Foamy Urine
Is This a Sign of Kidney Disease?

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Historically, persistent foamy urine noticed upon voiding is considered a warning sign of kidney disease. Foamy urine is characterized by the appearance and persistence of multiple layers of small to medium bubbles in urine voided into a container, such as a toilet bowl (see Figure 1). The appearance of a single layer of larger bubbles upon voiding, that quickly dissipate, can be considered normal. Traditionally, foamy urine has been considered by physicians, as well as by patients, as a marker of proteinuria. In fact, it is listed by most electronic health records in their customizable specialty templates as a symptom of kidney disease. Only about one third of patients volunteering this complaint will be found to have abnormal proteinuria, so most cases of "foamy" urine remain unexplained (1). We found no studies specifically examining the physio-chemical characteristics of urine that foams upon voiding.

Recently, this topic was discussed in the American Society of Nephrology Communities website where many nephrologists shared their inputs and understandings (https://community.asn-online.org/home). It was clear that we are far from fully knowing exactly what foamy urine means. A better understanding of this phenomenon might be achieved by looking at mechanisms of foam formation in general and asking several questions:

- How does foam form?
- Besides protein, what substances in urine make foam appear?
- Can foamy urine indicate something other than proteinuria?

Foam forms by trapping pockets of gas in liquid with the help of surfactant. A surfactant is an organic compound that is amphiphilic (or amphipathic), meaning containing both hydrophilic and hydrophobic ends. A surfactant diffuses in water and adsorb at interfaces between air and water where the water insoluble hydrophobic ends aggregate to form a bubble. The cleaning property of soap comes from its amphiphilic structure: when placed in an immiscible biphasic system consisting of aqueous (water) and organic solvents (fatty dirt), soap will partition the two phases, and the extent of the hydrophobic and hydrophilic portions determines the extent of partitioning. The foam in beer ("beer head") is dependent on an amphipathic protein (Lipid Transport Protein 1) derived from barley (2).

In general, proteins or polypeptides have amphiphilic properties that can function as a surfactant and form foam in the urine. On the other hand, certain free amino acids share this property and potentially can also contribute to foam formation. The classic example of this is aminoaciduria that can be seen in Fanconi syndrome. Among such amino acids are methionine and tyrosine, both of which have strong amphiphilic properties, and patients with Fanconi syndrome can excrete significant amounts of these amino acids in the urine, exceeding 500 mg in 24 hours (3). Aminoaciduria is also common in several disorders with proximal tubular dysfunction as seen in Dent disease (4), Wilson disease (5), cadmium toxicity (6), and multiple myeloma, and has been described in individuals with SLC5A2 mutation encoding SGLT2 (7). It is only our prediction, without being extensively validated by observation, that individuals with such disorders have the potential to form foamy urine even though a dipstick will be negative for albuminuria. It remains to be seen if the wider use of the SGLT2 inhibitors is going to increase the incidence of foamy urine.

Phospholipids, a constituent of the lipid bilayers of cell membranes, are also amphiphilic. It is not unreasonable to expect that ruptured cells releasing membrane phospholipids in the urine, as in microscopic hematuria and/or pyuria without proteinuria, can contribute to formation of urine foam.

To address this topic more broadly, we searched the human metabolome database (HMDB) looking specifically for metabolites in human biospecimens with amphiphilic properties (8). Our search defined a total of 88 metabolites detected in human body secretions out of which, 16 were detected in human urine as shown in Figure 1. Fifteen of these metabolites are either primary or secondary bile salts and one is a fatty acid ester. The content of these metabolites in human urine could not be found. It is important to point out that these substances with amphiphilic properties are present in normal urine, which could explain the tendency of some individuals to form a single layer of foam upon voiding, especially if the urine is concentrated. It is expected that persons with cholestasis can have excess of most of these metabolites in their urine,

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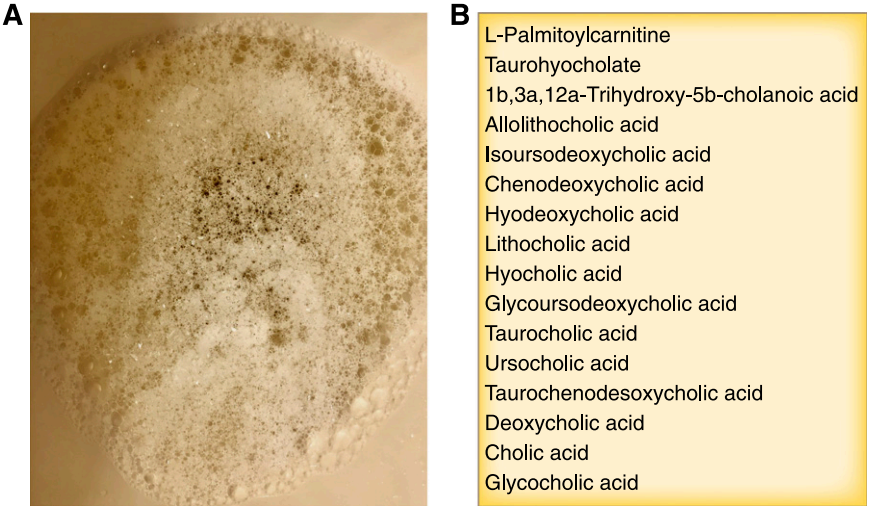

Figure 1. | **Foamy urine.** (A) Freshly voided urine by a patient with nephrotic syndrome. (B) List of amphiphilic metabolites in normal human urine.

contributing to foam formation. Moreover, laxatives that stimulate the flow of bile into the duodenum (cholagogue) or stimulate the production of bile by the liver (choleretic) can potentially increase bile salt excretion in the urine after escaping the enterohepatic circulation. Persons with enteric bacterial overgrowth potentially can have excessive amount of glycocholic acid and glycoursodeoxycholic acid, whereas those with carnitine palmitoyltransferase 2 deficiency and celiac disease can excrete excess L-palmitoylcarnitine in their urine. It is predicted that such conditions with relative excess in bile salts can potentially be the reason for urine foam formation in the absence of proteinuria.

As a subjective experience, foamy urine is a highly variable phenomenon, difficult to quantify and not referenced, but remains a free test and a spontaneous complaint that should not be ignored. Only about one third of patients volunteering this complaint will ultimately be found to have abnormal proteinuria, so most cases of foamy urine remain unexplained. The presence of abnormal (excessive) amounts of the normally present amphiphilic substances in the urine (as in cholestasis) as well as the possibility of other unidentified substances of similar chemical character originating from certain food items or medications may explain this discrepancy. Dipsticks can miss overflow free light chain proteinuria in monoclonal gammopathies, so if foamy urine of recent onset is a chief complaint, and the dipstick is negative or trace for albuminuria, we would recommend performing a urinary protein-to-creatinine ratio because a urinary albumin-to-creatinine ratio would be insufficient. Conditions that can have more than the usual bile salt concentrations in the urine might be other potential causes of this phenomenon. We encourage clinicians to stress foamy urine primarily with their patients who suffer from a relapsing glomerular disease or are members of families with certain genetic kidney disorders to facilitate early detection of disease relapse or early diagnosis, respectively, that can have a major impact on outcome. Better understanding of this phenomenon is expected when urinary metabolomic profiling becomes complementary to existing clinical and laboratory diagnostic modalities that will have the potential to uncover a variety of substances in the urine with amphiphilic properties. With the current understanding and the available knowledge, we do not recommend investigating foamy urine in patients who lack proteinuria. There is definitely much room for more research to better understand foamy urine.

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