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Research paper

Purple urine bag syndrome: A systematic review with meta-analysis

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ABSTRACT

Introduction: Purple urine bag syndrome (PUBS) is secondary to bacterial urinary tract infections in long-term catheterized patients. Our objective was to perform a systematic review of the literature to assess its predisposing factors, clinical presentation, management and outcomes.
Methods: The terms "purple AND urine" were searched in MEDLINE, EMBASE, LILACS, SciELO, Google Scholar and OpenGrey. A meta-analysis with individual patient-level data and another one with aggregate-level data were performed.
Results: Out of 6793 citations, 140 were included. A meta-analysis was done with 169 PUBS cases: 63.5% women, median age 78 years (IQR: 70–85), 59.4% asymptomatic. Outcome (n = 117): 7.7% deaths, 21.4% recurrence. Dementia was the only factor associated with recurrence (OR: 5.44; P = 0.046). In an aggregate-level data, meta-analysis (281 PUBS cases) prevalence of PUBS in chronically-catheterized patients was 11.7%. *Escherichia coli* and *Proteus mirabilis* were the microorganisms most frequently isolated.
Conclusion: PUBS usually affects chronically-catheterized women. Neither antibiotics nor catheter removal were associated with better outcomes.

1. Introduction

Purple urine bag syndrome (PUBS) is a unique condition where the urine bag and tubing of long-term catheterized patients turn purple. First reported by Barlow and Dickson in 1978, it is secondary to urinary tract infections (UTIs) with indigo- and indirubin-producing bacteria [1,2]. The reason for the purplish discoloration of the urine is the accumulation of the metabolites of tryptophan. Dietary tryptophan is normally metabolized to indole by the bacteria present in the gastrointestinal tract. Indole is then converted to indole sulfate in the liver. Certain bacteria possess enzymes like indole sulfatase and indole phosphatase which have the ability to metabolize indole sulfate, resulting in the formation of indirubin (red) and indigo (blue). These metabolites then concentrate in the plastic tubing and the catheter producing an intense purple color, giving rise to the PUBS [2,3].

It is an uncommon occurrence although incidence rates of 8.35 cases/100 patients-month follow-up has been reported in chronic catheterized institutionalized patients or 6.25 cases/100 patients-month follow-up in a Taiwan hospital [4,5]. Female gender, dementia, chronically debilitated states, alkaline urine, constipation, high bacterial loads in the urine and chronic kidney disease have all been described as risk factors for its development [6,7]. However, the clinical background, underlying diseases, microbiology and outcomes of PUBS have not been well documented because of lack of significant patient numbers. Most of the literature on PUBS are case reports, with some retrospective case collections [8,9], small observational retrospective studies [8,10], and small observational prospective studies [4–6,11], the largest of them including 41 cases.

Most patients who present with PUBS seem to be largely asymptomatic, and some authors have advocated that it is unnecessary to treat PUBS-affected patients aggressively [12,13]. However, some unfavorable outcomes have been reported [14–19]. Moreover, PUBS is an uncomfortable or troubling issue for some patients and their families [6], and makes clinical decision-making difficult, because some patients and their family members are frightened and demand correction.

We aimed to perform a systematic review of the literature on PUBS. A meta-analysis of individual patient-level data whenever possible was planned. Our objective was to evaluate the causative or associated factors, clinical presentation, microbiological results,

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management and outcomes of PUBS in long-term catheterized patients.

2. Methods

We performed a systematic review of the literature on PUBS. A specific review protocol was developed by all authors and is available on request.

2.1. Definition and inclusion criteria

We predefined a PUBS case as any adult ≥ 18 years old with an indwelling catheter (either temporal or permanent) with a change in the color of the urine collected in the urine collector bag to purple.

Predetermined eligibility criteria to include a study were: to adhere to the PUBS definition, to have been published in a medical journal, and to have a minimum information extractable from the publication. No contact with authors to obtain further information was attempted. Cases from conference abstracts were not included. Case reports, case series, observational studies and clinical trials were included. Studies were excluded if they did not fulfil PUBS definition, were not published in a medical journal or the data was not extractable from the manuscript. Data were used for the patient-level analysis if data were extractable at a patient-level. Otherwise, they were used for a pooled-data analysis.

2.2. Search strategy and study selection

The electronic databases MEDLINE, EMBASE, LILACS and SciELO were screened. Google Scholar and OpenGrey were also included as potential sources. The search was performed in October 2016. References of all the documents recovered were hand-searched for additional studies. The terms "purple AND urine" were entered in each database. No year restriction was considered. Only studies published in English, French, Portuguese, Italian, Spanish and Swedish were included. Two authors (JLG and PWJ) performed two independent searches screening publications by title and abstract. Eligibility and final inclusion in the review was decided by a full-text reading. The whole search was documented, including reasons for exclusion. Differences were solved by discussion.

2.3. Data collection and analysis

Two authors (MGL and APB) independently extracted the data using a standardized data collection form. The data extracted were: full citation, type of study, country of realization of the study, sex, age, ethnic origin, BMI, Charlson score, Barthel scale, comorbidities (DM, HBP, hypercholesterolemia, dementia, cardiovascular disease, COPD, chronic renal disease, neoplasia, immunesuppression), bedridden or wheelchair confined, nursery home residency, feeding route, type catheter placed, catheter material and temporality, nutritional situation, constipation or intestinal obstruction, symptoms (fever, other), urinary pH, creatinine, BUN, leukocytes, hemoglobin, glucose, time from catheterization to PUBS diagnosis, time from symptoms initiation to diagnosis, microbiological results, outcome, use of antibiotics and type, catheter management, time to resolution, time to recurrence.

2.4. Statistical analysis and data synthesis

Studies were used for the individual patient-level analysis if data were extractable at a patient-level. Otherwise, they were used for an aggregate-level data analysis.

2.4.1. Individual patient-level data analysis

A descriptive meta-analysis was done. Categorical variables are described as a percentage while quantitative variables are described as mean ± standard deviation (SD) if they follow a normal distribution or as a median and interquartile range (IQR) if not. A one-sample Kolmogorov-Smirnov test was used to assess variable distribution. To investigate causes of heterogeneity of the studies a subgroup analysis was done according to sex, older age, country of diagnosis, bedridden status and institutionalization. A bivariate analysis was done using χ^2 test (and Fisher's test when necessary) for categorical variables and Student's *t*-test or Mann-Whitney U-test for quantitative ones. Sex, older age, institutionalization, geographic origin, type of pathogen, type of catheter, catheter management after PUBS diagnosis, treatment with antibiotics and comorbidities were evaluated as variables potentially associated with unfavorable outcome or recurrence in the bivariate analysis.

2.4.2. Aggregate-level data meta-analysis

A descriptive meta-analysis was done using data from studies without patient-level information available and from our individual patient-level data meta-analysis.

MOOSE statement was followed for reporting [20].

3. Results

The initial screening yielded a total of 6793 citations. Of these, 194 were selected for full-text review and 133 studies were included in the individual patient-level analysis, including a total of 170 PUBS cases. Seven additional studies were included in the aggregate-level data analysis, representing 112 additional PUBS cases (Fig. 1). Fifty-four out of the 194 initially selected publications were excluded by: language restriction [6], insufficient extractable data [4], conference papers [4], double publication [2] and not fulfilling adult PUBS case definition [38].

3.1. Individual patient-level data meta-analysis

One hundred sixty-nine individualized PUBS cases were found from 133 publications (Table 1, supplementary material).

Most cases came from Europe (37.1%) and East Asia (26.9%), being Taiwan the country with more cases reported (33); 107 were women (63.5%) with a median age of 78 years (IQR: 70–85) (Table 1).

In 141 cases, microbiological results were available providing 204 isolates (2 patients had four microorganisms, 11 had three, 35 had two and 93 had one microorganism in the urine culture). *Escherichia coli* (28.4%), *Proteus mirabilis* (22.1%) and *Klebsiella pneumoniae* (11.8%) were the bacteria most frequently isolated. Only 12 isolates were reported as resistant to antimicrobials (Table 2 supplementary material).

The outcome was reported in 117 cases with nine deaths (7.7%); 2 had Fournier's gangrene as a complication (1.7%). Treatment information was available in 76 patients: 63 were treated with one antibiotic and 13 with a combination of two antibiotics. Antibiotics most commonly prescribed were cephalosporins (29) and quinolones (24), followed by combinations of a β-lactam with a β-lactamase inhibitor (11) and carbapenems (5). In the follow-up, 12 out of 56 patients had a new PUBS episode (21.4%).

A sub-analysis according to age, sex, Asiatic precedence, bedridden status, and institutionalization is shown in Table 2.

In a bivariate analysis, an unfavorable outcome was not statistically associated with sex ($P = 0.74$), older age ($P = 0.73$), institutionalization ($P = 1$), geographic origin ($P = 0.85$), type of pathogen ($P = 1$), type of catheterization ($P = 0.68$), symptoms ($P = 0.45$), polymicrobial infection ($P = 0.25$), decision about