



# Progression of research into the diagnosis and treatment of cystitis glandularis: a narrative review

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**Background and Objective:** Cystitis glandularis (CG) is a frequent urological condition. The symptoms recur on a regular basis and are non-specific. The specific pathogenesis of CG is not yet clear. The gold standard is cystoscopy and biopsy. At present, there is currently no standard and uniform treatment plan. Common treatment plans include surgical treatment, non-surgical treatment, surgical treatment combined with drug treatment, etc. This article aims to summarize the research progress of CG and provide reference for clinical diagnosis and treatment.

**Methods:** A search of publications before October 2021 was done. It was limited to publications in English. Searches were performed using PubMed, MEDLINE, Web of Science, and Google. The keywords used were: cystitis glandularis, cystitis cystica, bladder cancer, bladder lesions and bladder carcinoma.

**Key Content and Findings:** This narrative review provides an overview of the research progress of diagnosis and treatment of CG in recent years, with the aim of providing reference for clinical practice.

**Conclusions:** There are some debates and disagreements on the genesis and pathophysiology of CG, and no standardized protocol for clinical treatment. Treatment is still given priority to with surgical treatment. More further studies on CG are needed in order to provide more effective diagnosis and treatment strategies for clinic.

**Keywords:** Cystitis glandularis (CG); diagnosis; therapy

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## Introduction

Cystitis glandularis (CG) is a frequent urological condition. The most common clinical signs include frequent micturition, urgency micturition, and urodynia. These symptoms recur on a regular basis and are non-specific. Cystoscopy and biopsy are required to confirm the diagnosis. Mucosal pathological alterations were observed

in the bladder, with transitional epithelial hyperplasia and metaplasia predominating. The disease's genesis and method of action remain unknown. No consensus has been reached about clinical diagnosis and treatment. This review highlights current studies on CG diagnosis and treatment. We present the following article in accordance with the Narrative Review reporting checklist (available at <https://jxym.amegroups.com/article/view/10.21037/jxym-22-5/rc>).

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**Table 1** The search strategy summary

Items	Specification
Date of search	October 10th, 2021
Databases and other sources searched	PubMed, MEDLINE, Web of Science and Google
Search terms used	Cystitis glandularis, cystitis cystica, bladder cancer, bladder lesions and bladder carcinoma
Timeframe	Before October, 2021
Inclusion and exclusion criteria (study type, language restrictions etc.)	Inclusion criteria: the full article could be obtained Exclusion criteria: (I) full article was not available; (II) study was not related to cystitis glandularis
Selection process	The literature review and the data extraction were conducted independently by two reviewers (Z Li and B Fan)  A secondary search of the literature was manually conducted from the references of our primary search included papers by the application of the same inclusion and exclusion criteria  Doubts or disagreements regarding the inclusion or exclusion of manuscripts were resolved through a discussion between the reviewers until a consensus was reached

## Methods

The search included publications before October 2021. It was limited to publications in English and a subset of medical databases. Searches were performed using PubMed, MEDLINE, Web of Science and Google. The keywords used were: cystitis glandularis, cystitis cystica, bladder cancer, bladder lesions and bladder carcinoma. The materials used included textbooks, journals, magazines, newspapers, policy documents, academic papers, conference papers, internet materials which consist of abstracts, reviews, dictionaries, and encyclopedias (search strategy summary at *Table 1*). This review article aims to describes CG including its epidemiology, pathogenesis and etiology, pathology, classification, diagnosis, identification, therapy.

## Discussion

### *Epidemiology*

In 1968, the literature reported that CG was more prevalent in middle-aged and older women, with an incidence of between 0.9% and 1.9% (1). Due to the focus on urology and pathology departments and the ongoing advancement of medical technology, the incidence rate recorded in the subsequent literature is significantly higher. Wiener *et al.* performed an autopsy on 100 normal bladders ranging in age

from 12 days to 101 years in 1979. Brunn's nest detection rate was 89%, while CG detection rate was 60% (2). In 1987, Walther *et al.* discovered that 93.6% of Brunn's nests were detected in 125 patients (3). Additionally, CG can affect children (4).

### *Pathogenesis and etiology*

At the moment, the etiology and pathophysiology of CG remain unknown. It is commonly believed to be caused by persistent bladder stimulation, such as infection, stones, obstruction of the lower urinary tract, allergens, metabolic toxins, hormone secretion abnormalities, and HPV infection. These elements contribute to the bladder mucosa's abnormal change (5-8).

There are various widely accepted theories on the pathophysiology (9). The first is that it originates in the embryo and is caused by the endoderm's remnant embryonic glandular epithelium. The second point is about Pund degeneration theory, which refers to the degeneration of bladder urothelium due to its loss of normal function. The third perspective is that of epithelial metaplasia. Chronic irritation results in urothelial metaplasia of the bladder, which is glandular epithelium. The majority of scholars support the third view, which states that CG is a chronic pathological process of the bladder that typically progresses

from transitional urothelial hyperplasia to transitional epithelial buds (Brunn's buds), transitional epithelial nests (Brunn's nests), cystic cystitis, and CG.

### ***Pathology***

The creation of epithelial cell nests, glands, and tiny cysts can be detected under the microscope. Additionally, it can be noticed that plasma cells infiltrate the propria to varied degrees. Epithelial cells produce many granules into the cytoplasm and are densely packed with Golgi bodies and mitochondria. Cystic cystitis and CG, according to scholars, are distinct pathological stages of the same disease (10-12).

### ***Classification***

According to some experts, CG is classified into two types depending on its morphology: normal CG and intestinal CG. Typical CG is defined by a cavity-like shape in the lesion's center made of columnar or cubic epithelium. There is a distinct demarcation between the lesion's periphery and the transitional epithelium. Intestinal CG is characterized by the presence of a gland-like structure and a high density of goblet cells capable of secreting mucus in the intestinal metaplasia lamina propria. Intestinal CG has a subtype known as intestinal adenomatous CG, which has a high proclivity to develop into cancer (13-15).

According to some experts, CG is classified into four subtypes depending on its clinical manifestations: classic transitional epithelial type, intestinal epithelial type, prostate epithelial type, and mixed type (13,16).

### ***Diagnosis***

Due to the lack of particular clinical signs of CG, diagnosis is based mostly on the following examinations.

### **Ultrasound**

Due to its low cost, non-invasive nature, and high diagnostic yield, ultrasound has become one of the primary diagnostic techniques for CG. The bladder wall has been strengthened. The lesion's surface is smooth, and its base is broad, with cystic honeycomb echoes. Contrast-enhanced ultrasound and ultra-microvascular imaging techniques can be used to visualize blood flow and perforation of the basal blood vessels within the bladder lesion (17).

### **CT**

CT has a high sensitivity for CG, which presents as partial or even widespread thickening of the bladder wall. The lesion protrudes into the bladder and may be nodular, papillary, or a combination of the two. It is mostly manifested by a decrease in the density of soft tissues and a minor increase in strength when those tissues are reinforced (18).

### **MRI**

It has a better sensitivity than CT and can more precisely determine the nature, location, and size of the lesion. On T1WI, the lesion site is iso-signal; on T2WI, it has a slightly increased signal and may exhibit minor augmentation when boosted. However, due to the high cost and lack of diagnostic capability, MRI is not frequently suggested in clinical practice (19-21).

### **Cystoscopy and biopsy**

This procedure is considered the gold standard for diagnosing CG. Lesions with a variety of shapes and no invasive growth are typically found in the bladder neck, bladder triangle, and bilateral ureteral apertures during cystoscopy. The following are the major procedures performed during cystoscopy. The most frequent variety of follicular CG is a sheet-like infiltrating type of follicular edema, swelling, or villous hyperplasia. Villous edema CG is most commonly found in the bladder neck and resembles a papilloma. To differentiate it from a bladder papilloma, a pathological study is required. Chronic inflammatory CG is characterized by rough local mucosa, increased vascular roughness, and blurring, with the possibility of necrosis and bleeding. CG without major mucosal alterations is defined by the absence of visible abnormalities in the bladder mucosa, which often discovered through a pathological biopsy. The presence of Brunn's nests in the lamina propria confirms the diagnosis. This type is quite rare. Under a microscope, a biopsy is obtained and sent for pathological investigation. It is often advisable to collect samples from different areas and to pay close attention to the amount and depth of sick tissue (6,15,22,23).

### ***Identification***

The differential between CG and bladder cancer is the most clinically significant in clinical practice. In terms of the relationship between the two, such as whether CG is a

precancerous lesion of bladder cancer and the strength of the correlation, current research on CG is woefully lacking in depth and relevant trials. The relationship is inconclusive, and there are numerous disagreements.

According to some doctors, CG is associated with bladder cancer and should be considered a precancerous lesion of the bladder (24). Thrasher *et al.* discovered that the monoclonal antibody 7E12H12 against colonic glandular epithelial protein is expressed equally in CG and bladder cancer tissues (25). Rosin *et al.* discovered that p53 and p21 expression levels can be as high as those reported in bladder cancer tissue in CG with abnormal cell shape and/or atypical hyperplasia (26). Pantuck *et al.* determined that CG is a precancerous lesion after examining whether common tumor antigens exist between CG and bladder cancer (27). Bryan *et al.* discovered that the expression of beta-catenin is comparable to that of Barrett's esophagus in intestinal metaplasia type CG. Beta-catenin is a critical element in the development and progression of Barrett's esophageal cancer. They hypothesize that CG of the intestinal metaplasia type can progress to adenocarcinoma (28).

Others, on the other hand, say there is no evident relationship. Agrawal *et al.* discovered that CG is extremely prevalent in urothelial mutations. Its transition into bladder cancer is a lengthy process that does not require specific treatment. CG is not a precancerous condition (29). According to Wiener *et al.*, CG can be considered a non-specific variant of the typical urothelium (2). Smith *et al.* carried out a follow-up analysis on 136 patients who had been diagnosed with CG. During the 23-year follow-up period, only one patient with urothelial cell carcinoma of the upper urinary tract progressed into bladder urothelial carcinoma following a diagnosis of CG in the third month. Smith *et al.* do not believe that this finding supports CG's proclivity to develop malignant. The correlation between the two may be coincidental, but not always (19). Yi *et al.* conducted a retrospective analysis of the clinicopathological characteristics of 166 CG patients who were followed for 17 years and discovered that no secondary bladder cancers developed in patients with classic CG or intestinal CG (30).

Bladder cancer is more prevalent in elderly males clinically. The majority of patients appear with painless gross hematuria, which may be accompanied by inflammation of the urinary tract. Around 60% of bladder malignancies arise in the bladder's posterior wall, whereas 20% occur in the triangular area. CG can occur at any age, but is most prevalent in middle-aged women. It is most

frequently found in the triangle and neck of the bladder. Chronic urinary tract irritation is the primary clinical symptom (31,32).

The surface of bladder cancer lesions is not smooth in imaging examinations, with liquefactive necrosis and spot-like calcifications visible. The density is not consistent and is enhanced greatly during enhanced scanning. The CT value of bladder cancer is higher than that of glandular cystitis. Bladder cancer may metastasize to the pelvic lymph nodes and invade the bladder's muscularis and adventitia. CG lesions have a smoother appearance than bladder cancer lesions and an even interior density. Density can be increased during enhanced scanning, however the effect is subtle. The lesions are primarily submucosal in nature and do not infiltrate the muscle layer or adventitia (18).

Although biopsy is required to confirm the diagnosis of CG, doctors can make an earlier diagnosis and therapy recommendation based on the clinical and imaging presentations of patients.

### Therapy

There are no particular therapies for CG. There is no one-size-fits-all therapy plan. The following are the available therapy options.

#### Conservative treatment

According to some researchers, CG is a benign, reversible condition. It is sufficient to eliminate the inducement, conduct periodic reviews, and administer symptomatic treatment such as anti-inflammatory medication (2,3).

#### Minimally invasive surgical treatment

The most often used treatment for CG is transurethral bladder lesion removal. Transurethral electric resection, transurethral electric coagulation, transurethral electrovaporization, and transurethral laser resection are some of the surgical methods available. The procedure is conducted under either epidural or general anesthesia. The bladder is adequately filled with liquid during the operation to flatten the mucosal folds. This enables the complete eradication of all diseased mucosa and lamina propria. The resection range should be approximately 2 cm greater than the visible range of the naked eye and extend to the normal muscle layer. Because this procedure utilizes the natural lumen, it results in less trauma, fewer postoperative problems, and less pain for the patient (19,33-41).

### Open surgery

Currently, the most often used open surgical techniques include bladder mucosal dissection, partial cystectomy, and total cystectomy with urine diversion. Open surgery is often reserved for patients with a wide variety of bladder abnormalities, a significant depth of invasion, and a suspicion of malignancy. Because open surgery is more stressful, it is rarely the first option for treatment. Urologists should exercise strict control over surgical indications (35,36).

### Bladder perfusion therapy

Following transurethral surgery, bladder perfusion therapy is frequently supplemented. However, there are significant disagreements on whether or not to perform routine drug infusion therapy following surgery, as well as the frequency of bladder infusion following surgery. Chemically hazardous medicines, immunosuppressants, and anthracyclines are currently widely used. The majority of scholars oppose conventional medication infusion therapy following surgery. One study shows that there is no substantial difference in efficacy between resection combined with intravesical perfusion and simple resection (37). Bladder perfusion medications are quite effective. The bladder may develop cystitis as a result of the medication and exacerbate the patient's urinary tract symptoms (38). Additionally, certain researchers advocate for the addition of bladder perfusion therapy following surgery (39). Further research is required to establish the necessity, safety, and scientific validity of postoperative perfusion therapy for CG. Along with the aforementioned infusion medications, which are mostly used to treat bladder cancer, studies have demonstrated that sodium hyaluronate can be infused into the bladder. Sodium hyaluronate can stimulate the regeneration of the bladder's urothelial glycosaminoglycans layer, establishing a bladder mucosal barrier that protects the bladder mucosa from direct stimulation by numerous chemicals in the urine. As a result, the incidence of CG may be reduced (40-42).

Additionally, certain unique treatments such as bladder infusion curcumin (43), oral steroid hormones (44), submucosal injection of botulinum toxin A in the bladder (45), radiation therapy (46), hyperbaric oxygen therapy (47) and bioactive ingredient, such as Pachymic acid (PA) (48), can be used to treat CG.

Regardless of the method employed to treat CG, the CG therapy principle is to remove as much diseased tissue as feasible while maintaining safety, hence effectively minimizing the recurrence rate (49).

Follow-ups should be undertaken on a regular basis (50). If malignant alteration occurs, early detection and action can be used to produce the best possible therapeutic outcome. Additionally, certain psychiatric treatments can be employed to alleviate the patient's worry and other psychological difficulties produced by long-term urinary discomfort (51).

### Conclusions

There are some debates and disagreements on the genesis and pathophysiology of CG. There is no standardized protocol for clinical treatment. The urinary tract symptoms of CG have a significant impact on patients' daily lives. Additional research on CG cystitis is required immediately.

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### Footnote

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