

Risk factors of mortality in patients with purple urine bag syndrome

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ABSTRACT

Aim: Purple urine bag syndrome (PUBS) is rarely seen in clinical practice. Several studies have reported that PUBS is relatively benign in its clinical course, but this study aimed to identify risk factors for mortality related to PUBS.

Materials and methods: In a PubMed search from October 1980 to August 2016, using the search term “Purple urine bag syndrome (PUBS)”, 106 articles (n = 174 cases) were identified. This study excluded 58 cases. Among them, 14 cases did not include information on patient sex and four cases did not include information on patient age. Thirty-seven cases did not report the white blood cell (WBC) count, shock, fever, or etiology. Three cases did not report patient survival. This study considered 116 PUBS cases. Chi-square tests were used to compare the survival and mortality groups.

Results: In relative risk analysis, uremia (17.8), shock (14.4), diabetes (4.8), leukocytosis (1.1), and female sex (1.1) were significant risk factors for mortality after PUBS. However, it is possible that PUBS cases are under-reported worldwide.

Conclusions: PUBS is a warning sign of a urinary tract infection, and it often follows a relatively benign clinical course. This study found that female sex, leukocytosis, shock at presentation, comorbidity with diabetes, and uremia are risk factors for mortality associated with PUBS.

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Introduction

Purple urine bag syndrome (PUBS) was first described in 1978¹. It is very rarely seen in clinical practice and is indicative of urinary tract infection (UTI)². It occurs when a decrease in bowel motility causes bacterial overgrowth in the intestine, leading to increased metabolism of tryptophan to indole, resulting in high levels of indigo and indirubin in the urine^{3–11}. The majority of PUBS patients are bed ridden, primarily female, with an indwelling urinary catheter, experiencing constipation and a UTI with a urine alkaline pH^{3–5,8–12}. Most studies have reported that PUBS is benign, harmless, and even asymptomatic^{3,4,7,13}. However, there are some reports that it does not always have a harmless course¹². We aimed to identify the risk factors for mortality associated with PUBS. We collected all PubMed articles describing PUBS from October 1980 to August 2016 in order to analyze the risk of mortality after experiencing PUBS. We have adopted items that related to comparability and adjustment (which are not associated with studies) and retained items that focused on our selection, representativeness of cases, and ascertainment of exposure and outcomes¹⁴.

Materials and methods



In our PubMed search from October 1980 to August 2016 for “Purple urine bag syndrome (PUBS)”, we identified 106 articles

(174 patients). We excluded 58 cases of PUBS. Among these, 14 studies did not describe patient sex, and age was not reported in four cases. Thirty-seven studies did not report the white blood cell (WBC) count, shock, fever, or etiology. Three studies did not report survival data. We finally included 116 PUBS cases (Figure 1). We recorded age, sex, the presence of fever, shock, WBC count, urine pH, indwelling urinary catheter status, constipation, nursing home residency, history of diabetes, history of uremia, diabetes mellitus (DM), culture results from urine and blood and survival. We defined shock as the systolic blood pressure < 90 mmHg. Nursing home residency was defined as patients who lived in a home care unit rather than their home.

Comparisons are made between survival group and mortality group, and relative risks to mortality are also analyzed. Chi-square tests were used to compare the survival and mortality groups. Data were analyzed using IBM SPSS Statistics v. 20, 2011 (New York, NY).

Results

Female sex, higher WBC count, presenting with shock, a history of diabetes, and uremia were risk factors significantly correlated with mortality. However, age, urine pH values, fever, indwelling urinary catheter, constipation, and nursing home

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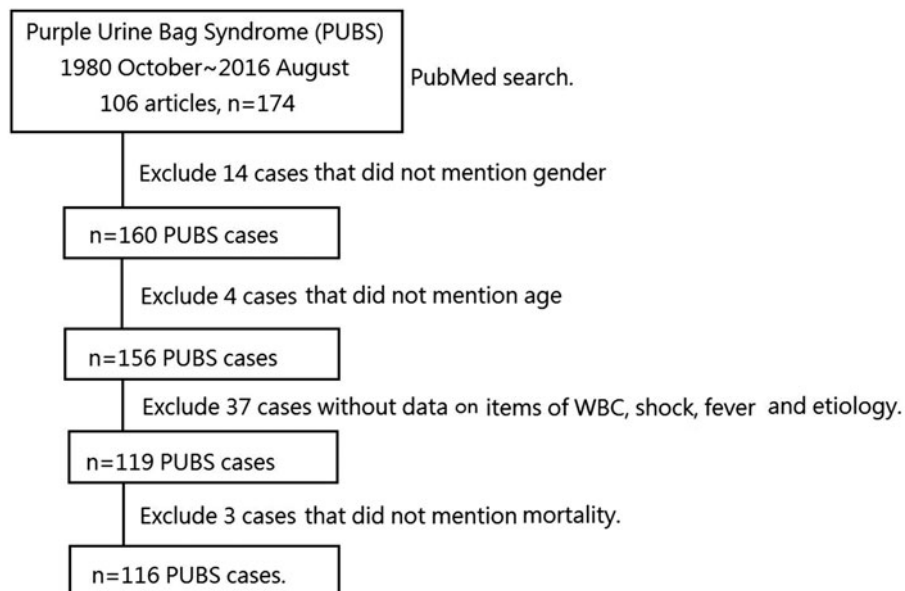


Figure 1. The process of enrolling 116 purple urine bag syndrome (PUBS) cases.

Table 1. Comparison between survival and mortality cases in PUBS.

Group (n, %)	Enrolled (116, 100%)	Survival (108, 93.1%)	Mortality (8, 6.9%)	Two-tailed <i>P</i>
Male:Female	47:69	44:64	3:5	0.043
Age (years)	75.5 ± 12.8	76.1 ± 12.5	69.3 ± 15.9	0.775
WBC (/μL)	12,695 ± 10,586	9999 ± 5790	14,120 ± 2934	0.009
Urine pH	8 ± 0.9	8 ± 0.9	8 ± 0.7	0.670
Fever	13/116, 11.2%	11/108, 10.2%	2/8, 25%	0.441
Shock	10/116, 8.6%	4/108, 3.7%	6/8, 75%	0.001
Indwelling urinary catheter	113/116, 97%	106/108, 98%	7/8, 88%	0.977
Constipation	45/116, 39%	43/108, 40%	2/8, 25%	0.845
Nursing home resident	35/57, 61%	33/53, 63%	2/4, 50%	0.970
DM	22/116, 19%	15/108, 14%	4/8, 50%	0.044
Uremia	21/116, 18%	15/108, 14%	6/8, 75%	0.010

Abbreviations. DM, diabetes mellitus; PUBS, Purple Urine Bag Syndrome; WBC, White Blood-cell Count.

Table 2. Relative risk of sex, white blood cell count, presentation of shock, diabetes, and uremia for mortality of PUBS patients.

Mortality rate	(n/N, %)	(n/N, %)	Relative risk (95% CI)
Gender	Men (3/47, 6.4%)	Women (5/69, 7.2%)	1.1 (0.26–5.0)
WBC count	Normal WBC (0/11, 0%)	Elevated WBC (8/105, 7.6%)	1.1 (1.03–1.1)
Diabetes mellitus	No DM (4/91, 4.4%)	DM (4/19, 21%)	4.8 (1.3–17.5)
Shock	No shock (4/96, 4.2%)	Shock (6/10, 60%)	14.4 (4.9–42.6)
Uremia	No uremia (2/91, 2.2%)	Uremia (6/21, 28.6%)	17.8 (3.3–96.6)

Abbreviations. 95% CI, 95% confidence interval; *n*, number of mortality cases; *N*, all PUBS cases; PUBS, purple urine bag syndrome; WBC, white blood-cell count.

Table 3. List of pathogens in all PUBS cases and fatal PUBS cases.

	Overall	Mortality group
<i>Escherichia coli</i>	28%	27%
Mixed infection	18%	13%
<i>Enterococcus faecalis</i>	13%	13%
<i>Proteus spp.</i>	9%	13%
<i>Morganella morganii</i>	9%	13%
<i>Klebsiella spp.</i>	9%	0%
<i>Providencia rettgeri</i>	8%	13%
<i>Pseudomonas aeruginosa</i>	6%	7%
<i>Streptococcus spp.</i>	2%	0%
<i>Staphylococcus spp.</i>	1%	0%

residency did not influence mortality. Mortality from PUBS was correlated with female sex and presence of sepsis, shock, diabetes, and uremia (Table 1). Sepsis is defined as a WBC count >12,000/μL or <4000/μL with immature form above 10%.

In relative risk (RR) analysis, uremia (17.8), shock (14.4), diabetes (4.8), leukocytosis (1.1), and female sex (1.1) were all significant risk factors for mortality after PUBS (Table 2). We listed the pathogens of all PUBS cases and those from the mortality group in Table 3. Among these, eight died of sepsis (mortality rate =7%).

Discussion

UTI is one of the most common infectious diseases in adults, and 40–50% of women experience >1 UTI in their lifetime¹⁵. In urological or emergency daily practice, many different stages of UTI might be seen. It could be asymptomatic UTI (bacteriuria), pyelonephritis, cystitis in female patients, prostatitis in male patients, or a catheterized febrile patient.

PUBS may present with one of the clinical aspects of UTI's as above.

Age and gender

PUBS is a warning sign of UTI². It is more commonly seen among women. In a Mexican study, 73% of PUBS cases occurred among women¹⁰. In our study, 60% of PUBS cases occurred among women, and the mean age was 75.5 years, indicating that PUBS is most often seen in elderly women.

Laboratory tests

PUBS is a sign of UTI, and the mean white blood cell (WBC) count in our study reached 12,695/ μ L. Red and white blood cells lyse when the urine pH is >6 , and a urine pH > 7.5 indicates a UTI¹⁵. So, PUBS is easily overlooked in clinical practice when the red and white blood cells are lysed. In our study, the mean urine pH in PUBS cases was 8, consistent with most articles reporting that PUBS cases are associated with alkaline urine. However, there have been cases with acidic urine¹⁶. There was no difference in urine pH between the surviving PUBS cases and the mortality group in our study (8 ± 0.9 vs 8 ± 0.7 , $p = 0.67$). Presentation with fever, an indwelling urinary catheter, constipation, and living in a long-term care unit are all predisposing factors not leading to mortality in cases of PUBS.

Constipation

Around 50% of older people living in nursing homes experience chronic constipation¹⁷. Chronic constipation is thought to be one of the factors leading to PUBS. It slows gut motility and changes intestinal bacterial flora. Bowel bacterial flora containing tryptophanase convert dietary tryptophan to indole, pyruvic acid, and ammonia^{3-5,8,10}. Indole is absorbed and enters the liver via the portal circulation. Indole is converted to indoxyl sulfate with both nephrotoxicity and cardiotoxicity¹⁸, and it is then catalyzed by bacterial phosphatases or sulfatases to indoxyl. In the urine, indoxyl is metabolized into two pigments, indigo (blue) and indirubin (red). Mixing of indigo and indirubin leads to purplish discoloration of the urine^{3,11}.

The reason why the majority of cases were not constipated may be that this information was not always recorded. There may also be other mechanisms responsible for this syndrome.

Pathogens

In cases of UTIs, women infected with *Escherichia coli* (*E. coli*) are often seen clinically¹⁹. The most commonly seen UTI pathogens are *E. coli* and *Klebsiella pneumoniae*. *E. coli* is the most commonly seen pathogen in UTI cases and in cases of fatality associated with UTIs²⁰.

In our study, the pathogens involved in PUBS were *E. coli* (28%), mixed microorganisms (18%), *Enterococcus faecalis* (13%), *Proteus spp.* (9%), *Morganella morganii* (9%), *Klebsiella spp.* (9%), *Providencia rettgeri* (8%), *Pseudomonas aeruginosa*

(6%), *Streptococcus spp.* (2%), and *Staphylococcus spp.* (1%). In our mortality group, the ranking of pathogens was similar to all cases: *E. coli* (27%), mixed microorganisms (13%), *E. faecalis* (13%), *Proteus spp.* (13%), *M. morganii* (13%), *P. rettgeri* (13%), and *P. aeruginosa* (7%). These findings suggest that the pathogen in PUBS is not one of the factors influencing mortality associated with PUBS.

The most common microorganism involved in PUBS is *E. coli*, mixed, *Enterococci*, and *Proteus spp.* *Enterococci* is highly associated with catheter-related UTIs, and *Proteus Spp.* is associated with patients who live in long-term care facilities. It is estimated that 63.6% of cases of enterococcal bacteremia occur after urinary catheter infection²¹. *K. pneumoniae* is commonly seen in catheterized patients or presents as a long-term hospitalized opportunistic infection²². Presence of an indwelling catheter and living in long-term care facilities are both predisposing factors for PUBS^{21,23}. *M. morganii* is an opportunistic infection often seen in post-operative wound and urinary tract infections²⁴.

Prognosis

Several studies describe PUBS as a benign process^{3,7,13}. In assessing the prognosis of catheterized urinary tract infections (CAUTIs), several risk factors, including female sex, emergency admission, and transfer from another healthcare facility are relevant²⁵. In another study from China, DM, prolonged catheter placement, and longer hospital and intensive care unit (ICU) stay were all high risk factors for mortality in CAUTIs²⁶. Patients with dementia or chronic kidney diseases may develop a bloodstream infection after urinary catheter placement²⁷. In our study, the RR of mortality in PUBS patients was significantly higher in cases presenting with shock (14.4), uremia (17.8), diabetes (4.8), leukocytosis (1.1), and of female sex (1.1). We should pay special attention to female patients with PUBS who are hypotensive, uremic, diabetic, and have leukocytosis. Age, urine pH, presence of fever, constipation, and nursing home residency were not associated with increased mortality.

Although most articles report PUBS as a relatively benign process, its mortality rate was 7% in our study, slightly higher than that of older people who develop a UTI (5%)²⁸. We conclude that not all PUBS cases are harmless in their clinical course, and we should pay more attention to patients who are female, have leukocytosis, and are uremic, diabetic, and hypotensive.

Our study has limitations. We collected all cases from PubMed. There is the possibility that PUBS cases are under-reported worldwide.

PUBS is a warning sign of UTI, and, although it often has a benign clinical course, we have found that women with leukocytosis who present with shock and have diabetes and uremia are at risk of mortality from PUBS. Prescribing antibiotic therapy after culture of urine or blood is mandatory to treat PUBS.

Transparency

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Declaration of financial/other relationships

The authors have no financial or other relationships to disclose. JDA peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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