Review

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Purple Urine Bag Syndrome: More Than Eyes Can See

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Key Words

Purple urine bag syndrome • Purple urine discoloration • Urinary tract infection

Abstract

Background/Aims: Purple urine bag syndrome (PUBS) is an uncommon clinical entity characterized by purple urine discoloration in the setting of urinary tract infections. Pathophysiology of PUBS has been correlated to aberrant metabolism of tryptophan. Multiple predisposing factors have been recognized, namely: female gender, advanced age, constipation, institutionalization, long-term catheterization, dementia and chronic kidney disease. Herein, we present a comprehensive review of all PUBS cases reported in PubMed, focusing on the predisposing factors and the microorganisms related to PUBS. ***Methods:*** We performed a search in PubMed database for articles referring to PUBS, published in English, French, Spanish and German from January 1978 until November 2017. The literature recruitment strategy was based on several keywords and Medical Subject Heading combination such as "purple urine bag syndrome" or PUBS or "urine discoloration". The finally selected articles were categorized into case reports/series (88 articles including 112 patients) and studies (10 articles including 134 patients). Demographical data as well as predisposing factors were recorded and further analyzed. ***Results:*** According to our findings, mean age of PUBS patients was 78.9 ± 12.3 years, 70.7% were female while 90.1% were suffering from constipation, 76.1% were in a bedridden situation, 45.1% were experiencing long-term catheterization, 42.8% had been diagnosed with dementia, 14.3% had recurrent urinary tract infections and 14.1% were chronic kidney disease patients. 91.3% of patients presenting with PUBS alkaline urine were observed while the most common microbe in urine cultures was *E. coli*. ***Conclusions:*** PUBS is considered benign process in the majority of catheterized patients. Clinicians should be aware of the syndrome that may indicate serious comorbidities.

Introduction

From ancient times, when Hippocrates was credited with being the original uroscopist, until the Victorian era, urine was used as the primary diagnostic tool [1]. Urinary color, smell, sediment even taste could provide important information related to several medical conditions. During the 7th century, the physician Theophilus Protospatharius presented the manuscript "De Urinis" which constituted the first publication exclusively on the subject of urine. The book described a range of urine discoloration and their clinical correlations [2]. In the 12th century, Gilles de Corbeil introduced the matula to assess color and clarity of urine under direct sunlight examination [1].

Urinary discoloration is generally due to changes in urochrome concentration associated with the presence of other pigments. A spectrum of urine colors can be seen

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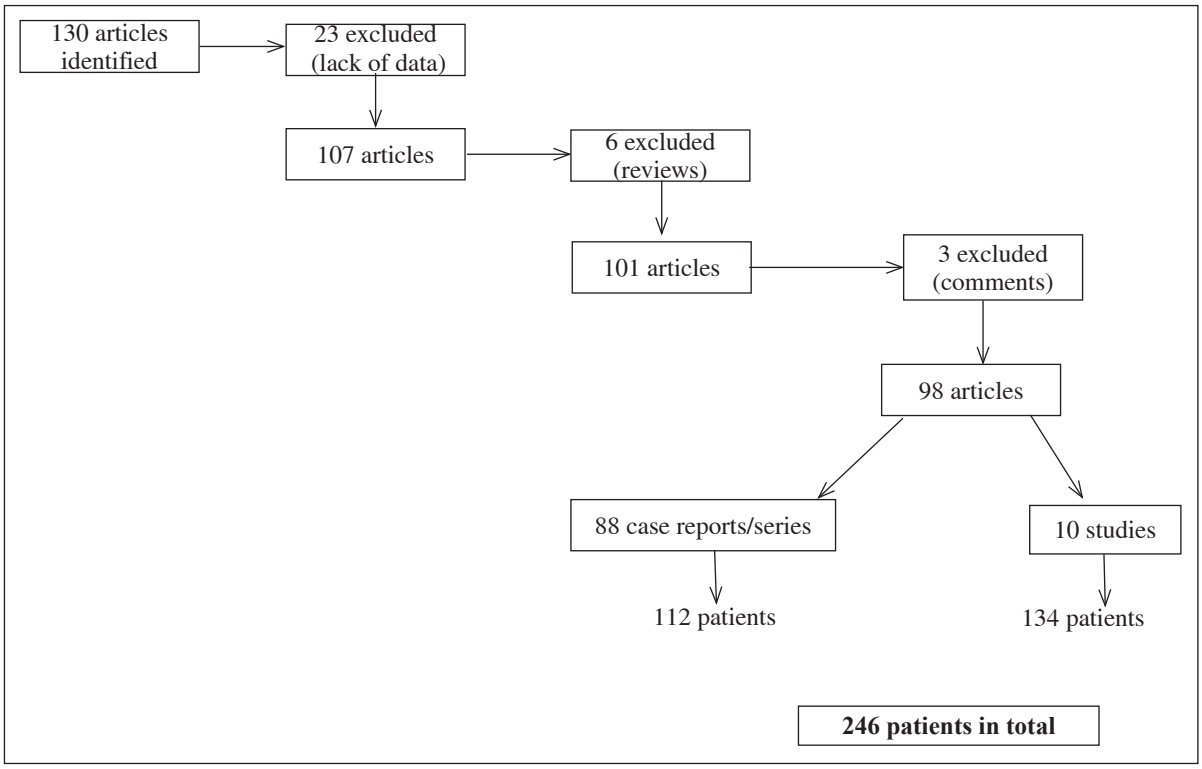

Fig. 1. Literature research process: flow chart.

in urine bags of hospitalized patients and may provide valuable information about presence of infections, medications, poisons, and hemolysis [3].

Urine discoloration is mostly benign, although worrisome to the patient. It usually resolves with removal of the offending agent. Purple urine bag syndrome (PUBS) is referred to a propitious condition caused by increased levels of indigo and indirubin, 2 pigments related to metabolism of the amino-acid tryptophan. Its existence is related mostly to urinary tract infections (UTI), even though other factors seem to play causative role. Among them the commonest are advanced age, female gender, constipation, dementia, bedridden situation, institutionalization, end-stage renal disease, dehydration, chronic catheterization, use of polyvinyl chloride urinary catheter or bag, recurrent UTI, high urinary bacterial counts and alkaline urine. Each factor is associated with PUBS appearance in the setting of certain pathophysiological procedures.

Herein, we present a comprehensive review of all cases of PUBS that are reported in the PubMed. The aim of our study is to record the prevalence of each predisposing factor and to further analyze the pathological mechanism through which the syndrome is manifested. Therefore, we can draw safe conclusions about its recognition and prevention.

Materials and Methods

Search Strategy

We performed a search with no date limits of the Medical Subject Heading (MeSH) terms "purple urine bag syndrome" or PUBS or "urine discoloration" in PubMed. Personal files and the bibliography of each identified report were also screened. Articles were selected for review if their title or abstract suggested that they reported individual patient or group data with diagnosis of PUBS.

Selection Criteria

For the final analysis, we selected reports or studies published as full length articles or letters, which included apparently individuals with PUBS. We exclusively retained well-documented original communications presenting subjects of both sexes and all ages. Reports published in English, Spanish, French or German were included. When more than one article reported on the same patient, only the more comprehensive one was retained. The diagnosis of PUBS was established according to the characterized urine discoloration.

Table 1. Characteristics of studies (n = 10)

Author	Year	Country or region	Type of study untry	PUBS patients, n	Mean age, year	Gender, M/F	Constipation, %	Dementia, %	CKD, %
Dealler et al.	1989	UK	Obs	7	84.8	0/7	100	100	NA
Mantani et al.	2003	Japan	C-C	14	78.9	2/12	NA	NA	NA
Su et al.	2005	Taiwan	Obs	13	79.3	2/11	84.6	100	NA
Ga et al.	2007	Korea	C-C	16	79.5	0/16	NA	NA	NA
Lin et al.	2008	Taiwan	Obs	10	75.3	5/5	30	90	30
Tsimura et al.	2008	Japan	C-C	5	66.6	5/0	100	NA	NA
Muneoka et al.	2008	Japan	Obs	6	87.7	3/3	100	NA	NA
Shiao et al.	2008	Taiwan	Obs	14	80.9	1/13	100	NA	NA
Yang et al.	2009	Taiwan	Obs	10	78.9	4/6	80	10	NA
Mumoli et al.	2013	Italy	Obs	41	78	11/30	80.5	61	60

Obs = Observational study; C-C = case control study; NA = not available.

Data Extraction and Analysis

From each report dealing with PUBS we recorded data on gender, age, risk factors such as dementia, alkaline urine, constipation, history of recurrent UTI, catheterization, institutionalization, existence of chronic kidney disease (CKD) and type of microbe. The literature search and the data extraction were performed independently by 2 investigators (E.P., N.S). Results are given either as frequency or as median.

Results

The literature search process is summarized in fig. 1. For the final analysis we selected 88 scientific reports [4–91] published between January 1978 and November 2017 in English (n = 74), Spanish (n = 7), French (n = 6) and German (n = 2). They had been reported from the following countries: the United States of America (n = 12), France (n = 8), Taiwan (n = 8), Spain (n = 7), Japan (n = 7), India (n = 6), United Kingdom (n = 5), Italy (n = 4), Belgium (n = 3), Mexico (n = 2), Malaysia (n = 2), Turkey (n = 2), Germany (n = 2), Pakistan (n = 2), Singapore (n = 2), Brunei (n = 2), Australia (n = 2), Portugal (n = 2), Brazil (n = 1), Colombia (n = 1), Chile (n = 1), Greece (n = 1), Bangladesh (n = 1), the Netherlands (n = 1), Austria (n = 1), Sweden (n = 1), Hong Kong (n = 1) and Canada (n = 1). We also extracted data from 10 studies [92–101] that conducted in Taiwan (n = 4), Japan (n = 3), Italy (n = 1), Korea (n = 1) and United Kingdom (n = 1) during the years 1989 to 2013 (table 1).

A total of 246 patients (112 case reports, 134 individuals in studies) affected with PUBS were included in the communications, ranging in age from 29 to 99 years (median 78.9 ± 12.3 years). Among them 29.3% were male and 70.7% female. The prevalence of alkaline urine was up to 91.3% (only 8 cases described to have acid urine).

Constipation was the main predisposing factor as it was observed in 90.1% of the cases and dementia was 42.8% (n = 48). A total of 76.1% of the patients were in a bedridden situation and 37.8% were institutionalized, while 45.9% of the patients experienced a long-term catheterization (> 3 months). There was a history of recurrent UTI in 16 patients (14.3%). In 4 cases, purple urine presented unilaterally in patients with bilateral nephrostomy, 2 patients presented with cystostomy and 5 with suprapubic catheter. Notably, 16 patients were under hemodialysis from a total number of 36 patients who referred with CKD. In 3 patients the syndrome resulted to septic shock and death.

Among the patients recorded (n = 112), all of them had evidence of UTI but only in 15 patients fever was noticed (13.4%). In 92 patients (82.1%) the responsible microbe was identified in a urine culture; 30.4% (n = 28) of them reported with mixed (> 2 microbes) culture while 69.6% (n = 64) reported with only one bacteria. The most common microbes identified as the causes of UTI related to PUBS were: *Escherichia Coli, Proteus Mirabilis, Klebsiella Pneumoniae, Enterococcus, Pseudomonas Aeruginosa, Providencia Stuartii, Morganella Morgannii, Proteus Vulgaris, Providencia Rettgeri, Streptococcus Faecalis, Enterobacter Cloacae* etc. (table 2).

Discussion

PUBS represents an alarming and distressing condition that is characterized by purple urine discoloration (fig. 2). This clinical entity was firstly referred in 1978 [102]. The estimated prevalence ranges from 8.3 to 42.1% in different series regarding hospitalized patients [97, 99,

Table 2. Percentage of type of microbes

Type of Microbe	Percentage (%)
Escherichia Coli	20.8
Proteus Mirabilis	16.2
Klebsiella Pneumoniae	13.6
Enterococcus spp	9.1
Pseudomonas Aeruginosa	9.1
Providencia Stuartii	5.8
Morganella Morgannii	5.2
Proteus Vulgaris	3.2
Providencia Rettgeri	2.6
Streptococcus Faecalis	2.6
Enterobacter Cloacae	1.9
Serratia Marcescens	1.9
Citrobacter Braakii	1.3
Alcaligenes spp	1.3
Citrobacter Freundii	1.3
Streptococcus Agalactiae	0.6
Citrobacter Diversus	0.6
Acinetobacter Baumannii	0.6
Klabsiella Oxytoca	0.6
Citrobacter Coser	0.6
Pseudomonas Testosterona	0.6

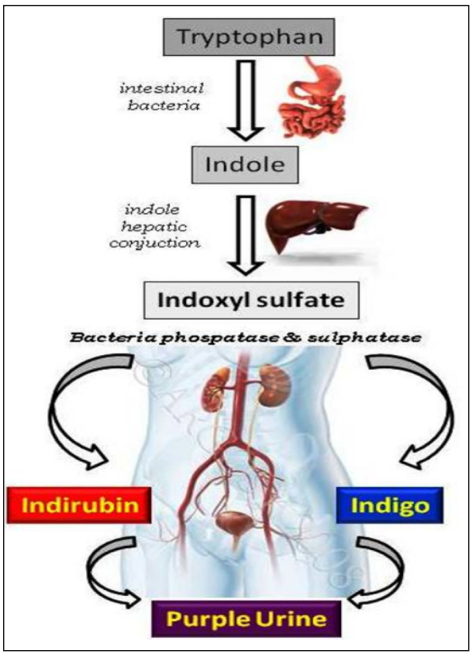

Fig. 3. Metabolism of tryptophan in pathophysiology.

Fig. 2. PUBS picture from personal files.

102] with increasing trends over the last few years [19]. The syndrome can be easily identified and treated but it remains a neglected entity, in spite of the fact that implies a considerable underlying pathology.

Pathophysiology is referred to a chain reaction regarding the metabolism of tryptophan that leads to urinary by-products: indirubin and indigo. Tryptophan is an α-amino acid used in the biosynthesis of proteins. This amino acid is transferred in the large intestine in order to be metabolized into indole by gut microbiota [103]. Afterwards it is diffused into the portal circulation and reaches the liver where it is converted into 3-hydroxyindole through cytochrome P450 2E1 (CYP2E1) [104]. Following that, 3-hydroxyindole is sulfonated through human liver SULT1A1 isoform, leading to indoxyl sulfate formation [105]. Indoxyl sulfate (indican) is excreted in the urine tract. There, under the influence of bacterial enzymes such as sulphatases and phosphatases, especially in an alkaline environment, indican formats 2 pigments: indirubin (red) and indigo (blue) [102]. The mixture of those 2 pigments is responsible for converting urine into purple (fig. 3).

The vast majority of patients with purple urinary catheter bags have been found to have increased levels of urinary indican [101]. Indican, which is a colorless organic compound, is soluble in water and can be easily detected through Obermeyer test [106]. It depicts a toxin that is overproduced under certain conditions such as bacterial overgrowth or altered microbiota (gut dysbiosis), and more specifically in a plethora of chronic diseases, namely, obesity, type 2 diabetes mellitus, chronic constipation, malabsorption syndromes and Parkinson's disease [107]. Nevertheless, there have been some reported

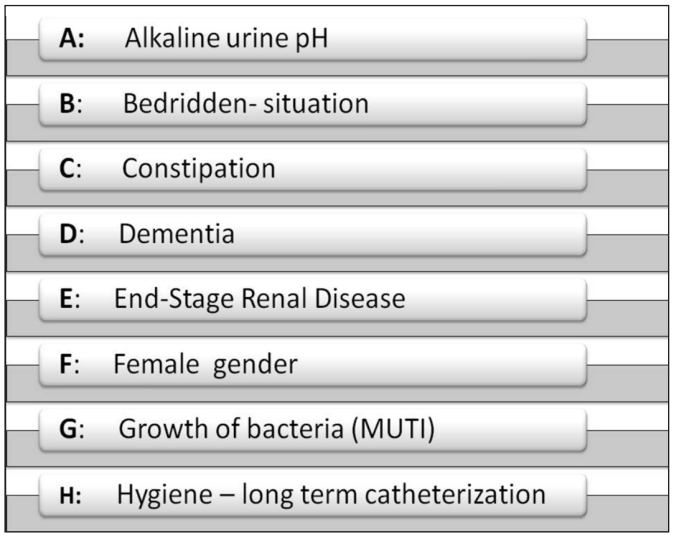

Fig. 4. The susceptible patient: The ABCDEFGH rule.

cases of PUBS that are presented without any evidence of indicanuria [87, 89]. In these cases the violet pigment in the urine is thought to be due to the activity of a steroidal or bile-acid conjugate [99].

Numerous factors have been associated with purple discoloration of urine. In accordance with our review, the most important are advanced age, female gender, constipation, dementia, bedridden situation, institutionalization, end-stage renal disease, dehydration, chronic catheterization, use of polyvinyl chloride urinary catheter or bag, recurrent UTI, high urinary bacterial counts and alkaline urine (fig. 4).

Regarding our research, PUBS affects patients with a mean age of 79 years. There are many reasons why elderly people are highly predisposed to the syndrome. Old age is associated with lots of comorbidities, among them dementia, constipation and renal failure can represent independent risk factors for PUBS [93]. Furthermore, lots of elderly people are immobilized or institutionalized, presenting high odds of long-term urinary catheterization. Chronic catheterization, especially when hygiene precautionary measures are not taken into account, is predisposed to UTI that may lead to PUBS [99, 100].

Usually this syndrome comes as a result of UTI even in the absence of dysuria or fever [108]. In these cases, urinary bacteria produce enzymes sulphatase/phosphatase that convert urinary indoxyl sulphate into idirubin and indigo, resulting in urine discoloration [102]. High urinary bacterial count represents an important risk factor according to Mantani et al. [100] who showed that there is a proportional tendency of discoloration of urine bags to the urinary bacterial yield. It is noteworthy that the presence of these bacteria in urine is not always associated with PUBS and no causative relationship between specific bacterial species and PUBS can be documented [100]. Nevertheless, the association between bacteria and PUBS cannot not be excluded since the purple discoloration usually resolves after antibiotics administration and urinary catheters replacement [86, 89, 109].

Most cases (91.3%) report PUBS in an alkaline urine environment. Unambiguously, alkaline environment is an important condition for the catalysis of indoxyl into indigo and indirubin [48]. However, alkaline urine is a promoting but not an obligatory requisition for PUBS since few reports of the syndrome have been exhibited in patients with slightly acidic urine (pH 6.0–6.5) [7, 29, 55, 66, 71, 75, 82, 100].

PUBS is frequently associated with constipation. According to our findings 90.1% of patients that presented with PUBS were suffering from chronic constipation. Chronic constipation is characterized by reduced gut motility and prolonged transit time. Those phenomena lead to bacterial overgrowth in bowel lumen [14], where the conversion of tryptophan to indole takes place. On the other hand, patients suffering from constipation usually use laxatives or long-term application of suppository bisacodyl. Those treatments are able to cause damage to colorectal mucosa and changes of normal intestinal microbiota, leading to the preferential growth of certain bacterial species which produce indigo as a by-product [110].

In terms of gender, it seems that PUBS affects women predominantly, since the study revealed that 70.7% of PUBS patients were female. This is mostly explained as female urethra is particularly prone to colonization by colonic gram negative bacilli, owing to its proximity to the anus, its short length and its termination beneath the labia [100]. Contrariwise, male specific factors such as zinc, a potent antibacterial agent that is secreted by the prostate, act protectively [111]. Consequently, it is well understood why female gender represents a highly recognized risk factor.

Last but not least, in CKD, elevated levels of indican have been demonstrated in several studies. In patients with CKD, production and absorption of noxious by-products can contribute to malnutrition, inflammation and uremic toxicity [112]. Uremia results in the depletion of key protein constituents in the colonic epithelial tight junction, a phenomenon that can account for the impaired structural

and functional intestinal barrier [113]. Simultaneously, in uremic milieu, qualitative and quantitative modifications of gut microbiota are observed. These alterations are intensified, due to constipation which is more frequent in end-stage renal disease patients under hemodialysis as a result of insufficient hydration, phosphate-binders intake and strict dietary restrictions concerning fruit and vegetables. In combination, impaired intestinal epithelial barrier and alteration of the intestinal microbiota can lead to endotoxemia and accumulation of the gut-derived uremic toxins such as indican [115].

Furthermore, in CKD patients, the reduced glomelular filtration rate causes higher serum and urine concentration of indican [114]. Especially in CKD patients under hemodialysis, removal of indican is limited as it is highly bound to albumin. Consequently, serum indoxyl sulphate concentration is further increased [115], suggesting that patients with CKD under hemodialysis have higher possibility of developing indicanuria leading to PUBS. Correspondingly, it is observed that in hemodialysis patients without sufficient residual diuresis, the urinary tract is a significant reservoir for infections [118] and another reason for why they are more prone to PUBS.

Conclusions

During the last decades, life expectancy has been increased. This fact drives the world population in demographic aging, associated with high prevalence of chronic diseases such as dementia, diabetes mellitus and CKD. Correspondingly, high incidence of resistant infections is noted worldwide due to irrational use of antibiotics.

PUBS is usually connected to UTI. It is a benign condition that can easily be identified without expensive investigations. Precautionary hygiene measures of catheterized patients and preservation of general well-being are essential in prevention of the syndrome. It is also necessary to strengthen the management of antibiotics in the context of an individualized approach. Clinicians of primary and secondary health involved in geriatric care should be of great awareness about the syndrome that may indicate serious underlying comorbidities.

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