



# Workup and treatment of nipple discharge—a practical review

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**Abstract:** In this review, we present an overview of the treatment and management of pathologic nipple discharge (PND). PND is a clinical diagnosis that warrants a thorough work-up, not only because of the risk of malignancy, but also because of the concern it causes patients. Mammography should be the initial study in women 40 years of age or older and men 25 years of age or older. Ultrasound (US) should be the initial study in pregnant patients, women under 40, and men under 25. Image-guided biopsy should be performed for any abnormal imaging findings. Ductoscopy can be useful if initial imaging studies are negative, although it is not widely available. Cytology alone should not influence surgical decision-making. MRI can be considered as part of the initial work-up, if the patient qualifies based on her personal risk of breast cancer and family history. While all patients previously underwent surgical intervention, conservative management with close follow-up, biannual US, and yearly mammogram can now be considered in select patients. This group includes patients with no palpable abnormality and negative imaging work-up (mammogram, US, and MRI) who do not desire surgical intervention for palliation of their symptoms. Patients with PND who should still undergo surgical excision include those with imaging abnormalities, a personal or family history of breast cancer, BRCA1/2 mutations, or PND that persists for over 2 years. In these patients, and in patients who desire cessation of the discharge, ductal excision is typically both diagnostic and therapeutic. By taking into account each patient's unique history, imaging findings, risk factors, and personal preferences, we can safely tailor our treatment plan to better meet the needs of our patients.

**Keywords:** Nipple discharge; duct excision; breast imaging; ductoscopy; ductography

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## Introduction

Up to 80 percent of women will have an episode of nipple discharge during their reproductive years. Nipple discharge accounts for 3–5 percent of all breast complaints (1–3). The focus of this paper is the evaluation and management of pathologic nipple discharge (PND) in contrast to lactational nipple discharge or physiologic nipple discharge. Lactational nipple discharge is a normal physiologic process during pregnancy and lactation. When it occurs without a recent pregnancy, it is defined as galactorrhea and is most commonly caused by increased prolactin levels which can be due to manual stimulation, medications, renal failure, thyroid

disease or a prolactin-producing tumor. Physiologic discharge is characterized by bilaterality with a variety of colors and consistencies of fluid emanating from multiple ducts.

PND is defined as fluid that occurs spontaneously and is serosanguinous, serous or watery. It is generally unilateral and arises from a single duct. Most PND is due to a benign etiology such as an intraductal papilloma (35–56% of cases) and duct ectasia (6–59% of cases) (4,5). The risk of malignancy in patients who are evaluated surgically ranges from 5–23% of cases with predominantly ductal carcinoma in situ, but also invasive cancer (4,5). The risk for malignancy may increase with age, as seen in a study by Seltzer, which included 318 patients with PND and found



**Figure 1** Example of pathologic nipple discharge.

a higher incidence of breast cancer in patients over 50 (9% compared to 1% in patients younger than 50) (1). The rate of malignancy is also increased when PND is accompanied by radiologic or palpable findings on evaluation (6-8). Therefore, ruling out malignant lesions should be the primary aim in patients presenting with PND. Patients with PND have traditionally been considered for surgical excision of the involved duct, however, there has been a management shift towards observation in low risk patients.

### History and clinical examination

A thorough history and physical examination are crucial when evaluating a patient with the complaint of nipple discharge. The history should include duration of symptoms, frequency, color and quantity, spontaneous or expressed and any associated other symptoms, such as a mass. History of recent pregnancy or lactation, current medications, history of recent trauma or nipple stimulation, and smoking status, as well as patient hormonal status and history of breast or ovarian disease are relevant to determine etiology. Physical exam includes visual inspection and palpation of both breasts looking for clinical features that are associated with a pathologic presentation such as unilaterality, reproducibility, emanation from a single duct, and watery/serous/bloody output in patients who are not pregnant or lactating. When examining patients, document if discharge is uniductal or multiductal and as unilateral or bilateral. The color should be evaluated, which can be done by placing the fluid onto a gauze. At one time, hemocult testing of ductal fluid was common practice, however bloody nipple discharge carries no greater significance for malignancy than serous or watery discharge and therefore documenting the presence of blood in the

fluid does not enhance the diagnostic work-up. Simmons *et al.*, demonstrated that hemocult testing had a 50% sensitivity and specificity was 0% (9). A common finding when evaluating a patient with watery discharge is to see it become pink stained with manipulation during exam and is often indicative of an intraductal papilloma which is characteristically quite friable and bleeds easily. Nipple discharge is defined as normal milk production during lactation, physiologic nipple discharge, such as galactorrhea or opalescent fluid, or PND based on the characteristics of presentation above.

### Imaging studies

Imaging evaluation normally begins with diagnostic mammography (DM) when age appropriate and ultrasound (US) (Figure 1). When an imaging finding is seen in a woman with a nipple discharge, the likelihood of malignancy increases, although it may not always be helpful in identifying the lesion (7). Additional imaging is not indicated in patients with physiologic nipple discharge, and these patients can continue age appropriate screening (10).

### Mammogram

DM is the standard initial step in evaluation of a patient with PND, although no current studies address the diagnostic accuracy of tomosynthesis versus digital mammography in the specific setting of nipple discharge. DM should be repeated if the prior mammogram was performed more than 6 months ago. If the patient had a mammogram within the past 6 months, US should be used as the initial examination (10). Tomosynthesis better characterizes noncalcified lesions compared with conventional mammographic workup and may therefore be useful in the workup of nipple discharge (11-14). Most cases of PND are due to benign intraductal papillomas, and DM often does not identify these lesions due to their small size, lack of calcifications, and intraductal location (10). When visible on DM, imaging findings include asymmetrically dilated ducts, a circumscribed benign-appearing subareolar mass, or grouped microcalcifications (10).

For detection of malignancy in patients with PND, studies have reported sensitivity of DM varied widely between 15% and 70%, and a specificity between 35% and 95% with a positive predictive value (PPV) of 42% and negative predictive value (NPV) of 90% (7,10,15,16). When combined, identification of malignant and high-

risk lesions, DM has a reported sensitivity of 10% to 26%, specificity of 94% to 95%, PPV of 18%, and NPV of 88% (15,16). This wide variation may be due to differences in technology as well as breast density among patient cohorts. When looking specifically at the detection of malignancy in patients with PND, a recent meta-analysis found that DM had a sensitivity of 22%, a specificity of 93%, diagnostic accuracy of 76%, PPV of 46%, and NPV of 80% (17). Mammography still remains a part of the evaluation of PND because of its high specificity and NPV, as well as its widespread accessibility.

### **Ultrasound**

When DM is negative, the retroareolar region should be evaluated with US. In the past, US was ancillary to DM alone or combined with ductography, although, more recently, ductography has fallen out of favor as US can show the extent of the lesion more accurately than can a ductogram (10). US maneuvers have been described such as 2 hand compression, peripheral compression, and rolled-nipple techniques which may be needed for successful imaging of the retroareolar region (10). Lesions that are identified on US should undergo an US guided biopsy. US should be the initial imaging modality in conjunction with mammogram in women younger than 40 years of age, while mammography should be the initial imaging modality in women 40 years of age or older (10).

### **Ductography (Galactography)**

Several imaging modalities have been utilized in the workup of PND. Ductography is a method of cannulating the duct producing secretions and instilling an iodinated contrast medium. Historically, ductography or galactography was the procedure of choice to evaluate patients with nipple discharge. It was performed following negative DM and US and, in that situation, ductography was shown to detect underlying abnormalities in 14% to 86% of cases although with variable success (6,18-20). Ductography is good at identifying peripheral intraductal lesions and assessing the likelihood of malignancy, although definitive diagnosis still requires central duct excision (CDE) as a negative ductogram does not completely rule out malignancy (6). It is a technically demanding procedure for the radiologist and patients report it to be painful and it is not currently commonly used.

### **Fiberoptic ductoscopy**

The fiberoptic ductoscopy system (FDS) was introduced in the 1990s as a safe alternative to ductography. Ductoscopy is a minimally invasive microendoscopic technique which provides video or direct images inside the lactiferous duct and allows ductal lavage and retrieval of cells for cytologic evaluation (21,22). Cytologic evaluation has been used with FDS after ductal lavage or alone for evaluation of nipple discharge with variable outcomes. FDS-positive cytological findings could be grouped into three categories: malignant cells, cells with atypia, and clumps of normal ductal cells. Negative cytological findings referred to no cells, single or sporadic normal ductal cells, or other types of normal cells, such as lymphocytes and histiocytes (23). Ductoscopy where available, may allow for direct biopsy of an intraductal lesion and some surgeons are enthusiastic about its use during ductal excision.

### **Cytology**

Cytologic evaluation of PND is considered a simple, non-invasive, and inexpensive approach for histological sampling-based detection of alterations in breast tissue, which could aid in the diagnosis of PND (24). The cytological analysis uses standard cytospin preparations, Papanicolaou and Diff-Quick staining (23). Some consider cytological findings to be helpful as an adjunct to other modalities, particularly interpreting them in light of the clinical and radiologic findings (25). In literature, reported sensitivity and specificity of cytology have a wide range of 46–95%, and in some cases, retrospective studies have shown sensitivity to be as low as 11% and specificity only 76% (9,26). A recent meta-analysis found an overall pooled sensitivity of only 38% but a high pooled specificity of 90%, making it a possible adjunctive study, but inappropriate as the only modality for evaluation of nipple discharge (17).

### **MRI**

The use of breast MRI to evaluate PND is evolving. The sensitivity of breast MRI for breast cancer detection is high, ranging from 93–100% (10). Although MRIs are highly sensitive, their specificity is still lacking (10,17). A small study looking at the additional diagnostic value of MRI in patients with PND in the absence of additional physical findings and negative imaging, demonstrated cancer in less than 2% of patients (5). However, multiple other studies

support the use of MRI in cases where other imaging modalities have failed to identify an underlying cause of PND (10). Filipe *et al.* found that ductoscopy outperformed MRI for the detection of malignancy in patients with PND and should be considered prior to obtaining an MRI, however, ductoscopy is not widely available (17). MRI is also known to have a high sensitivity at identifying benign papillary lesions and at times can allow detection of index lesions in peripheral ducts that are beyond the area evaluated with a terminal duct excision, ductogram, or targeted US (10,15). Therefore, in clinical practice, using MRI in patients with negative initial imaging may not only identify the cause but also add valuable information for surgical planning by identifying etiologies that are remote from the nipple.

### Special populations

Recommendations for the evaluation of male patients and pregnant patients with PND differ from those for non-pregnant women.

Nipple discharge in the male patient is uncommon, but warrants a thorough work-up, as previous studies have found carcinoma in 23–57% of male patients presenting with nipple discharge (10,27). While US is the initial imaging modality of choice in women younger than 40 years old, mammography should be the initial imaging modality in men 25 years of age or older (10,27).

Up to 20% of pregnant women will experience isolated bloody nipple discharge during their pregnancy or early lactation (28). Without an associated mass, self-limited bloody nipple discharge is rarely seen as the presenting complaint in pregnancy-associated breast cancer (29). Increased vascularity and proliferative changes in the breasts can result in unilateral or bilateral physiologic bloody nipple discharge and is commonly referred to as “rust pipe syndrome” (28–30). This type is usually spontaneous, occurs after the first trimester, involves multiple ducts, and resolves within 2 months (30). However, persistent bloody nipple discharge during pregnancy could be associated with infection, papilloma, or breast cancer, so work-up is warranted (28,31). Patients should first be evaluated with US, followed by DM with retroareolar magnification views as needed. There is no role for MRI during pregnancy, as IV gadolinium crosses the placenta and enters fetal circulation. MRI is also not considered first line during lactation, as increased breast vascularity may limit sensitivity. All suspicious lesions

should be biopsied, and patients should be counseled on the risks of bleeding and milk fistula formation (28). Most patients require only reassurance for this typically self-limited symptom.

### Surgery

Surgical intervention for PND is comprised of either total subareolar duct excision or selective duct excision of the affected duct. Total subareolar duct excision reduces the requirement of repeated duct excisions due to higher detection rates of occult cancers, but can cause difficulties with breastfeeding, loss of nipple sensation, or areolar necrosis (32). Selective duct excision may result in the need for repeated duct excision, but preserves remaining ductal systems in continuity with the nipple, and is therefore typically the best option for women planning to breastfeed (32). It is important to ascertain a woman’s plans for future lactation prior to a ductal excision and give informed consent accordingly.

There are likely as many techniques for ductal excision as surgeons. The technique described here is that of the senior author and uses lacrimal probes to map out the duct to be excised. With the patient prepped, draped and sedated, circumferential pressure at the edge of the areola is applied to see if a specific trigger point can be identified. Before instilling local anesthetic, the duct from which the fluid is emanating can be cannulated with a 3-0 or 4-0 lacrimal probe. Insertion of the probe can be painful, thus communicating with the anesthesiologist about the timing of cannulation is helpful to give the patient adequate sedation. If local anesthetic is injected before cannulating the duct, it can cause bleeding or compress the duct making it difficult to be certain the correct duct has been identified. Once the lacrimal probe has been inserted, the course of the probe directs incision placement at the edge of the areola in the quadrant toward which the probe is traversing.

After local anesthesia has been injected, a periareolar incision is made. The dermis of the areola can be grasped with an Allis clamp and the areola is elevated sharply off the subareolar tissue progressing centrally until the probe is palpable. The duct containing the probe is then grasped with an Allis clamp and the duct is incised just below the surface of the papilla. If the duct is dilated, it can be cannulated within the wound with another lacrimal probe and the original one going through the nipple can be removed. While grasping the duct and the probe with an Allis clamp, circumferential dissection around the



**Table 1** Recommended initial imaging study in patients with PND

Women $\geq 40$ years old without mammogram within past 6 months	Mammography
Women $\geq 40$ years old with mammogram within past 6 months	Ultrasound
Women $< 40$ years old	Ultrasound + Mammography
Men $\geq 25$ years old	Mammography
Men $< 25$ years old	Ultrasound
Pregnant women	Ultrasound

PND, pathologic nipple discharge.

probe, which is easily palpable, can be performed far into the periphery using this technique. Once the specimen is removed, the ductal orifice should be marked with a stitch and the probe is removed. Inspection of the wound is important to make sure there is no more discharge visible and whether any dilated ducts are obvious, in which case, additional tissue should be taken.

Another technique commonly used is to instill methylene blue into the duct and excise the blue-stained duct. Surgeons who have access to a ductoscope can use the scope for direct visualization of the duct as a guide for performing a microductectomy (32).

While surgery was once considered the primary course of treatment for PND a transition in management is occurring. Surgical resection is no longer recommended in patients with PND, normal imaging (mammography, US, and MRI), and no other suspicious findings (33,34). Since the risk of malignant lesions is low, and since the most common malignant lesions that are seen are typically low-grade DCIS or small invasive tumors, a consideration is that these patients forego surgery in favor of a two year follow-up regimen consisting of US and clinical examination every six months combined with annual mammography (33,34). Ashfaq *et al.* have determined that unnecessary operations may be avoided in 66% of patients with PND by using this algorithm (35). They also found that 81% of patients experienced resolution of their discharge without surgical intervention. Patients with PND for whom surgical intervention is still recommended include those with abnormal imaging findings and personal history or family history of breast cancer (33,34). Dupont *et al.* found that patients with BRCA 1/2 mutations, history of ipsilateral breast cancer, and atypia on core needle biopsy had higher rates of upstage to malignancy at time of surgery (36). Bloody discharge and imaging abnormalities were also strong risk factors for underlying carcinoma and atypia

in their study. For patients with copious nipple discharge, nipple discharge that causes discomfort, or nipple discharge that persists for more than two years even if imaging is negative, surgery should be considered (33).

## Conclusions

PND is a clinical diagnosis that warrants a thorough work-up, not only because of the risk of malignancy, but also because of the concern it causes patients. Mammography should be the initial study in women 30 years of age or older and men 25 years of age or older. US should be the initial study in pregnant patients, women under 30, and men under 25. We have created a table of recommended imaging studies for patients based on age, gender, and pregnancy status (*Table 1*). Image-guided biopsy should be performed for any abnormal imaging findings. Ductoscopy can be useful if initial imaging studies are negative, although it is not widely available. Cytology alone should not influence surgical decision-making. MRI should be considered in the work-up of patients with negative mammogram and US. While all patients previously underwent surgical intervention, conservative management with close follow-up, biannual US, and yearly mammogram can now be considered in select patients. This group includes patients with no palpable abnormality and negative imaging work-up (mammogram, US, and MRI) who do not desire surgical intervention for palliation of their symptoms. Patients with PND who should still undergo surgical excision include those with imaging abnormalities, a personal or family history of breast cancer, BRCA1/2 mutations, or PND that persists for over 2 years. In these patients, and in patients who desire cessation of the discharge, ductal excision is typically both diagnostic and therapeutic. By taking into account each individual patient's history, imaging findings, risk factors, and personal preferences, we can safely tailor

Table 2 Case scenarios

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- I. A 45-year-old female with spontaneous, unilateral bloody nipple discharge. The discharge cannot be induced in your clinic. How would you manage this? Start with mammogram and ultrasound. If these are negative, follow up with an MRI. If imaging shows an abnormality, biopsy the area of concern. If biopsy shows intraductal papilloma, proceed with excision. If biopsy shows malignancy, proceed with surgical management. If MRI is negative or shows benign findings, proceed with central duct exploration vs. observation and unilateral ultrasound and mammogram in 6 months
- II. A 65-year-old female who presents with spontaneous, clear, watery unilateral nipple discharge from a single duct. How do you proceed? Start with a mammogram and ultrasound, followed by an MRI if negative. If MRI is negative or shows benign findings, repeat unilateral ultrasound and mammogram in 6 months. If discharge does not spontaneously resolve, follow with biannual ultrasound and yearly mammogram for up to 2 years or proceed with central duct excision at any time
- III. A 32-year-old female with nonspontaneous discharge that occurs with manipulation of the nipple. Ultrasound shows dilated ducts. What are your next steps? Obtain mammogram and galactorrhea laboratory work-up. If imaging and laboratory values are negative or benign, proceed with short term follow-up in 6 months. If mammogram shows an abnormality, proceed with biopsy and treat according to pathology. Central duct excision can also be considered for palliation of symptoms
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our treatment plans to better personalize patient care in the treatment of PND (Table 2).

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