Trends in the epidemiology of purple urine bag syndrome: A systematic review

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Abstract. Purple urine bag syndrome (PUBS) is rarely observed in clinical practice. The present study aimed to identify the epidemiological trends in PUBS in recent decades. A search of PubMed articles published between 1980 October and 2016 August was conducted, in which 106 articles (174 cases) described PUBS. Of these cases, 58 cases were excluded: 14 cases without mention of gender, 4 cases without description of age, 37 cases without mention of white blood cell (WBC) count, shock status, fever status or description of etiology, and 3 cases without information on mortality. The remaining 116 PUBS cases were collected and analyzed in the present study. The articles were divided into three groups by publication year: 1991 to 2000, 2001 to 2010 and 2011 to 2016. The χ^2 test was used for statistical analysis, with P<0.05 (two-tailed) defined as the threshold for significance. Of the total enrolled cases, there were 47 men (40.5%) and 69 women (59.5%), with a mean age ± standard deviation of 75.6±12.8 years. Of these, 98 cases (84.5%) were elderly (≥65 years old). A total of 93.1% of cases had a urine pH >7 while 6.9% of cases had acidic urine (pH <7). Furthermore, although WBC count elevated progressively, the mortality rate of patients with PUBS decreased over subsequent decades. This necessitates the advancement of antibiotics and application of early goal-directed therapy. Additionally, the overall mortality rate of PUBS (1980-2016) was 6.8%, which decreased to 4.3% in the last 5 years (2011-2016). In conclusion, although PUBS has previously been considered a benign process in the majority of indwelling catheterized patients, emphasis is required on early examination and aggressive antibiotic administration.

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Introduction

Purple urine bag syndrome (PUBS) is an uncommon condition that occurs in urinary catheterized patients with urinary tract infection (UTI). It was first described in 1978, though a possible mechanism was not established until 1988 (1,2). With regard to the mechanism, tryptophan is metabolized by intestinal bacteria, after which the by-product indoxyl sulfate is expelled into the urine and digested into indoxyl by sulfatases/phosphatases produced by certain bacteria including *Escherichia coli (E. coli), Proteus mirabilis*, *Morganella morganii (M. morganii)*, *Klebsiella pneumoniae*, *Providencia stuartii*, *Providencia rettgeri* and *Pseudomonas aeruginosa* (2,3). This indoxyl may convert into indigo and indirubin in the urine drainage bag and create purple discoloration (2).

A higher prevalence of PUBS has been reported in females and in patients with alkaline urine, an indwelling urinary catheter and constipation (3). The majority of patients with PUBS are catheterized due to significant disability, typically being chair-bound or bed-bound elderly patients (3). In previous years, PUBS has been considered to be a benign syndrome rather than a disease with lethal potential, and appropriate empirical oral antibiotics including ciprofloxacin remain to be suggested for its treatment (3). To the best of our knowledge, there have been no previous studies on the clinicopathological or epidemiological trends of PUBS; therefore, the current study retrospectively reviewed PUBS cases for characteristic analysis. A systematic review of PUBS cases reported between October 1980 and August 2016 was conducted, in which data regarding patient age and gender, comorbidities (diabetes mellitus, uremia, constipation and residence in long-term care facility), vital signs (presence or absence of fever), laboratory tests results [seral white blood cell (WBC) count, urine pH value] and mortality were evaluated. This aimed to identify trends in the epidemiology of PUBS. Through the systematic approach, the different clinicopathological aspects and general trends of PUBS were determined.

Materials and methods

Search strategy and article selection. A systematic review was designed to investigate clinicopathological characteristics

in PUBS, including patient age and gender, urine pH value, presence of fever, shock (defined by hypotension), WBC count, constipation and comorbidities (diabetes mellitus, uremia), urine culture bacteriology, rates of patients in long-term care units and mortality. To determine the trends in the epidemiology of PUBS, the differences in these characteristics over three decades were also analyzed. A search was performed for articles in the PubMed database (https://www.ncbi.nlm.nih.gov/pubmed/) including the word 'purple urine bag syndrome' in the title, published in the period from January 1, 1980 to September 1, 2016. A total 106 relevant articles were identified. Of these, 33 articles were excluded owing to ineligibility or lack of essential information. The full exclusion criteria are depicted in (Fig. 1). Therefore, 71 articles with patient data on 116 cases (4-74) were collected for review (Table I). The articles were divided into three groups by publication year: 1991 to 2000, 2001 to 2010 and 2011 to 2016. The following clinical features were defined as: i) Elderly patients: age ≥65 years old; ii) fever: body temperature ≥38˚C; iii) hypotension: systolic blood pressure <90 mmHg or diastolic blood pressure <60 mmHg.

Statistical analysis. The data was analyzed with SPSS statistical software for Windows, version 11.5 (SPSS Inc., Chicago, IL, USA). Values are presented as the mean ± standard deviation. Statistical χ^2 tests were performed and the threshold for significance was set at P<0.05 (two-tailed).

Results

Description of the selected articles. In the present study, 106 relevant articles were retrieved. Following application of the inclusion and exclusion criteria, 71 eligible articles (4-74) were selected (57 in English, 4 in French, 3 in Spanish, 3 in Japanese, 1 in Chinese, 1 in German, 1 in Icelandic and 1 in Czech; Fig. 1 and Table I). All the selected articles were images in clinical medicine, individual case reports or serial case reports. The 71 articles included a total of 116 PUBS cases aged from 36 to 100 years old with a mean age ± standard deviation of 75.6±12.8 years. Of these, 47 cases were male (40.5%) and 69 were female (59.5%). Of these, 98 cases (84.5%) were elderly (≥65 years old).

Clinical characteristics in PUBS. The mean age of the patients was 75.6 years old, and PUBS was more commonly observed in females than in males (1.5:1 ratio). As PUBS is associated with infectious pathology, mean WBC was determined for the cases, which was elevated to 12,242 cells/μl. Only 11.8% of cases presented with fever, and 8.6% of cases with shock. There were 6.9% of cases with acidic urine (pH<7), while the remaining cases (93.1%) had urine pH>7. The majority of cases (69.8%) had constipation, and 58.3% lived in long-term care units. Regarding chronic co-morbidity, 19.2% of cases had diabetes mellitus and 18.8% were uremic patients. Overall mortality rate was 6.8%, thus indicating that PUBS may be associated with patients' mortality and not always a benign process.

Clinical characteristics in trend per decade of PUBS cases. Regarding patient age, urine pH value, the presence of fever, shock or uremia, a history of diabetes, and residence in a long-term care unit, there were no significant changes over subsequent decades among the PUBS cases (Table II). However, an increase in WBC count from 2001-2010 to 2011-2016 (P=0.002; Table II), and in the male: female ratio with each decade (P=0.018; Table I and Fig. 2) were identified. Notably, WBC count reached 17,060±14,480 cells/μl in the most recent five years. Conversely, decreases in constipation rates (P=0.011; Table II) and mortality rates (P=0.001; Table II and Fig. 3) were also identified over the subsequent

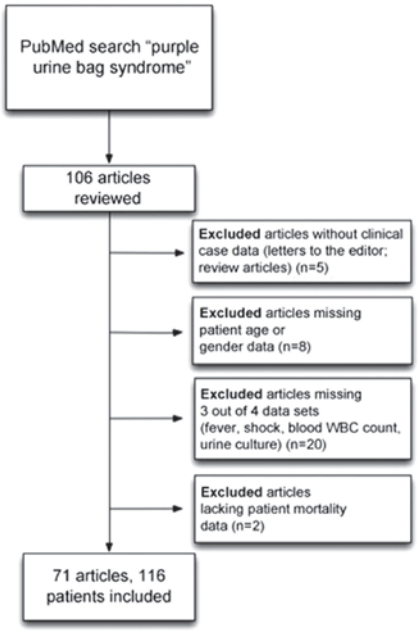

Figure 1. Study inclusion process and enrollment criteria.

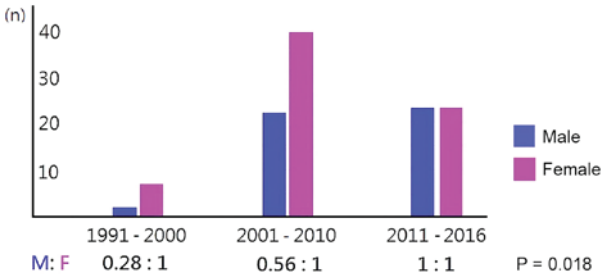

Figure 2. Male to female ratio of purple urine bag syndrome cases per decade.

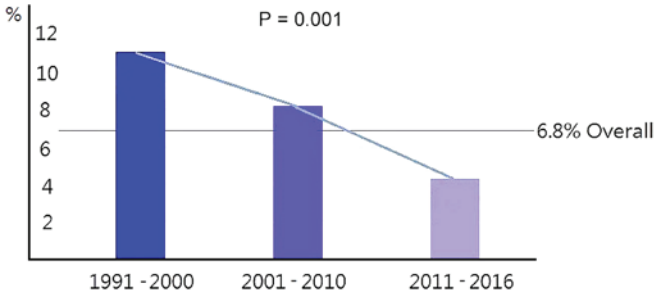

Figure 3. Mortality rate of purple urine bag syndrome cases per decade.

Table I. Case demongraphics of the 71 articles included in the present study.

Author	Year	Language	Country	Cases	Mean age ± SD (years old)	Refs.
Umeki	1993	Japanese	Japan	4	80±1.41	(4)
Nobukuni *et al*	1995	Japanese	Japan	5	60.4±10.61	(5)
Al-Jubouri and Vardhan	2001	English	UK	1	85	(6)
Ihama and Hokama	2002	English	Japan	1	93	(7)
Vallejo-Manzur *et al*	2005	English	USA	1	72	(9)
Wang *et al*	2005	English	Taiwan	2[a]	61	(10)
Rohaut *et al*	2005	French	France	1	81	(8)
Achtergael *et al*	2006	English	Belgium	1	77	(11)
Beunk *et al*	2006	English	UK	1	84	(12)
Tang	2006	English	Hong Kong	2	76±8.49	(13)
Su *et al*	2007	English	Taiwan	1	61	(20)
Nair *et al*	2007	English	UK	1	83	(18)
Bar-Or *et al*	2007	English	USA	1	68	(14)
Gautam *et al*	2007	English	India	1	70	(15)
Ting *et al*	2007	English	Taiwan	1	72	(21)
Lazimy *et al*	2007	French	France	1	74	(17)
Harun *et al*	2007	English	Brunei	2	60±21.21	(16)
Pillai *et al*	2007	English	UK	1	76	(19)
Lin *et al*	2008	English	Taiwan	10	75.3±2.12	(24)
Chiang *et al*	2008	Chinese	Taiwan	1	73	(22)
Chung *et al*	2008	English	Taiwan	1	85	(23)
Vidarsdottir *et al*	2008	Icelandic	Iceland	1	72	(27)
Shiao *et al*	2008	English	Taiwan	14	80.9±11.5	(26)
Muneoka *et al*	2008	Japanese	Japan	6	87.7±16.26	(25)
Tasi *et al*	2009	English	Taiwan	2	64±19.8	(30)
Al-Sardar and Haroon	2009	English	UK	1	82	(28)
Wu *et al*	2009	English	Taiwan	1	95	(32)
van Iersel and Mattijssen	2009	English	Netherlands	1	72	(31)
Pillai *et al*	2009	English	Singapore	1	69	(29)
Ferrara *et al*	2010	English	Italy	1	81	(33)
Hirzallah and D'Souza	2010	English	Jordan	1	78	(34)
Siu and Watanabe	2010	English	USA	1	48	(35)
Su *et al*	2010	English	Taiwan	1	81	(36)
Kang *et al*	2011	English	Korea	3	74.7±0	(37)
Keenan and Thompson	2011	English	USA	1	97	(38)
Khan *et al*	2011	English	USA	1	39	(39)
Peters *et al*	2011	English	Australia	1	82	(40)
Zeier *et al*	2011	English	Singapore	1	75	(41)
Bocrie *et al*	2012	English	France	1	87	(42)
Cantaloube *et al*	2012	French	France	2	81.5±0.71	(43)
Dominguez Alegria *et al*	2012	Spanish	Spain	1	78	(44)
Meekins *et al*	2012	English	USA	1	67	(45)
Montasir and Mustaque	2013	English	Bangladesh	1	86	(46)
Bhattarai *et al*	2013	English	USA	1	87	(47)
Canavese *et al*	2013	English	Italy	3	79±19.52	(48)
Duff	2013	English	USA	1	57	(49)
Iglesias Barreira *et al*	2013	Spanish	Spain	2	93.5±2.12	(50)
Mohamad and Chong	2013	English	Brunei	1	78	(51)
Ungprasert *et al*	2013	English	USA	1	44	(52)
Wolff *et al*	2013	French	France	1	90	(53)
Yaqub *et al*	2013	English	Pakistan	1	83	(54)
Agapakis *et al*	2014	English	Greece	1	82	(55)

Table I. Continued.

Author	Year	Language	Country	Cases	Mean age ± SD (years old)	Refs.
Chassin-Trubert *et al*	2014	Spanish	Chile	1	72	(56)
Delgado *et al*	2014	English	Mexico	1	60	(57)
Hloch *et al*	2014	Czech	Czech Republic	1	73	(58)
Restuccia and Blasi	2014	English	Italy	1	81	(59)
Sheehan	2014	English	USA	1	80	(60)
Abubacker *et al*	2015	English	India	1	36	(61)
Alex *et al*	2015	English	India	1	83	(62)
Karim *et al*	2015	English	USA	1	83	(63)
Kenzaka	2015	English	Japan	1	72	(64)
Mohamed Faisal *et al*	2015	English	Malaysia	1	68	(65)
Mondragon-Cardona *et al*	2015	English	Colombia	1	71	(66)
Neweling and Janssens	2015	German	Germany	1	78	(67)
Redwood *et al*	2015	English	USA	1	90	(68)
Van Keer *et al*	2015	English	Belgium	2	80.5±0.71	(69)
Demelo-Rodriguez *et al*	2016	English	Spain	1	83	(70)
Faridi *et al*	2016	English	India	1	76	(71)
Richardson-May	2016	English	UK	1	94	(72)
Sriramnaveen *et al*	2016	English	India	1	85	(73)
Tul Llah *et al*	2016	English	USA	1	52	(74)

[a]The same patient with two purple urine bag syndrome episodes. SD, standard deviation.

decades. These decreasing rates may be attributed to advancements in antibiotic treatment and the application of early goal-directed-therapy (EGDT).

Bacteriology statistics. Bacterial species identified in urine cultures of the PUBS patients are listed in Table II. Culture results were not available for 9 cases, and there was no bacteria growth for 2 cases. Among the 105 patients with positive results, 3 patients yielded unidentified mixed organisms. The top five most common bacterial species identified were *E. coli*., *Enterococcus spp*., *Proteus spp*., *M. morganii* and *Klebsiella spp*.

Discussion

It is well established that urinary tract infection (UTI) may occur at variable ages, while PUBS is commonly observed in elderly compared with non-elderly patients (3), as in the present report (84.5 vs. 15.5%). As we know, PUBS can be observed in sepsis of asymptomatic bacteriuria (ABU) or CA-UTI.

The mechanism of PUBS originates from the dietary digestion and absorption of tryptophan in the bowel. Bacteria in the intestine metabolize the tryptophan to indole, and further hepatic enzymes form the conjugate indoxyl sulfate for secretion into urine by the kidneys. In the urinary tract, gram-negative bacteria phosphatases and sulfatases metabolize the indoxyl sulfate to indoxyl, and through oxidation, this may convert to indigo and indirubin (2). For patients with indwelling catheters, blue indigo deposited on the urine drainage bag surface and red indirubin dissolved in the urine mixes into a purple discoloration (2). A previous study demonstrated that not all bacterial organisms of the same species produce the phosphatase and sulfatase enzymes (2). Based on the above mechanism, bacteriuria should be present in all patients with PUBS, which should be diagnosed as ABU for those without clinical symptoms or signs including fever or shock. A case control study reported that bacterial counts in urine were significantly higher (by 1 to 2 logs) in patients with PUBS compared with those without the syndrome, thus suggesting that a higher bacterial load in the urine is an important factor leading to PUBS (75).

Regarding gender, females are generally more vulnerable to UTI and PUBS, and female gender has been previously considered a risk factor of catheter-associated (CA)-UTI among urinary catheterized patients (76,77). In the present study, the number of PUBS cases became equal between the genders within the most recent 5 years. A similar finding was observed in a recent prospective observational study performed between November 2011 and October 2013 (78). This study analyzed the incidence of healthcare-associated urinary tract infections in patients admitted to the urology ward of University Hospital 12 de Octubre in Spain with an indwelling urinary catheter. The incidence of CA-UTI in males vs. females was 8.22 vs. 8.46% without significant difference (78). The study also analyzed the four most frequently cultured bacteria species in CA-UTI (*E. coli*, *Enterococcus*, *Klebsiella*, *Pseudomonas*) and identified no significant difference between genders. The diversities in the results of these studies results may be affected by other unidentified factors, including urinary catheter management or personal hygiene influence.

In accordance with PUBS being associated with infectious pathology of the urinary tract, the mean WBC count of all reviewed cases was elevated to 12,242/μl. Furthermore, WBC

Table II. Comparisons of purple urine bag syndrome cases (n=116) over the last three decades.

Characteristics	Total period, mean ± SD or % (total cases, n)	Decade, mean ± SD or % (total cases, n)			P-value (two-tailed)
		1991-2000	2001-2010	2011-2016	
Age	75.6±12.8 (116)	69.1±13.1 (9)	75.9±11.3 (59)	75.8±16.8 (48)	0.857
Mean WBC count, cells/μl	12,242.7±10,661.5 (27)	NA	9,203.3±3,736.7 (15)	17,060.0±14,480.4 (12)	0.002
Urine pH value	8.0±0.9 (72)	8.1±0.7 (6)	8.0±0.9 (36)	8.0±1.1 (30)	0.368
Male: female	47:69 (116)	2:7 (9)	22:39 (61)	23:23 (46)	0.018
Fever	12.1 (14/116)	22.2 (2/9)	9.8 (6/61)	13.0 (6/46)	0.360
Shock	8.6 (10/116)	0.0 (0/9)	9.8 (6/61)	8.7 (4/46)	0.418
Constipation	69.8 (44/63)	100.0 (4/4)	68.4 (26/38)	66.7 (14/21)	0.011
Diabetes mellitus	19.2 (19/99)	11.1 (1/9)	25.6 (11/43)	14.9 (7/47)	0.266
Uremia	18.8 (21/112)	11.1 (1/9)	20.0 (12/60)	18.6 (8/43)	0.267
Long-term care unit	58.3 (35/60)	NA	60.0 (27/45)	53.3 (8/15)	0.057
Mortality	6.8 (8/116)	11.1 (1/9)	8.2 (5/61)	4.3 (2/46)	0.001

WBC, white blood cell; NA, not available; SD, standard deviation.

count significantly increased with time between 2001-2010 and 2011-2016.

There were 11.8% of PUBS cases presenting with fever and 8.6% of cases presenting with hypotension without significant difference between the decades. A total of 58.3% of subjects lived in long-term care units, and 19.2% had a history of diabetes. Urine pH value was the most stationary variable in each decade, varying between 8.0 and 8.1, which is compatible with the recognized conclusion from studies on PUBS: That PUBS more readily occurs in alkaline over acidic urine (2-4).

A small cohort study of Taiwanese patients demonstrated chronic kidney disease (CKD) to be a risk factor for PUBS (79). The serum and urine levels of indoxyl sulfate are increased markedly in patients with chronic kidney disease or in those undergoing dialysis due to impaired renal clearance (80). In the present study, 18.8% of PUBS cases had a history of uremia. Previous studies have also indicated comorbid conditions including diabetes mellitus, dementia and iron deficiency anemia are independent risk factors for ABU and UTI (80,81).

It has previously been concluded there is an association of CA-UTI with increased mortality rate and prolonged length of stay in acute care facilities (82). Furthermore, for PUBS involving Fournier's gangrene in immunosuppressed patients, the morbidity and mortality rates were increased (30). Nevertheless, in uremic patients with PUBS, the elimination of indoxyl sulfate during dialysis is limited as it is bound to albumin, leading to exponential increase in serum indoxyl sulfate concentration. When treating patients with CKD and PUBS, clinicians should consider the elevated serum and urinary concentration of indoxyl sulfate due to its potential role in the progression of CKD, as well as its contribution to cardiovascular events (57).

Constipation is considered to be a predisposing factor in PUBS due to the increased time it elicits for bacterial deamination. In the present study, constipation rate significantly decreased after 2001, though this may have been an artifact based on the relatively small number of cases reported in the decade of 1991-2000.

Table III. Urine culture data of purple urine bag syndrome patients.

Bacteria	Cases, n	%
Escherichia coli	41	23.0
Polymicrobial	36	20.2
Enterococcus spp	22	12.4
Proteus spp	16	9.0
Morganella morganii	15	8.4
Klebsiella spp	15	8.4
Providencia rettgeri	13	7.3
Pseudomonas aeruginosa	11	6.2
Streptococcus spp	4	2.2
Unidentified mixed organisms	3	1.7
Staphylococcus spp	2	1.1
Total	142	100.0

Polymicrobial indicates ≥2 bacterial species.

Overall mortality rate was 6.8%, thus indicating that PUBS is not always a benign process. However, mortality rate declined with time over the three decades, concordant with the introduction of EGDT for severe sepsis in 2001 (83). Therefore, this progress may be attributed to the new recommendation of EGDT, which may achieve aggressive correction of septic shock when combined with early appropriate antibi-

otic administration. Nonetheless, the mortality rate of patients with severe sepsis declined following the implementation of EGDT (84-87). A recent meta-analysis study also concluded that important factors contributing to improved outcome are time-to-first antibiotic administration and appropriate antibiotic use (88).

In conclusion, the ratio of males: females with PUBS increased over recent decades. Therefore, the urine color in catheterized patients should be monitored not only in female but also male patients. PUBS may not always be a benign process, and emphasis is required on early examination and aggressive antibiotic administration. Although WBC count was elevated over the recent decades, the morality rate was lowest in the most recent five years and decreased by decade; the overall mortality rate was 6.8%, and lowered to 4.3% in the last five years.

This was a case-controlled study that searched relevant articles in the PubMed database. A limitation of this may have been the exclusion of cases based on inadequate information, leading to bias and introducing confounding factors. Furthermore, the relatively small number of PUBS studies in each decade may have limited the accuracy of statistical analyses. There may also be cases of PUBS unreported in the PubMed database which were unaccounted for.

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Availability of data and materials

The analyzed data sets generated during the study are available from the authors on reasonable request.

Authors' contributions

The final version of the manuscript has been read and approved by all authors. YHW collected the data and wrote the draft. SYJ planned and revised the study and is the primary correspondent.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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