	0	0	

M, mucous; P, purulent; PM, purulent-mucous.
[a] Fisher's exact test.

Table 4
Microbiological efficacy of cefditoren pivoxil.

	Number of patients					Eradication rate (%)
	Eradicated	Presumably eradicated	Persisted	Substituted microbism	Indeterminate	(95% CI)[a]
EOT	4	2	4	0	1	60.0% (26.2–87.8)
TOC	3	5	1	0	2	88.9% (51.8–99.7)

TOC, test of cure; EOT, end of treatment.
Eradication rate (%) = ("eradicated" cases + "presumably eradicated" cases)/(all cases − "indeterminate" cases) × 100.
[a] Clopper-Pearson method.

negative ampicillin-resistant strains, which are among the most common causes of community-acquired pneumonia and chronic respiratory tract infection [32]. Furthermore, cefditoren pivoxil enhances complement-mediated immunity in the presence of specific antibodies against *S. pneumoniae* [33]. Its preferable pharmacological data and efficacy in the treatment of community-acquired pneumonia have also been reported with the high doses used in this study [34]. In contrast to macrolides, the anti-inflammatory action of beta lactam antibiotics has been scarcely reported [35], except T-cell modulation of some beta lactam antibiotics other than cefditoren pivoxil [36]. Therefore, the improvement of COPD exacerbation was probably associated with the antibacterial efficacy of cefditoren pivoxil [37].

The European Respiratory Society/American Thoracic Society guidelines for the management of COPD exacerbations recommend that antibiotics should be prescribed for ambulatory patients [38]. However, antibiotics should only be given to patients with presumed bacterial infection based on clinical criteria. Increased sputum purulence is a relevant parameter that can suggest the onset of a bacterial exacerbation [39–41]. In the present study, cefditoren pivoxil worked effectively in the patients presenting with either purulent or mucopurulent sputum, but it was less effective in the patients presenting with only mucous production. Procalcitonin is another biomarker that can be used to differentiate active bacterial infection from viral infection or chronic bacterial colonization. Recent meta-analyses indicate that procalcitonin-guided treatment can safely reduce antibiotic overuse in patients with acute exacerbations of COPD [42,43]. Accordingly, we should consider using this approach to select those patients most likely to benefit from antibiotics.

Some patients are susceptible to frequent exacerbations (i.e., two or more exacerbations per year) but the precise factors affecting exacerbation frequency are unknown [1]. The present study showed that a history of frequent exacerbations could also predict treatment failure in patients with acute exacerbations treated with cefditoren pivoxil.

Our study has several limitations. First, this study is a single-arm evaluation of cefditoren pivoxil without placebo or other antibacterial drugs. Second, the sample size was limited because we applied relatively strict criteria for the patient enrollment/exclusion (Table S1). However, in this study, patients with mucous-type sputum might have viral infection other than influenza. As all viral infections cannot be detected, we should routinely assess procalcitonin levels to select antibiotics or antiviral agents for acute exacerbations of COPD in future. Finally, while we included patients with an $FEV_{1.0}$/FVC of <0.70 at baseline, we did not repeat spirometry after the administration of an inhaled bronchodilator in all patients. Thus, the severity of airflow limitation was not confirmed in all cases. Accordingly, we could not perform subgroup analyses regarding the causative organisms or severity of COPD.

In conclusion, we have provided positive evidence regarding the efficacy and safety of cefditoren pivoxil for the treatment of acute exacerbations of COPD. When patients are clinically judged to require antibiotic therapy, cefditoren pivoxil should be considered as a safe and effective option.

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Conflicts of interest

All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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Appendix A. Supplementary data

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