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Original Article

Purple Urine Bag Syndrome in the Elderly

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SUMMARY

Background: Purple urine bag syndrome (PUBS) is rarely seen in clinical practice. Although it is most commonly seen in the elderly, we wanted to understand how this syndrome differs between the elderly and non-elderly.
Methods: PubMed articles were searched from 1980 October to 2016 August; 106 articles reported on PUBS. Among them, 174 PUBS cases were described. We excluded 58 cases and 116 PUBS cases were enrolled in this study. The chi-square test was used for statistical analysis, and a p value less than 0.05 (2-tailed) was considered to denote statistical significance.
Results: There were 47 men and 69 women enrolled in this study with a mean age of 75.6 ± 12.8 years (mean ± SD). Of these, 98 (84.5%) cases were found in elderly patients. The elderly PUBS patients presented with fever and shock less frequently than did non-elderly PUBS patients (8.2% vs. 27.8%, p = 0.02; 6.1% vs. 22.2%, p = 0.03). The overall mortality rate in PUBS was 6.8%. Elderly PUBS patients had relatively lower mortality rates, but the difference was not statistically significant (5.1% vs. 16.7%, p = 0.08).
Conclusion: PUBS in the elderly is associated with significantly lower rates of urosepsis symptoms, such as fever and hypotension. Although PUBS used to be considered a benign presentation in the majority of indwelling catheterized patients, for clinically afebrile and normotensive elderly patients, physicians should refer to patient's condition (consciousness, appetite), biomarker (C-reactive protein, and pro-calcitonin) to prevent from mortality in clinical practice.

1. Introduction

Purple urine bag syndrome (PUBS) is an uncommon phenomenon among urinary catheterized patients with urinary tract infection. It was first described in 1978 and the explanation of its possible mechanism was proposed in 1988.[1,2] Bacteria produce phosphatase and sulfatase, which are converted to indoxyl sulfate [IS] in the urine and into indirubin and indigo. Indirubin dissolves in the plastic urine bag and blue indigo deposits on its surface to create a purple discoloration. A higher prevalence of PUBS has been identified in females, those with alkaline urine, those with indwelling urinary catheters, and patients with constipation. Most PUBS patients are catheterized due to significant disability and are chair-bound or bed-bound elderly.[3] Since PUBS is relatively more common in elderly patients than in non-elderly patients, we gathered cases from 1978 onwards from a database and retrospectively analyzed the cases to determine the differences in PUBS between elderly and non-elderly patients.

2. Materials and methods

A retrospective cohort study was designed to investigate the differences in the clinical features of PUBS between elderly and non-elderly patients. We searched the PubMed database using the keyword "Purple urine bag syndrome." Articles published between January 1, 1980 and September 1, 2016 were included in the study. One hundred and six relevant articles were gathered. Thirty-five articles were excluded due to ineligibility. Exclusion criteria are shown in Fig. 1. Seventy-one articles with data from 116 patients were enrolled in the study. Clinical features were defined as: 1) elderly patients: age ≥ 65 years old; 2) fever: body temperature ≥ 38 °C; and 3) hypotension: systolic blood pressure (SBP) < 90 mmHg or diastolic blood pressure (DBP) < 60 mmHg. The combined data and descriptions of PUBS are listed in Table 1. The data were analyzed using commercial statistical software (SPSS for Windows, version 11.5, SPSS Inc., Chicago, IL, USA). Statistical χ^2 tests were performed and the significance level was set at a p-value of less than 0.05 (2-tailed). Ethical approval was not required because this article was based on a review of literature of reported cases in the PubMed database.

3. Results

3.1. Description of the selected articles

We retrieved 106 relevant articles for this study. After rigorous application of the inclusion and exclusion criteria, 71 eligible articles

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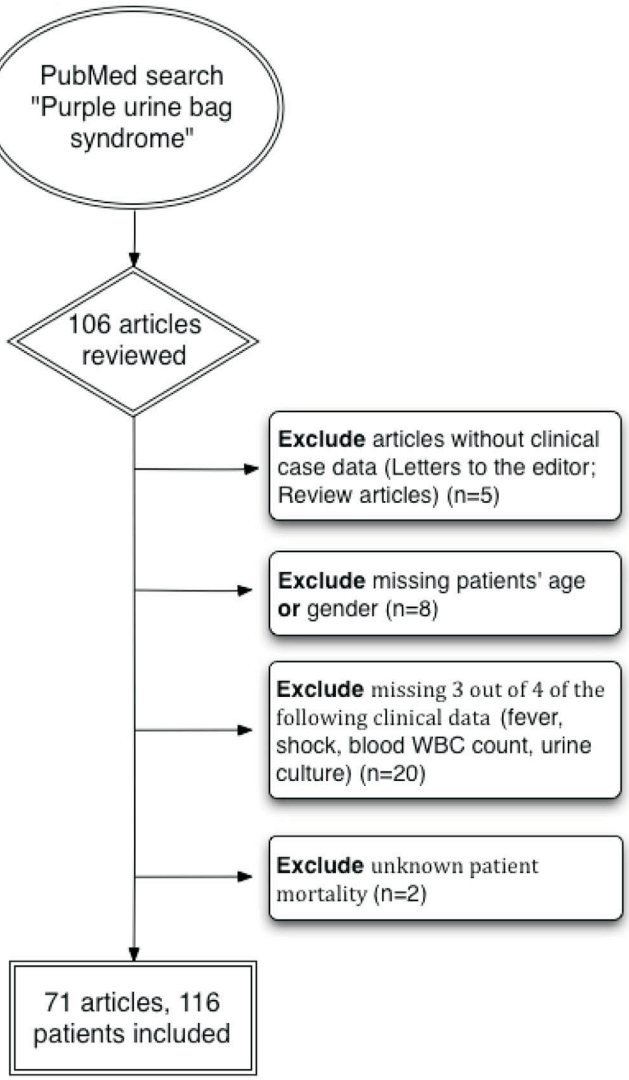

Fig. 1. Study inclusion and exclusion criteria.

were included of which 57 articles were written in English; four in French; three in Spanish; three in Japanese; one in Chinese; one in German; one in Icelandic; and one in Czech. All enrolled articles were of the following types: image in medicine, individual case report, or serial case report. The 71 articles included a total of 116 cases of PUBS, with patient-age ranging from 36 to 100 years, with a mean ± SD of 75.56 ± 12.79 years. These patients included 47 males (40.34%) and 69 females (59.66%). The language of the articles and patient characteristics are listed in Table 1.

3.2. Clinical characteristics between elderly patients and non-elderly ones

The elderly accounted for 84.5% (n = 98) of cases and 18 cases (15.5%) were non-elderly. Female predominance was observed in both groups. The male to female ratio was 1:1.5 in the elderly group, and 1:1.25 in the non-elderly group. The elderly PUBS patients were less likely to present with fever and shock than non-elderly PUBS patients (8.2% vs. 27.8%, p = 0.02; 6.1% vs. 22.2%, p = 0.03) [Table 2]. Constipation was observed in 71.6% of elderly patients, but only in 33.3% of patients in the non-elderly group. Two comorbid diseases, diabetes and uremia, had a relatively higher prevalence in the non-elderly group; however this difference was not statistically significant (29.4% vs. 17.3%, p = 0.25; 23.5% vs. 17.9%, p = 0.58). The prevalence of long-term care unit residents was higher in the elderly group (61.6% vs. 33.3%, p = 0.19). There was no statistically significant difference in white blood cell (WBC) count and urine pH between the elderly and non-elderly groups (Table 2).

Although the mortality rate in elderly PUBS patients was lower than that in the non-elderly ones, the difference was not statistically significant (5.1% vs. 16.7%, p = 0.08).

3.3. Bacteriology statistics

Bacterial growth in the urine culture of PUBS patients are list in Table 3. In our study, there were 39.7% PUBS cases that had polymicrobial bacteria in urine cultures. Culture results were not available in nine cases, and there was no bacterial growth in two cases. Among 105 patients with positive results, three patients yielded urine cultures with unidentified mixed organisms. The five most common identified bacterial species were *Escherichia coli., Enterococcus Spp., Proteus Spp., Morganella morganii, and Klebsiella Spp*.

4. Discussion

Urinary tract infection (UTI) is one of the most common infections in adults above 65 years of age.[4] Asymptomatic bacteriuria (ABU) occurs in up to 25–54% of women in nursing homes, but in men, the prevalence is only half of that.[5] For chronic catheter users, the rates of UTI are even higher (nearly 100% for indwelling catheters). PUBS refers to purple discoloration of the urinary drainage bag occurring in patients with long-term urinary catheterization, and was thought to be rare. However, prevalence from previous reports range from 8.3% to 16.7% in long-term urinary catheterized patients.[2,3,6] In one study in a geriatric hospital, 27% of elderly patients with dementia and chronic urinary catheterization developed PUBS.[7]

The mechanism of PUBS starts from tryptophan ingested through the diet and absorbed by bowel, and bacteria in the intestines metabolize it to indole, then further hepatic conjugation converts it to IS which is excreted in the urine by the kidneys. In the urinary tract, bacterial phosphatases and sulphatases metabolize IS to indoxyl, which gets converted to indigo and indirubin through an oxidation reaction. Blue indigo deposited on the surface of the plastic bag and red color indirubin dissolved in the urine creates purple discoloration.[2] The mechanism is demonstrated in Fig. 2. Previous studies showed that not all organisms of the same species produce phosphatase and sulphatase enzymes.[2] Moreover, a specific concentration of the pigments may be required for discoloration to become visible, so bacteriuria should be present in every patient with PUBS, and should be diagnosed with ABU for those without clinical symptoms and signs, such as fever or shock. A case control study reported that bacterial counts in the urine were significantly higher (by 1–2 logs) in patients with PUBS than in those without the syndrome. This means that a higher bacterial load in the urine is an important factor for the development of PUBS, in addition to other risk factors, such as female sex and the alkaline urine.[8] Hence, catheter-associated urinary tract infection (CA-UTI) among patients with comorbidities or those who are in an immunocompromised state is more likely to progress to PUBS.

Although leukocytosis is not always observed in UTI patients, it usually indicates a more severe clinical situation. A case study described 57 cases of UTI and leukocytosis (WBC count > 12,000/μL) or leukopenia (WBC count < 4000/μL) which were significantly more frequent (68% vs. 29%) in the urosepsis group.[9] That is, the presence of leukocytosis might correlate with UTI severity. In our study, there were two cases in the elderly group in which extremely high WBC counts (32400 and 58000/μL) were observed.[10,11] These two pa-

Table 1
Language of the 71 articles and the characteristics of the patients in each study.

Author	Year	Language	Country	No.	Mean age ± SD (years old)
Umeki, S.	1993	Japanese	Japan	4	80 ± 1.41
Nobukuni, K. et al.	1995	Japanese	Japan	5	60.4 ± 10.61
Al-Jubouri, M. A. et al.	2001	English	UK	1	85
Ihama, Y. et al.	2002	English	Japan	1	93
Vallejo-Manzur, F. et al.	2005	English	USA	1	72
Wang, I. K. et al.	2005	English	Taiwan	2	61a
Rohaut, B. et al.	2005	France	France	1	81
Achtergael, W. et al.	2006	English	Belgium	1	77
Beunk, J. et al.	2006	English	UK	1	84
Tang, M. W.	2006	English	Hong Kong	2	76 ± 8.49
Su, Y. J. et al.	2007	English	Taiwan	1	61
Nair, U. V. et al.	2007	English	UK	1	83
David Bar-Or. et al.	2007	English	USA	1	68
Gagan Gautam. et al.	2007	English	India	1	70
Ting, I. W. et al.	2007	English	Taiwan	1	72
Lazimy, Y. et al.	2007	France	France	1	74
Harun, N. S. et al.	2007	English	Brunei	2	60 ± 21.21
Rekha Neelakanta Pillai. et al.	2007	English	UK	1	76
Lin, C. H. et al.	2008	English	Taiwan	10	75.3 ± 2.12
Chiang, H. C. et al.	2008	Chinese	Taiwan	1	73
Chung, S. D. et al.	2008	English	Taiwan	1	85
Vidarsdottir, H. et al.	2008	Icelandic	Iceland	1	72
Shiao, C. C. et al.	2008	English	Taiwan	14	80.9 ± 11.5
Muneoka, K. et al.	2008	Japanese	Japan	6	87.7 ± 16.26
Tasi, Y. M. et al.	2009	English	Taiwan	2	64 ± 19.8
Al-Sardar, H. et al.	2009	English	UK	1	82
Wu, H. H. et al.	2009	English	Taiwan	1	95
van Iersel, M. et al.	2009	English	Netherland	1	72
Pillai, B. P. et al.	2009	English	Singapore	1	69
Ferrara, F. et al.	2010	English	Italy	1	81
Hirzallah, M. I. et al.	2010	English	Jordan	1	78
Siu, G. et al.	2010	English	USA	1	48
Su, H. K. et al.	2010	English	Taiwan	1	81
Kang, K. H. et al.	2011	English	Korea	3	74.7 ± 0
Keenan, C. R. et al.	2011	English	USA	1	97
Khan, F. et al.	2011	English	USA	1	39
Peters, P. et al.	2011	English	Australia	1	82
Zeier, M. G. et al.	2011	English	Singapore	1	75
Bocrie, O. J. et al.	2012	English	France	1	87
Cantaloube, L. et al.	2012	France	France	2	81.5 ± 0.71
Dominguez Alegria, A. R. et al.	2012	Spanish	Spain	1	78
Meekins, P. E. et al.	2012	English	USA	1	67
Al Montasir, A. et al.	2013	English	Bangladesh	1	86
Bhattarai, M. et al.	2013	English	USA	1	87
Canavese, C. et al.	2013	English	Italy	3	79 ± 19.52
Duff, M. L.	2013	English	USA	1	57
Iglesias Barreira, R. et al.	2013	Spanish	Spain	2	93.5 ± 2.12
Mohamad, Z. et al.	2013	English	Brunei	1	78
Ungprasert, P. et al.	2013	English	USA	1	44
Wolff, N. et al.	2013	France	France	1	90
Yaqub, S. et al.	2013	English	Pakistan	1	83
Agapakis, D. et al.	2014	English	Greece	1	82
Chassin-Trubert, C. Am. et al.	2014	Spanish	Chile	1	72
Delgado, G. et al.	2014	English	Mexico	1	60
Hloch, O. et al.	2014	Czech	Czech Republic	1	73
Restuccia, M. R. et al.	2014	English	Italy	1	81
Sheehan, M.	2014	English	USA	1	80
Abubacker, N. R. et al.	2015	English	India	1	36
Alex, R. et al.	2015	English	India	1	83
Karim, A. et al.	2015	English	USA	1	83
Kenzaka, T.	2015	English	Japan	1	72
Mohamed Faisal, A. H. et al.	2015	English	Malaysia	1	68
Mondragon-Cardona, A. et al.	2015	English	Colombia	1	71
Neweling, F. et al.	2015	German	Germany	1	78
Redwood, R. et al.	2015	English	USA	1	90
Van Keer, J. et al.	2015	English	Belgium	2	80.5 ± 0.71
Demelo-Rodriguez, P. et al.	2016	English	Spain	1	83
Faridi, M. S. et al.	2016	English	India	1	76
Richardson-May, J.	2016	English	UK	1	94
Sriramnaveen, P. et al.	2016	English	India	1	85
Tul Llah, S. et al.	2016	English	USA	1	52

[a] The same patient with 2 PUBS episodes.

Table 2
Clinical features and laboratory data of PUBS in elderly and non-elderly patients.

	All (n)	Elderly (n)	Non-elderly (n)	Two-tailed p value
Age (years)	75.6 ± 12.8 (116)	80.2 ± 7.6 (98)	53.3 ± 8.3 (18)	0.00
Male:Female	47:69 (116)	39:59 (98)	8:10 (18)	0.71
Fever	11.8% (116)	8.2% (98)	27.8% (18)	0.02[a]
Shock	8.6% (116)	6.1% (98)	22.2% (18)	0.03[a]
Constipation	69.8% (63)	71.6% (60)	33.3% (3)	0.16
Blood WBC (cells/mL)	12242 ± 10661 (27)	13113 ± 11959.(21)	11232 ± 2701 (6)	0.71
Urine pH value	8 ± 0.9 (72)	7.97 ± 1 (58)	8.14 ± 0.535 (14)	0.54
Diabetes mellitus	19.2% (99)	17.3% (81)	29.4% (17)	0.25
Uremia	18.8% (112)	17.9% (95)	23.5% (17)	0.58
Long-term care unit	58.3% (60)	61.6% (54)	33.3% (6)	0.19
Mortality	6.8% (116)	5.1% (98)	16.7% (18)	0.08

(n = available case number).
[a] = < 0.05.

Table 3
Findings from urine culture of the PUBS patients.

Pathogen	n	(%)
Escherichia coli	41	28.9%
Enterococcus Spp.	22	15.5%
Proteus Spp.	16	11.2%
Morganella morganii	15	10.6%
Klebsiella Spp.	15	10.6%
Providencia rettgeri	13	9.2%
Pseudomonas aeruginosa	11	7.8%
Streptococcus. Spp.	4	2.8%
Unidentified mixed organisms	3	2.1%
Staphylococcus. Spp.	2	1.3%
Total	142	100%

tients recovered after antibiotic treatment, and leukemoid reactions were considered rather than hematologic diseases. Leukemoid reactions are thought to be linked to a grave prognosis among elderly patients with sepsis.[8] Although the mean blood WBC count and standard deviation are slightly higher in the elderly group, without being significantly different (13113 ± 11959 vs. 11232 ± 2701; p = 0.71), relatively more comorbidities and shock were found in non-elderly cases. It did not lead to higher mortality rates in elderly PUBS patients.

Fever is one of the typically objective signs of CA-UTI, but the elderly tend to have subtle clinical signs when they encounter infectious diseases. In our study, the elderly group had significantly lower rates of fever (8.2% vs. 27.8%, p = 0.015). Some of the major factors include immunoscenescence (declining humoral and cell-mediated immune function)[12] and poor nutritional state. A retrospective chart review study shown that febrile responses may be subtle in up to 47% of elderly septic patients.[13] Although fever and leukocytosis are early signs of UTI, these may be subtle in the elderly group. These can later present as hypotension, which is very severe and is associated with rapid progression to septic shock.[12,14,15] Our study also showed lower rates of fever and shock in the elderly group (8.2% vs. 27.8%, p = 0.02, 6.1% vs. 22.2%, p = 0.03), but there were no significant differences in mortality (5.1% vs. 16.7%, p = 0.08).

Chronic kidney disease (CKD) was shown to be a risk factor for PUBS in a small cohort study of Taiwanese patients.[16] The serum and urine levels of IS increased markedly in patients who had chronic kidney disease or who were undergoing dialysis because of impaired renal function.[17] Other comorbid factors including diabetes, dementia, and iron deficiency anemia (IDA) which have all been described as independent risk factors for ABU and UTI.[18,19]

Doctor Chant reported an association between CA-UTI and prolonged length of stay (more 13 days of LOS) in acute care facilities,

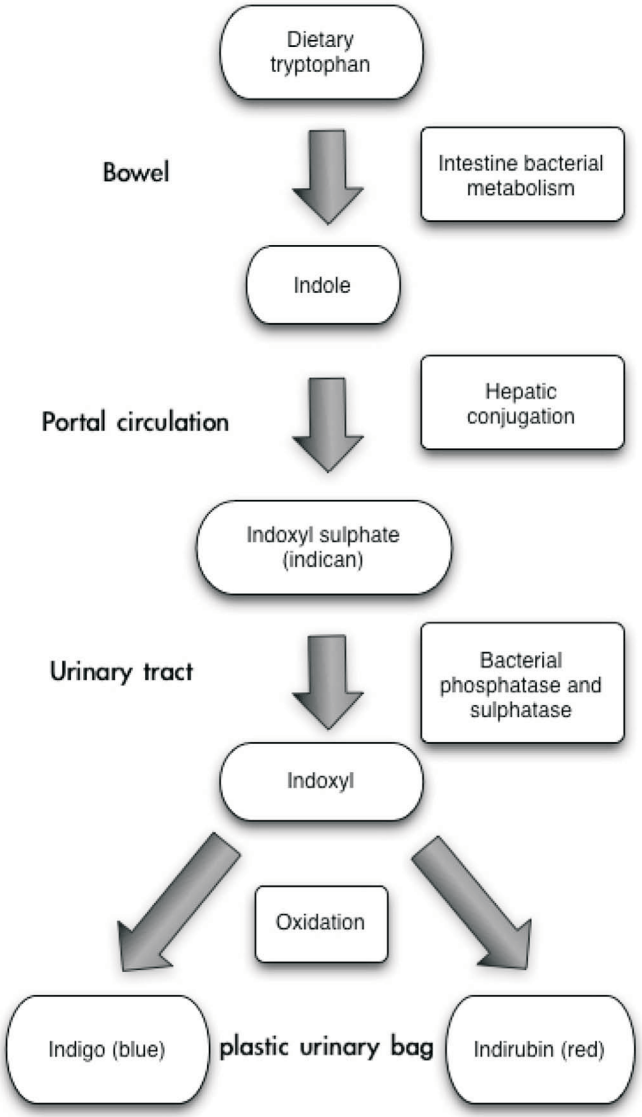

Fig. 2. Mechanism of purple urine bag syndrome.

and these associations are likely related to higher mortality.[20] It has been reported that PUBS can progress to Fournier's gangrene in immunosuppressed patients, with increased rates of morbidity and mortality.[21] Nevertheless, in uremic patients with PUBS, the removal of IS during dialysis is limited because it is bound to albumin, leading to an exponential increase in serum indoxyl sulphate concentration.

Thus, when treating CKD patients with PUBS, clinicians must always keep in mind the increasing serum and urinary concentration of IS, which are related to uremic toxin and are not only involved in the progression of CKD, but also lead to cardiovascular events.[22] We know that CA-UTI with comorbidities (uremia, immunocompromised state) worsens with PUBS and leads to a higher mortality rate. In our study, the elderly group had a lower prevalence of both diabetes and uremia (17.3% vs. 29.4%, p = 0.25; 17.9% vs. 23.5%, p = 0.58), whichwere correlated with lower mortality (5.1% vs. 16.7%, p = 0.08). Lower comorbidity rate in elderly PUBS patients compared to non-elderly ones seems to be a factor resulting in lower rates of urosepsis and mortality in the elderly group.

Female gender is a risk factor for UTI and PUBS. In our study, female gender was predominant in both groups without a significant difference. Mean urine pH value also shows an alkaline nature in both elderly and non-elderly PUBS patients, and it is compatible with the conclusions of previous studies that increments of urine alkalinity might facilitate indoxyl oxidation in the urinary tract.[23]

Constipation is considered to be a well-known risk factor for developing PUBS because it increases the time for bacterial deamination.[6] Our study also revealed similar results in that up to 71.6% of elderly PUBS cases had constipation. Conversely, there were only 33.3% non-elderly PUBS patients who had constipation.

There were 58.3% PUBS patients who lived in long-term care facilities. The proportion of patients living in long-term care units in elderly PUBS cases is higher (61.6%) than that in non-elderly cases (31.3%) but the difference is no statistically significant.

PUBS is thought to be the presence of UTI and in the majority of cases, were not severe. In our study, overall mortality was 6.8% and 5.1% in elderly group. Mortality in PUBS is lower than in adults with CA-UTI (10%).[24] Long-term follow up and prospective studies are helpful for further assessing the actual outcome in PUBS. As shown above, elderly PUBS patients should not be overlooked. In the early stages of UTI, symptoms might be subtle, but this might possibly progress to life threatening urosepsis. Timely parenteral antibiotic administration after bacterial culture is warranted to save lives in elderly PUBS patients.

Elderly patients with PUBS have significantly lower rates of urosepsis symptoms, such as fever and hypotension, without significant differences in mortality rate compared to the non-elderly group. From our study, we found that although PUBS used to be considered a benign process in the majority of indwelling catheterized patients. For clinically afebrile and normotensive elderly patients, physicians should refer patient's condition (consciousness, appetite), biomarker (C-reactive protein, procalcitonin) to prevent from devastating course. Physicians should not overlook those elderly PUBS patients who have no fever and are normotensive, because life threatening urosepsis can occur if they are not treated promptly.

This was a case-control study conducted by gathering data from the PubMed database. Incomplete or inadequate information on key clinical features may cause major inclusion bias, and confounding factors in prevalence calculation might be a major concern. A relatively small number of patients in PUBS studies also limited the accuracy of statistical analyses. However, there might still be cases treated by physicians all over the world that have not been reported in the PubMed database.

Funding statement

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Appendix A. Supplementary data

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