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Recurrent Cystitis: Patients' Needs, Expectations, and Contribution to Developing An Information Leaflet. A Qualitative Study

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ABSTRACT: Objectives: Recurring cystitis (RC) is a common complaint among women. It has a significant impact on patients' quality of life. Although contributing factors are known, the underlying physiopathological process in not well understood, resulting in various treatment approaches in spite of existing guidelines. This study aimed to develop a patient information leaflet after assessing women's needs and expectations. **Design:** We conducted a prospective, qualitative study using recorded semi-structured interviews with patients suffering from RC. **Setting**: face-to-face interviews were conducted in Southern France in various settings. **Participants**: Twenty-six patients participated. **Interventions**: Interviews took place from 01/2018 to 04/2018, lasting about 20 minutes. **Results**: Women's knowledge of the condition was heterogeneous, they reported a major impact on their daily life, a high level of anxiety, various management strategies and wished to avoid taking antibiotics, preferring alternative approaches. Patients complained of a lack of understanding and sympathy on the part of physicians and society and wished for more autonomy with delayed/back-up prescriptions, a multidisciplinary follow-up and most of all suitable information. **Conclusion**: The information leaflet should improve patients' knowledge and capacity for self-care, contribute to standardize practice and limit inappropriate antibiotic use. **Practice Implications**: physicians should allow time for discussion of this resource with women suffering from RC. This should reassure them and, in many cases, avoid inappropriate antibiotic prescriptions.

Keywords: recurrent cystitis; patient involvement; patient information leaflet; inappropriate medication; qualitative research.

Word count: 4 420 words

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study highlights the needs and expectations of women suffering from recurrent cystitis (RC).
- It points to the need for improved antimicrobial stewardship on the part of physicians managing patients with RC.
- It also points to the need for physicians to provide patients with reassurance, written explanations, and a broader scope for self-management.
- The study resulted in the development of a detailed information leaflet for women to understand and manage their condition.
- The study was conducted on a relatively small sample in a limited geographical area.

1. INTRODUCTION

Cystitis is an extremely frequent complaint, one out of two women developing an episode over her lifetime [1]. It is a benign condition generally treated with antibiotics prescribed by the primary care physician.

Recurring cystitis (RC) is defined as the occurrence of at least three episodes of cystitis over a 12-month period. Although the prevalence rate of RC among the female population is not known, some studies on small cohorts of patients suggest it may be quite high [2, 3, 4].

Many women complain of the major impact of the condition on their daily life, as pain and urinary frequency can be invalidating, as well as on their sexual activity [5]. The significant psychological consequences, which are dominated by anxiety, have rarely been explored [6]. According to the French National Agency for Medicines and Health Products Safety (ANSM), urinary tract infections (UTI) currently rank third among ambulatory antibiotic prescriptions in France [7]. Choice of antimicrobial agents and duration of treatment both appear inappropriate: fluroquinolone and third generation cephalosporin prescriptions and treatment duration are excessive [8] and do not take either the epidemiology of antimicrobial-resistant bacteria nor the impact on the gut microbiota into account, and thus do not comply with recommendations [9, 10]. In some countries, treatment is discussed with patients and alternatives to antimicrobial treatment are offered which have not shown an increased rate of complications or recurrence compared to patients treated with antibiotics. [11, 12]. In France, the needs and expectations of patients suffering from RC have not been evaluated.

As part of the aims of a working group (RéSO InfectiO PACA EST) on infectious diseases at Nice University Hospital, it was decided to develop an information leaflet

specifically intended for patients with RC, in order to improve and standardize management of RC and select and educate certain patients to self- treat.

Prior to developing such a leaflet, patients' needs and expectations were investigated to develop a content that met their demands.

2. METHODS

Qualitative semi-structured interviews were undertaken by a single researcher trained in qualitative research methods, with a purposive sample of patients with a definite diagnosis of RC, *i.e.* at least three episodes of cystitis over 12 consecutive months, over 18 years of age, with no cognitive impairment [13].

2.1 Patient and Public Involvement

Patients were necessarily involved in the conduct of this research as it consisted in direct face-to-face interviews during which patients were asked to express their experience of recurrent cystitis and their needs and wishes to help them cope with the condition. They were also partly instrumental in recruiting other patients via a snowball effect. Lastly, but most importantly, their input was needed to develop an information leaflet tailored to their wishes.

2.2 Geographic study setting: the Ajaccio area conurbation in Corsica (CAPA).

Patients were recruited via their community-based general practitioner, gynaecologist or urologist as well as via hospital-based physicians. Recruitment was subsequently extended to include patients attending medical laboratories (where information describing the study was delivered through leaflets posted in waiting rooms), pharmacists, and via social networks. A snowball effect was produced as recruited patients had contacts with women with similar complaints. Recruitment continued until content saturation was achieved, as observed through immediate de-briefing and ongoing data analysis [14, 15, 16].

2.3 Interview

The interview guide included a brief introduction, a qualitative section with seven neutral, open-ended questions that followed a guiding thread with the possibility of using topical probes if necessary, and a quantitative section with socio-demographic (age, educational level, socio-professional category, area of residence) and medical details related to RC (attending physician, age at start of RC, main past or current medical conditions). The interview guide was initially tested on two patients and proved satisfactory. No further alteration was required.

2.4 Data collection

Recorded Interviews were conducted and recorded according to patients' availability and in any quiet location they chose by a trained researcher (LB). The aims of the study and the interviewing procedure were explained, and patients provided written informed consent to participate.

2.5 Data analysis

Each recorded interview was transcribed verbatim by a trained secretary, with as many details as possible, both verbal and non-verbal. A de-briefing procedure by the researcher took place immediately following each interview to record the overall impression and identify the main ideas put forward by the patients and was shared with co-authors. This allowed to identify the point when data saturation was reached and discontinue recruitment. [14]

Thematic analysis was performed using NVivo© software. This included several stages: getting acquainted with the content of the interview was followed by initial coding, identification of overarching themes, grouping of themes or categories of ideas, exploration of links and interaction between themes, description and supporting quotations, according to an iterative procedure. On an on-going basis, the data analysis procedure was discussed among the co-authors and conducted in accordance with their comments.

Each category was summarized in the results section. At the end of the results section, the implications derived from these results were illustrated in a table intended to be used as a basis for developing the information leaflet.

2.6 Ethical Approval

Ethical approval was not required as, according to French law and the Ethics Committee, the present study is not considered as research on human subjects but as a satisfaction survey. In France, ethical approval is not required according to Article R1121-1-1 of the French Public Health Code [17].

3. RESULTS

3.1. Quantitative results

3.1.1. Participants

A breakdown of patient inclusion is illustrated in the patient flowchart shown in Figure 1

Patient characteristics are shown in Table 1.

Mean age	**42 years (range 18 – 79),**
Educational level:	
• High school or less	6
• Some college or tech school	10
• Bachelor's degree or higher	10 (of which 5 registered nurses)
Work status	
• employed	19
• retired	5
• jobless	2
Mean age of initial occurrence	30 years (Range: 16 – 70 years)
Mean duration of complaint	13 years (Range: 1 – 31 years)
Type of recurring cystitis	
Simple	20
At risk for complication	6

Table 1. Patient characteristics.

Among the stated risk factors, many women mentioned insufficient hydration, sexual intercourse, pregnancy and parturition, withheld micturition, constipation, and stress.

3.1.2. Physicians

Among the 53 physicians contacted, 50 agreed to participate in recruiting patients (33 community-based practitioners: 31 general practitioners (GPs), 2 gynaecologists, and 17 hospital-based practitioners: 9 Accident and Emergency physicians, 4 gynaecologists, 2 urologists, and 2 infectious disease specialists).

3.1.3. Interviews

The interviews were conducted between January 30th, 2018, and April 3rd, 2018. Their mean duration was 22 minutes (range 9-39 minutes). Sixteen interviews took place in a medical setting, 6 in patients' home, 3 in patients' workplace and 1 in a coffee shop.

3.1.4. Recruitment

Among the 26 patients interviewed, 8 had been recruited via their physician (mainly GPs), 5 via leaflets, 7 via Facebook and 6 through snowball sampling.

3.2. Qualitative results

Qualitative results are shown in Table 2.

Patient quotes are detailed in Appendix 1

Table 2. Summary of results and implications. FT: Fosfomycin-Trometamol

THEME	KEY FINDINGS	QUOTES	IMPLICATIONS
KNOWLEDGE OF THE CONDITION, ITS CAUSES AND RISK FACTORS	Patients were confused regarding the difference between cystitis and urinary colonisation: they had queries regarding the link between smelly urine and infection, requesting a definition of cystitis, an explanation of the causes and risk factors. Several patients mentioned hormonal causes - pregnancy, menopause, endometriosis and oral contraception - as risk factors. Many patients associated cystitis with sexual intercourse. Hereditary factors were also mentioned. Patients also identified stress and fatigue, post-voiding residual urine, insufficient hydration. They wished for written explanations.	13Q1 12Q1 4Q1, 4Q3 16Q1, 26Q1, 20Q1, 14Q1 22Q1, 26Q2 1Q1, 1Q2, 28Q3, 6Q1	Patients need a clear definition and understanding of RC, UTI and colonisation, and causes thereof, with clear, written, illustrated information.
IMPACT ON DAILY LIFE	Patients described intense pain and anxiety interfering with their social, professional, family, and sexual life. A burning sensation upon voiding and urinary frequency were particularly invalidating and resulted in social isolation: home confinement, interference with work or having to take sick leave. Patients also complained of a major impact on their sexual activity, leading to abstinence during episodes, but also to reduced sexual activity at other times.	10Q1,10Q2, 27Q2, 19Q1 1Q1, 16Q2 19Q2	The link with hygiene, diet, hormonal status (vaginal dryness) should be explained and accompanied with a diagram illustrating anatomical details.
COPING STRATEGIES	Few patients resorted to analgesics. Preventative measures regarding hygiene and diet, particularly increased fluid intake, were usually known but unevenly implemented, though some wished for more information on the subject. Many patients resorted to various forms of cranberry preparations. Half of them had a back-up prescription for antibiotics provided by their physician.	Q4, 24Q1, 6Q2	Patients should be encouraged to increase their fluid intake and resort to analgesics, and should be provided with a back-up prescription of antibiotics in anticipation of future episodes
INVESTIGATIONS	Several patients had undergone various investigations (ultrasound examination, urinary tract scan, cystoscopy…), others wished for further testing or specialist advice. One patient confused Urine Test and Cervical swab.	19Q3, 24Q2	Patients need a definition of urine microscopy and culture

			The relevance of urine dipstick test and urine culture for the management strategy of RC should be explained.
ANTIMICROBIAL THERAPY AND POSSIBLE ALTERNATIVES	Various antibiotic treatment strategies were used: fluoroquinolones, fosfomycin-trometamol, cotrimoxazole, nitrofurantoine, amoxicillin, with frequent self-medication, mainly with FT but also nitrofurantoine or cotrimoxazole leftovers from a previous infection.	17Q2,	Patients need to be reminded of indications for antibiotic therapy and preferential compounds according to type of RC.
	Patients considered there should be alternatives to antibiotics. They were concerned that antibiotics would harm their health, result in adverse events, and lead to emergence of bacterial resistance.	14Q6	A short explanation on bacterial resistance should be given, as well as advice on non-antibiotic strategies.
VIEWS ON PHYSICIANS' APPROACH	Patients resented the constraint of repeated visits to the GP, who was often difficult to reach immediately. Several wished to self-manage their infection and requested back-up prescriptions for urine culture and single dose FT treatment. Lack of anticipation on the part of physicians led to patients performing a urine culture without a prescription (so were not reimbursed) and to self-medication. Patients complained of lack of information, empathy and support, investigations and follow-up. Some were fatalistic, accepting their condition as inevitable (referring to female family members and friends with the same problems).	14Q5, 1Q2, 20Q1 18Q1	atients require clear, written management dvice, and should be informed on how and when to self-treat and be provided with ack-up prescriptions accordingly. The relevance and timeliness of investigations should be explained, and guidelines for an investigation strategy for simple cystitis and for cystitis at risk for complications
	Antibiotics were considered over-prescribed and banal, and conducive to neglecting investigations into causes and risk factors. Women wished for information regarding diet and hygiene measures. They also wished for alternatives. Some tried « natural » approaches, i.e. phytotherapy or aromatherapy, despite their cost.	11Q2	A multidisciplinary approach and a yearly dedicated medical consultation should be made available.

The Patient Information Leaflet resulting from the analysis of these interviews can be found in the Supplementary Material.

4. DISCUSSION

4.1. Strengths and limitations

4. 1.1. Strengths

This qualitative study in the form of individual interviews revealed the expectations and needs of patients suffering from RC, as well as their opinions and attitudes. The method provided the opportunity for an in-depth approach of the subject, thanks to the conversational character of the interviews which were able to overcome any embarrassment these might have caused. The semi-structured interview guide contained open questions that allowed to adjust the interview as it progressed. It was tested and found suitable after two pilot-interviews.

The various recruitment approaches resulted in a diverse and complementary theoretical sample, with a substantial number of respondents with varied characteristics, regarding age, number of years with the condition, age when it began, educational level.

To reduce loss of information to a minimum, each interview was followed by immediate debriefing. Thematic analysis was optimal thanks to the use of N-Vivo© software.

4.1.2. Limitations

The fact that this survey was conducted in a specific geographical area in France could question the relevance of our findings outside this particular context. However, the opinions and comments expressed by the interviewees are in line with those reported in the UK and other countries [18, 19].

Participants' response was subject to their level of comprehension and motivation and the time they could allow for the interview. As in all qualitative face-to-face surveys, adjusting to the patient introduces an inevitable bias linked to the interaction between patient and interviewer.

Of the 31 GPs contacted, only five recruited patients. This may be because they omitted or forgot to inform patients, or because patients refused to participate. Recruitment was thus extended to laboratory waiting rooms and pharmacists via leaflets and to social networks to reach an adequate sample. It is doubtful however that such diverse recruitment methods could impact the content of the interviews.

Several patients' profession was related to healthcare, as information on the study and contact details were provided in healthcare facilities, and also due to snowball sampling. This may have translated into heightened health-related awareness of their condition, and thus stronger support for the proposed intervention.

Lastly, qualitative thematic analysis and interpretation of results necessarily imply a degree of subjectivity on the part of the researcher. Co-authors were involved in every step of the analysis.

4.2. Interpretation of findings in the light of published research

4.2.1. Patients' knowledge of the condition, its causes and risk factors

Confusion regarding the difference between cystitis and urinary colonisation could explain patients' inadequate strategies, such as resorting to antibiotics because of smelly urine. Few patients had any idea of the origin of their condition. Indeed, the physiopathology of recurrent cystitis remains obscure and multifactorial. In the case of relapsing RC, the possible presence of intracellular uropathogenic E coli within the bladder epithelium could interfere with an effective immune response and give rise to re-emergence of infection from this reservoir [20 21], which may require reconsidering treatment approaches.

Several patients mentioned hormonal causes. Oestrogen insufficiency has been described as a causative factor [22, 23]. The SPILF suggests local oestrogen therapy after menopause if approved by the gynaecologist [9]. Oestrogen insufficiency results in decreased Lactobacillus vaginal colonisation and E. coli proliferation, and a study of local prophylactic treatment with probiotics shows encouraging results [24]. In the present study, none of the patients took topical oestrogens and only one took probiotics.

Some patients mentioned hereditary factors, and a history of UTI in mothers has been noted by infectious disease specialists, suggesting possible genetic susceptibility to infection [25], although this may also be related to behavioural factors within families [26]. The high frequency of RC upon initiation of sexual activity is described in the literature [27]. However, stress, fatigue and apprehension of further episodes were also identified as risk factors, as well as bowel dysfunction, as identified in an ongoing prospective study conducted in our area [28, 29].

4.2.2. Impact on daily life

Social isolation, sexual abstinence during episodes, but also reduced sexual activity at other times were mentioned and have also been described in an Italian study [6].

The major psychological impact, namely anxiety, resulting both from the RC episodes themselves (but which could also be a possible cause) and from the lack of adequate management, emphasizes the need for a multidisciplinary approach, taking the stress factor into account.

4.2.2.1. Patients' coping strategies

The variety of strategies to cope with RC point to a wish by many patients to avoid antibiotics and to self-manage their condition: herbal medicine, aromatherapy... The importance of increasing fluid intake was widely known, if not sufficiently applied. Although many patients resorted to various forms of cranberry preparations, these have not been evaluated in terms of effectiveness, while French recommendations advise a minimum daily dose of 36mg proanthocyanidin [30 ,31 32]. Back-up antibiotic prescriptions, often mentioned in this survey, have been advocated, along with guidance as to their appropriate use [19].

4.2.3. Investigations

While urine culture was performed too often for simple RC, dipstick tests were infrequent despite recommendations by the French language society for infectious diseases. [9]. However, the cost of dipstick tests is not endorsed by the National health insurance, which limits their use. Another inappropriate approach was to treat urinary colonisation revealed by an unnecessary follow-up urine microbiology and culture after a clinically effective antibiotic course, which should not lead to further antimicrobial prescription.

4.2.4. Antimicrobial therapy and possible alternatives

Although a wish to avoid antibiotics was expressed, these were used by many patients, especially FT due to the convenience of a single dose, but also inappropriate use of other compounds, whether self-administered or inadequately prescribed by a physician. Such variable coping measures when confronting initial signs of cystitis highlight the need for standardized approaches since the stated treatment strategies did not conform with recommendations: self-medication with fluoroquinolones, systematic urine culture , secondary adaptation of antibiotic treatment to susceptibility test results for uncomplicated RC; regular empirical antibiotic treatment for potentially complicated RC, with a single, thus suboptimal, FT dose; nitrofurantoïne as antibiotic prophylaxis, which is strictly contra-indicated according to French guidelines [9, 10, 33]. Many non-antibiotic options for RC have been explored [34]. Treatment strategies have been evolving in Scandinavian countries and in Germany, where pain killers/ non-steroid anti-inflammatory drugs (NSAIDs) can be offered for treating cystitis with mild/moderate symptoms in a watch and wait approach although their efficacy remains controversial [12, 35, 36]. Chinese phytotherapy has recently been shown to be effective [37]. French guidelines state that topical oestrogens can be beneficial to menopaused women [38], while, according to a Spanish study, prevention with D-Mannose significantly decreased the frequency of UTI [39]. Immunotherapy using a vaccine based on a bacterial extract is currently being tested [40]. Lastly, among the various approaches aiming to alleviate pain and stress, hypnosis could prove useful: it has been shown to alleviate symptoms in irritable bowel syndrome and to reduce the need for analgesics during surgical procedures [41]. Preliminary results of its use in RC are promising [42, 43].

4.2.5. Patients' views on physicians' approach

The lack of physicians' and society's understanding regarding RC contrasts with the major impact of the condition on patients' activities, perception and degree of anxiety [4443]. Ignorance of the cause of RC, cost of antibiotic alternatives, lack of investigation or of conclusive results thereof led patients to adopt a fatalistic attitude. This was noted by Italian authors who concluded to the "cost of resignation" related to physicians' lack of involvement [6]. Certain patients even expressed surprise at being questioned regarding their opinions on their management of RC.

Patients' request for more autonomy has been addressed in France with a strategy put forward in 2014, targeting selected, educated women with no risk factor, subject to twice-yearly re-assessment: this consists in self-treatment thanks to a delayed prescription, following a (non-reimbursed) dipstick test to confirm cystitis [9]. A recent qualitative survey conducted in the United Kingdom pointed to the need for addressing physicians' knowledge and skill gaps on UTI in women under the age of 65 years, including non-pharmaceutical recommendations for self-care [45].

Lastly, the request for more thorough, multidisciplinary management relying on various strategies is not in line with recommendations put forward by the SPILF for uncomplicated RC in 2014 [9]: in non-menopausal women with a normal pelvic and urethral clinical examination, no further investigation is systematically required. In other situations, for women at risk for complications, management should be decided by a multidisciplinary team. Few women (25%) had consulted a urologist or a gynaecologist, while infectious disease specialist advice was very rarely sought.

Clarification of this trajectory should result in more standardized approaches and reduce patients' anxiety.

3. Practice Implications

3.1. Information leaflet

Based on the requests put forward by the interviewees, an information leaflet should be made available and include the following items to meet the needs and expectations of patients with RC:

- A reminder of the definitions
- Description of the known causes and risk factors of RC supported by a diagram and information on the usefulness and timeliness of urinalysis, dipstick test and urine microscopy and culture
- Procedure to be followed when first signs of cystitis appear
- Role of antimicrobial treatment and preferred compounds
- Summary of possible non-antibiotic treatments

Clear suggested strategy for initial investigations/specialist referral

Such an information leaflet can be considered as a means of patient empowerment, as recommended by the French Language Society for Infectious Diseases (SPILF) in 2014 and which has still not been put into practice. It can contribute to patient education, aiming to involve patients in their healthcare and quality of life, while reducing inappropriate antibiotic use [9].

The effectiveness of information leaflets has been demonstrated in various contexts, namely regarding paediatric antibiotic prescriptions when coupled with GP online training [46]. A patient-

clinician shared decision-making leaflet was developed in the UK that addressed the consultation barriers and promoted patient empowerment, with both leaflet and corresponding explanations delivered by the physician [47]. A systematic review published in 2015 exploring the effect of patient information leaflets during general practice consultations for common infections concluded that these could reduce antibiotic prescriptions and consultations [48].

Although the use of such a leaflet will depend on the physician's wish to grant patients more autonomy and on the time available for dialogue, it should prove beneficial for both in the long run by lifting part of the GPs workload while reassuring patients with RC. A recent symptom score questionnaire has been translated in many languages to assess patient-reported outcomes [49]. Patients would have a clear, handy and relevant resource which would contribute to reduce their anxiety by addressing several of their queries and describe the procedure to follow in case of cystitis. For previously selected and educated patients provided with back-up of urine microbiology and culture and/or antibiotics, the leaflet would increase autonomy. A printed resource facilitates memorisation and assimilation. Clear and explicit definitions can eliminate any confusion and thus prevent inadequate treatment. A diagram can help understand the links between risk factors and hygiene and dietary measures to adopt. Improved understanding should lead to better adherence to the suggested management strategy. A summary of various non-antibiotic treatments, whether validated or not, can meet patients' request, describe how each should be administered and allow patients to test their respective effectiveness. Lastly, its use would contribute to improve to harmonize the currently highly disparate management approaches reported by patients.

Such an approach reflects most patients' demands. The leaflet could thus contribute to train physicians from various specialties in good clinical practice. This could even be complemented with a specific resource for physicians.

Assessment of this resource on a wider scale is now necessary, by distributing it to the RésO GPs and their patients, to confirm its relevance and consequently offer it to all women suffering from RC.

a. Contributorship statement: Véronique Mondain: Conceptualization, project administration, supervision, review and editing, validation; **Pia Touboul**: Conceptualization, methodology, supervision, formal analysis, validation; **Louisa Bey:** investigation, data analysis, writing-original draft. All authors have agreed to the published version of the manuscript.

b. Competing interests: None

c. Funding: This study received no external funding

d. Data sharing statement: Face to face interviews, conducted in French, were recorded and transcribed verbatim for analysis. These transcriptions are available upon request. The most relevant quotes are listed in the Patient quotes

e. Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Nice University Hospital.

f. Informed Consent Statement: Participants freely accepted to be interviewed.

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Figure Legend

Figure 1. Flowchart.

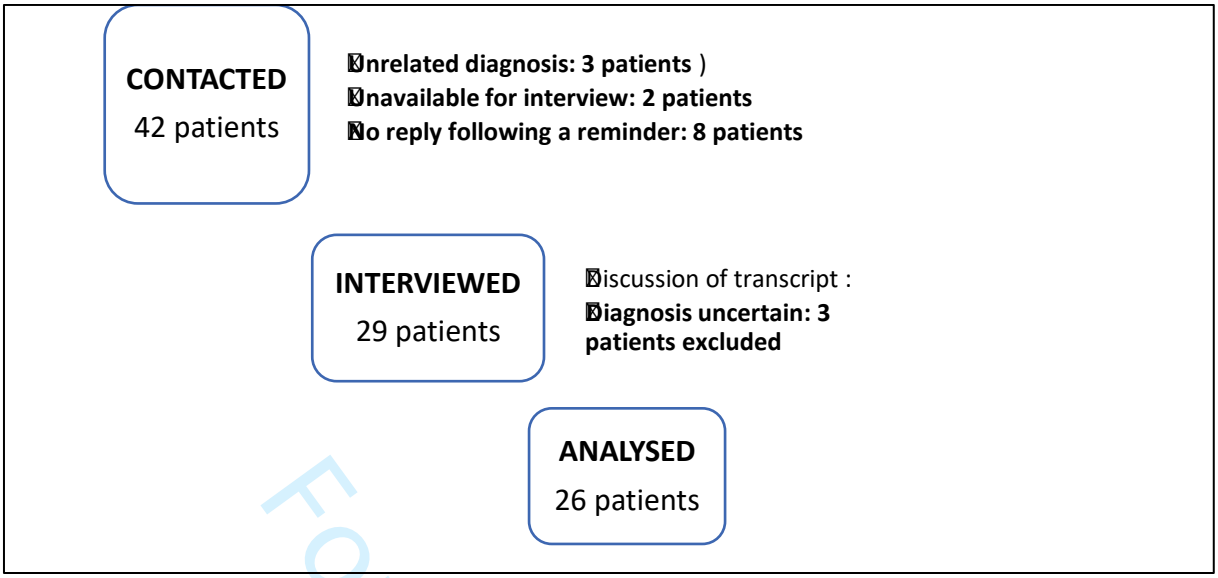


Figure 1 : Patient Flowchart

INFORMATION LEAFLET FOR PATIENTS WITH RECURRENT CYSTITIS

WHAT IS CYSTITIS?

Cystitis or lower urinary tract infection is a bladder inflammation caused by bacteria. The main symptoms include a burning sensation when passing urine, urgency to urinate (pollakiuria), and sometimes blood in the urine (hematuria). **Recurrent cystitis** is usually defined as four episodes of bladder infection within the previous 12 months.

A **urine dipstick test** is the first step in guiding the diagnosis when leukocytes and/or nitrites are detected.

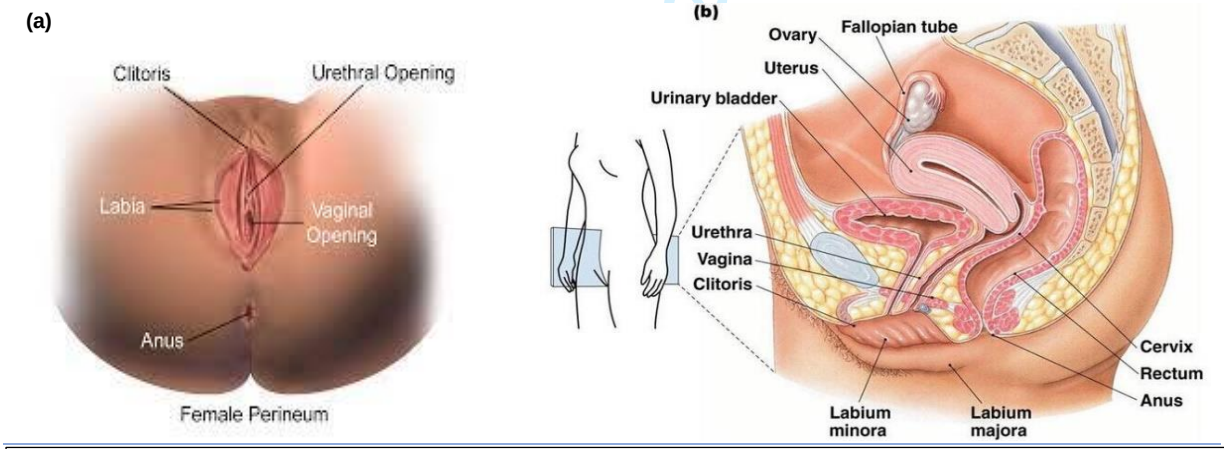
Urine culture can be performed in order to identify the bacteria involved and their antibiotic susceptibility.

WHAT IS THE DIFFERENCE WITH URINARY TRACT COLONIZATION? WHAT ARE THE OTHER TYPES OF URINARY TRACT INFECTION?

If your urine is cloudy and/or foul-smelling but you do not experience any discomfort, it is therefore not cystitis but **urinary tract colonization.** There are bacteria in the urine, however they do not cause any infection. In such cases, you don't need to take an antibiotic but should simply increase your fluid intake.

Cystitis refers to an infection of the bladder, while **pyelonephritis** refers to an infection of the kidneys. Common symptoms of pyelonephritis include fever and/or chills and/or back pain. The infection must be rapidly treated with a different antibiotic than the one recommended for the treatment of cystitis.

WHAT CAUSES CYSTITIS? HOW CAN I PREVENT IT?



Bacteria present on the **perineum** (from the digestive tract and vaginal flora) can enter the bladder through the urethra. To prevent these bacteria from going into the bladder and multiplying, you can use the following tips:

- Drink at least 1,5 L of water each day, *avoid bladder irritants (coffee, tea, tobacco, alcohol…)*
- Do not delay going to the toilet, do not void in a standing or crouching position, *always urinate after sexual intercourse*
- *Wipe front to back, avoid diarrhea or constipation*
- Maintain good intimate hygiene: **external wash only**, once a day, using a neutral pH soap
  Symptomatic treatment of vaginal dryness if necessary (estriol cream)
- *Apply vaseline to the meatus after urination or before activities that promote infection (sexual intercourse, sitting while commuting, sports that promote infection...)*

WHAT SHOUD I DO IF CYSTITIS SYMPTOMS APPEAR?[1]

IN ORDER TO AVOID ANTIBIOTICS:

- Increase hydration to 3L per day[2] (forced diuresis)
- Relieve pain with:
  Phloroglucinol
  Ibuprofen[2]

IF FAILURE AFTER 72h

SIMPLE RECURRENT CYSTITIS….

Do a urine dipstick test[3]

Then self administer[4] : Fosfomycin Trometamol **OR** Pivmecillinam

… OR WITH RISK OF COMPLICATIONS

Try to wait for the urine culture and antibiotic susceptibility test results[4] to choose the most suitable antibiotic with your doctor, **OTHERWISE** Fosfomycin Trometamol **OR** Nitrofurantoin

In 40 % of cases, antibiotics are not necessary for cure. They act directly on the normal bacterial flora (microbiota) and may have adverse effects, e.g. fungal infection (thrush) or diarrhoea. Their use also increases the likelihood of bacterial resistance to antibiotics[5].

If your cystitis episodes keep occurring very frequently (> 1 / month), or are specifically related to sexual intercourse, you need to discuss with your physician whether you should take a **prophylactic antibiotic treatment**, i.e. an extended antibiotic course to prevent cystitis (Fosfomycin Trometamol 1 sachet/week or Trimethoprim 1 pill, as prescribed by your doctor).

…WHAT ABOUT NON-ANTIBIOTIC TREATMENTS?

- Phytotherapy :
  - cranberries if infection due to *E. Coli*: 36 mg/d of proanthocyanidins, during 3 to 6 months
  - *Other: treatment of the episode with Busserole[6], Heather, or Hibiscus*
- *Prevention or treatment of the episode using D-Mannose if E. Coli infection.*
- *Treatment of the episode with Aromatherapy[6]: essential oils of thyme, cinnamon, tea tree, savory*
- *Relaxation and pain management techniques : sophrology, yoga, hypnosis*
- *Vaccines: oral route or vaginal suppository but non-commercialized in France (available in Switzerland or Belgium)*

WHICH FURTHER EXAMINATIONS SHOULD BE CARRIED OUT?

If the urological or the gynecological examination results are normal, **no further investigation will be systematically performed** except for menopausal women and/or women with specific medical histories. For all other cases, management should be discussed by a **multidisciplinary team** including an infectious diseases specialist, and conclusions communicated to the general practitioner.

[1]Subject to your general practitioner review, at least twice a year. Should treatment failure occur, contact your doctor
[2]In the absence of medical contraindication: check with your doctor
[3]After 4 to 6 episodes of cystitis, you should have a urine culture to look for antibiotic resistance
[4]Talk to your doctor about anticipatory prescribing of urine culture and/or antibiotics according to your situation
[5]This is why Fluoroquinolones and third generation Cephalosporins are not recommended
[6] Make sure you know how essential oils are used. Let your physician or pharmacist help you with the correct prescription. Contraindicated in case of pregnancy and breastfeeding

Appendix 1

Patient quotes

N°	*Interview*	*Quote*
1Q1	***1***	*« it's really related to stress, at least, that's my feeling »*
1Q2		*"So, yes, I have problems because when I pee, my bladder doesn't empty itself"*
1Q3		*« I try to get the doctor to write me a prescription I can keep. But they don't always do it… they say: « you must do an urine culture beforehand » But when it happens, I need to take the antibiotic quickly to avoid the pain. Admittedly, I haven't often done the test, to be honest! When it happens, I tend to rush to call the doctor and ask: "I've already been to the pharmacy and… can I have the prescription? » ».* *"I think it would be good to have a prescription, even for a urine culture, or to be able, from the susceptibility test, to find the antibiotic I need."*
4Q1	***4***	*« I met women much older than me, who also had recurring cystitis, they don't even know why they have this! It makes your life hell, you know! »*
4Q2		*« Well, I can't carry out my usual activities, I can't go shopping because I know I'll need to pee, and it burns, it's horrible! »*
4Q3		*"Why do we get so many RC episodes?".*
6Q1	***6***	*"I think the best thing would be to have a little booklet explaining because we don't have time to discuss it when we visit the GP."*
6Q2		*"nobody tells you to do tests, or… ummm, it's really NOT NORMAL to take antibiotics every 6 months! »*
6Q3		*"'This is what you should avoid, this is what you should rather do, this is when you should see your doctor', …that wouldn't be bad! "*
7Q1	***7***	*« I asked for further investigations because I get very tired taking antibiotics every month. So, at one point I said maybe we should look a bit deeper since I'd had episodes of cystitis but also of pyelonephritis. So, there I think it's also perhaps because the infection wasn't properly cured. So that's why I asked the doctor – I often change my GP – and I was sent to see a urologist ".*
7Q2		*« Since when do you have recurring cystitis? Since my pregnancies."*
10Q1	***10***	*« It's awful, because you're stuck at home*
10Q2		*«Well, the worst thing is to have to go to the toilet all the time and… NOT TO PEE!*
10Q3		*That's the worst, because you pee ONE DROP, and that drop, its… AWFUL! It burns, burns, burns !!! »*
11Q1	***11***	*"I don't go to the doctor's because I know antibiotics will be prescribed. If there was a follow up, we could discuss it each time and see if there's something else."*
11Q2		*« There's no follow-up. Although we get this regularly… »*
12Q1	***12***	*"So I'd really like to know why… what is cystitis? What's going on in the vagina? …and why does it start again each time?"*
13Q1	***13***	*. "Because I don't always have this burning sensation. Sometimes, it's only turbid and smelly urine. So, in that case, if I've run out of FT, then I take herbal teas."*
14Q1	***14***	*"… I'd like to know, is there a link with contraception or not? Are there means of contraception that favour cystitis, or not?"*
14Q2		*« after sexual intercourse, there's often a beginning of urinary tract infection"*
14Q3		*«since I'd told her I'd had a few episodes of cystitis during the year, the gynaecologist did a cervical swab."*
14Q4		

		« Well … prefer, hum… perhaps not, but to think "I'm trying something else and if it doesn't work, resort to antibiotics".
14Q5		*"Because in my view, antibiotics are really effective … it's a bit like a bomb, setting off suddenly, acting quickly! And that way, just using it when it's needed, if prior treatment hasn't worked. » (Int 14)*
14Q6		*« Isn't there something else that would be just as effective? Because taking antibiotics straight away, you see, always taking antibiotics, I don't know if that's really… good! Doesn't it generate … I don't know… resistance too in bacteria that…can cause cystitis? So, wouldn't there be other ways (and that takes us back to prevention), that would avoid taking antibiotics every time? »*
14Q7		*« Well, for a start, to know if I've properly identified all the causes that can lead to cystitis, because maybe there are things that I do every day that I'm unaware of and that can contribute to cystitis. »*
14Q8		*« To make matters worse, doctors are always jam-packed, so you need to wait a week to treat cystitis, It's a bit LONG!!! And just to get an antibiotic prescription that I can go and ask several times from the pharmacist. It's not very realistic in case of cystitis which occurs quite suddenly and can be treated very quickly, but that must be done right away! »*
14Q9		*« So that's rather a nuisance, the fact that there's no follow-up, for instance when you go to the GP and you've already been several times because of cystitis… you really get the impression that it stays in the file, because for the doctors, it's a bit anecdotal… They're going to ask if our pain in the arm (if you came once for that), if that's over now, etc., but for cystitis, even if you've been five times for that, they're not bothered... it's not something that I feel is important for them. » (Int 14)*
14Q10		*« Even at work, when you say, "I can't come, I've got cystitis", well, people don't understand, they tend to consider it trivial, it's not serious; even the doctors! »*
14Q11		*"Written yes, I think, with drawings it's important also, to understand the links with the anatomy and to know how it works."*
16Q1	***16***	*"So I had it in fact during each of my pregnancies, practically every month"* *Because when I get it, generally we avoid intercourse because … it hurts too much!*
16Q2		*« In fact, the only information I have is the one I was given as a child. My parents were very careful so I was often told 'you don't drink enough, you should go to the toilet more often, that kind of thing. In fact, that's the only information I have about urinary tract infection, because recently I didn't have another one. That's why I can't identify the cause any more. »* *Or… perhaps there are other reasons, so I'd really like them to be identified,*
17Q1	***17***	*« OK, usually I don't sit down, but, often, I still clean the toilet! But I think that even if you don't sit down and you're above it… maybe if there's really a bacterium there, one that's too strong, maybe as I have a weakness, maybe… » (17)*
17Q2		*« If it's too strong, or if it's in the evening (and if I think I can't wait till the next day) I take either my FT, or an antibiotic that I have at home. » (Int 17)*
18Q1	***18***	*« Yes! Really… it's dealt with on the spot with a urine culture and an antibiotic, but nothing's done over the long term in fact! So, they should try to see with the gynaecologist if there's something wrong or send me to get tests which I've never done, although I've been having cystitis for over 30 years! » (Int 18)*

18Q2		*"Well, I'd like to know why"*
18Q3		*"What I'd like, is that it weren't a condition that's taken lightly!"*
19Q1	***19***	*"There were times when I couldn't even go to work"*
19Q2		*"We can't have intercourse anymore because it's too painful."*
19Q3		*"I'd had an ultrasound examination of the bladder, to see if there was anything…But there was nothing."*
20Q1	***20***	*"Because I've had endometriosis, in fact, for a long time, and, well, the uterus is very near, the ovaries too and I think maybe with age and the course of the disease, today, maybe there's possibly something wrong with the bladder"*
20Q2		*« I'd like to be able to take the antibiotic myself, without having to go to the doctor and have the same test done over and over again every six or eight weeks, when I know the result perfectly well… I'm quite capable of telling the difference, it's been so long! And it's so constraining! I really feel I'm always going there to ask for the same thing, and my doctor always gives me the same answer: Cipro, urine test »(Int 20)*
20Q3		*« I have the feeling that cystitis is really considered a trivial complaint, but for me it's detrimental and important. If you say: 'I can't come to work, I've got cystitis', people don't understand, It's not serious, even for the doctors! »*
		« Besides paying for the visit during which, anyway, she's not even going to examine me, since I go in, I tell her « I've got a tummy ache, I pee three drops, I have to go every 10 minutes, it burns… », –"Yes, OK, here you are: Prescription… that's it!". » (Int 20)
22Q1	***22***	*"I know it's frequent after sexual intercourse »*
22Q2		*« All the doctors said is cranberries, drink a lot, take care when wiping, washing, choose appropriate underwear, avoid tight jeans… I tried to change all that a bit. It didn't do anything. Cranberry, I did that, it didn't work. Ah yes, they also said to use special mineral water so that the urine wasn't acid, well I still get it..."*
23Q1	***23***	*« Since I get this regularly, I always have a prescription, I have dipstick tests at home, so I always do that … But generally, I know I have it! So, it's usually positive…I always have urine test containers in advance because the lab gives them to me. » (Int 23)*
23Q2		*« On the contrary, we can work hand in hand, to have a wider scope, saying "OK, conventional medicine doesn't work with you. Apparently, we can't find the cause, nor an effective treatment."*
23Q3		*« I think medical practice should be more open to natural therapies »*
		« Couldn't a naturopath suggest something else? But then those treatments are not covered by the health insurance. So, it's difficult for people who don't have the means. »
23Q4		*« I often drink cranberry juice, I buy packets of cranberry, I eat dried cranberries, even though the taste isn't necessarily…especially the juice, it's acid! »*
24Q1	***24***	*« If I can bear it, I'm not going to go and have a dipstick test or urine culture, I'll stick to cranberries, water, cotton underwear and that's it. I only take antibiotics when I don't feel well."*
24Q2		*« Perhaps there's something else that might explain cystitis, I didn't have an ultrasound … would an ultrasound examination show something, I don't know if a malformation of the urinary tract or something that could explain cystitis recurring like this? »*
25Q1	***25***	*"So what information did you get from your doctor(s) and how?" "None at all. Sorry! "*
		« I'd like to be given a guideline! »

25Q2		*« In my case, management was alright since, every time, my cystitis went away. However, considering overall management, … maybe that's what was missing: proper treatment but also proper information. The type of management I would like? real medium- and long-term support, that would be it. »*
25Q3		*« As there's never been a urine culture done, it's always been dipstick tests … »*
25Q4		*« I mean… I don't go to the doctor's, because I know what I'll automatically get antibiotics, so, hum… So, if there's a follow-up, afterwards, we can talk about it each time and see if there's something else… »*
26Q1	***26***	*"Just after menopause, that's true."*
26Q2		*"A hereditary factor, family, you see? It's possible, because my mother had it too."*
27Q1	***27***	*« Yes, I saw Dr A…who prescribed a weekly dose of FT for 6 months… It worked perfectly for about 7 months, and then it started again! »*
27Q2		*« I always have this fear, when I go somewhere, I always take my FT dose with me. »* *"I take cranberry… I try to drink regularly."*
28Q1	***28***	*«I had taken antibiotics for cystitis, it was AUGMENTIN… Well, for a start, the taste was horrible. And even with probiotics, I got diarrhoea. And this time I got thrush, with lots of mouth ulcers, and that was due to CIPRO! …So, yes, if I can avoid taking them, perhaps.»*
28Q2		*"Besides, I had the baby at the time, which didn't help my libido!"*
28Q3		*"… Well, I admit it, it's true that I don't drink enough."*

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Recurrent cystitis: patients' needs, expectations, and contribution to developing an information leaflet.

A qualitative study

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ABSTRACT

Recurring cystitis (RC) is a common complaint among women. It has a significant impact on patients' quality of life. Although contributing factors are known, the underlying physiopathological process is not well understood, resulting in various treatment approaches in spite of existing guidelines. The physical discomfort and psychological distress related to RC are rarely addressed and women's needs in terms of information and advice have not been sufficiently explored, particularly in France in spite of their frequent episodes of RC. This study aimed to assess women's needs and expectations in view of developing a patient information leaflet to help them understand and better cope with their condition, thus offering them more autonomy and empowering them to self-manage whenever possible. We conducted a qualitative study using recorded semi-structured interviews with patients suffering from RC.

Twenty-six patients participated from 01/2018 to 04/2018. Their knowledge of the condition was heterogeneous, they reported a major impact on their daily life, a high level of anxiety, various management strategies and wished to avoid taking antibiotics, preferring alternative approaches. Patients complained of a lack of understanding and sympathy on the part of physicians and society and wished for more autonomy with delayed/back-up prescriptions, a multidisciplinary follow-up and most of all suitable information. The information leaflet should improve patients' knowledge and capacity for self-care, contribute to standardize practice and limit inappropriate antibiotic use.

Key words: recurrent cystitis, patient involvement, patient information leaflet, inappropriate medication, qualitative research.

Strengths and limitations

- This qualitative study, in the form of individual interviews, facilitated the expression of the expectations, needs, opinions and attitudes of patients suffering from recurrent cystitis.
- The conversational character of the interviews, which were able to overcome any embarrassment these might have caused, provided the opportunity for an in-depth approach of the subject.
- The various recruitment approaches resulted in a diverse and complementary theoretical sample, with a substantial number of respondents with varied characteristics.
- Participants' response was subject to their level of comprehension and motivation and the time they could allow for the interview.
- Physicians' involvement was lower than expected as only five of all 31 contacted GPs recruited patients.

Introduction

Cystitis is an extremely frequent complaint, one out of two women developing an episode over her lifetime [1]. It is a benign condition generally treated with antibiotics prescribed by the primary care physician.

Recurring cystitis (RC) is defined as the occurrence of at least three episodes of cystitis over a 12-month period. Although the prevalence rate of RC among the female population is not known, some studies on small cohorts of patients suggest it may be quite high [2, 3, 4]. Many women complain of the major impact of the condition on their daily life, as pain and urinary frequency can be invalidating, as well as on their sexual activity [5]. The significant psychological consequences, which are dominated by anxiety, have rarely been explored [6].

According to the French National Agency for Medicines and Health Products Safety (ANSM), urinary tract infections (UTI) currently rank third among ambulatory antibiotic prescriptions in France [7]. Choice of antimicrobial agents and duration of treatment both appear inappropriate: fluroquinolone and third generation cephalosporin prescriptions and treatment duration are excessive [8] and do not take either the epidemiology of antimicrobial-resistant bacteria nor the impact on the gut microbiota into account, and thus do not comply with recommendations [9, 10]. In some countries, treatment is discussed with patients and alternatives to antimicrobial treatment are offered which have not shown

an increased rate of complications or recurrence compared to patients treated with antibiotics. [11, 12, 13]. Such an approach should be made more broadly available to women with RC and with no risk of complications. The UK National Action Plan aims to prevent the need for antimicrobials and improve the publics' infection prevention behaviours. Indeed, the primary objective of a recent qualitative study conducted in the UK was to explore patients' needs on provision of self-care, which could reduce consultations and unnecessary antibiotic use. An information leaflet was developed to this end [14].In France, the needs and expectations of patients suffering from RC have not been evaluated.

The ReSO-InfectiO PACA EST includes a group of healthcare institutions, laboratories, and health authorities in the Provence Alpes Côte d'Azur (PACA) region in South-Eastern France and aims to conduct research and harmonize the management of infectious diseases across the area. Infectious diseases physicians of the RéSO InfectiO PACA EST, coordinated by infectious diseases specialists at Nice University Hospital, consulting women referred for RC, conducted a survey of trigger factors, care pathways, and management [15]. This showed that women wished for more autonomy and treatment options. To this end, a qualitative survey was conducted among women with RC to inform the contents of an information leaflet intended to improve patients' knowledge and to help them manage their condition [9, 10,].

Methods

Qualitative semi-structured interviews were undertaken by a single researcher trained in qualitative research methods, with a purposive sample of female patients with a definite diagnosis of RC, i.e. at least three episodes of cystitis over 12 consecutive months, over 18 years of age, with no cognitive impairment [16].

Geographic study setting: the Ajaccio area conurbation in Corsica (CAPA).

Patients were recruited via their community-based general practitioner, gynaecologist or urologist as well as via hospital-based physicians. Recruitment was subsequently extended to include patients attending medical laboratories (where information describing the study was delivered through leaflets posted in waiting rooms), pharmacists, and via social networks. A snowball effect was produced as recruited patients had contacts with women with similar complaints. Recruitment continued until content saturation was achieved, as observed through immediate de-briefing and ongoing data analysis [17, 18, 19].

Interview

The interview guide (Appendix 1) included a brief introduction, a qualitative section with seven neutral, open-ended questions that followed a guiding thread with the possibility of using topical probes if necessary, and a quantitative section with socio-demographic (age, educational level, socio-professional category, area of residence) and medical details related to RC (attending physician, age at start of RC, main past or current medical conditions). The interview guide was initially tested on two patients and proved satisfactory. No further alteration was required.

Data collection

Recorded Interviews were conducted and recorded according to patients' availability and in any quiet location they chose by a single trained researcher (LB). The aims of the study and the interviewing procedure were explained, and patients provided written informed consent to participate.

Data analysis

Each recorded interview was transcribed verbatim by a single trained secretary, with as many details as possible, both verbal and non-verbal. A de-briefing procedure by the researcher (LB) took place immediately following each interview to record the overall impression and identify the main ideas put forward by the patients and was shared with co-authors (PT, VM). This allowed to identify the point when theoretical data saturation was reached after discussion and agreement from all researchers, *i.e.* no new ideas arose, and discontinue recruitment. [16,18,19]

Inductive thematic analysis [16,18] was performed using NVivo© software. This included 6 stages: getting acquainted with the content of the interview (familiarisation), followed by initial coding where codes were approved by all researchers after discussion, identification of overarching themes, grouping of themes or categories of ideas, exploration of links and interaction between themes, description and supporting quotations, according to an iterative procedure [18,19]. On an on-going basis, this data analysis procedure was discussed among all the co-authors at all the different stages to reach agreement and conducted in accordance with their comments.

Each category was summarized in the results section and illustrated with relevant quotes (Appendix 3). At the end of the results section, the implications derived from these results were illustrated in a table intended to be used as a basis for developing the information leaflet (Appendix 3).

Ethical approval was not required according to Article R1121-1-1 of French Public Health Code.

RESULTS

Quantitative results

Participants

A breakdown of patient inclusion is illustrated in the flowchart shown in Figure 1

Patient characteristics are shown in Table 1.

Table 1: Patient characteristics

Mean age	42 years (range 18 – 79),
Educational level:	
• High school or less	6
• Some college or tech school	10
• Bachelor's degree or higher	10 (of which 5 registered nurses)
Work status	
• employed	19
• retired	5
• jobless	2
Mean age of initial occurrence	30 years (Range: 16 – 70 years)
Mean duration of complaint	13 years (Range: 1 – 31 years)
TYPE OF RECURRING CYSTITIS	
Simple	20
At risk for complication	6

Among the stated risk factors, many women mentioned insufficient hydration, sexual intercourse, pregnancy and parturition, withheld micturition, constipation, and stress.

Physicians

Among the 53 physicians contacted, 50 agreed to participate in recruiting patients (33 community-based practitioners: 31 GPs, 2 gynaecologists, and 17 hospital-based practitioners: 9 Accident and Emergency physicians, 4 gynaecologists, 2 urologists, and 2 infectious disease specialists).

Interviews

The interviews were conducted between January 30th, 2018, and April 3rd, 2018. Their mean duration was 22 minutes (range 9-39 minutes). Sixteen interviews took place in a medical setting, 6 in patients' home, 3 in patients' workplace and 1 in a coffee shop.

Recruitment

Among the 26 patients interviewed, 8 had been recruited via their physician (mainly GPs), 5 via leaflets, 7 via Facebook and 6 through snowball sampling.

Qualitative results

Results of patient interviews are detailed in Table 2.

Table 2: Summary of results and implications (Patient quotes are listed in Appendix 2)

THEME	KEY FINDINGS	QUOTES	IMPLICATIONS
KNOWLEDGE OF THE CONDITION, ITS CAUSES AND RISK FACTORS	Patients were confused regarding the difference between cystitis and urinary colonisation: they had queries regarding the link between smelly urine and infection, requesting a definition of cystitis, an explanation of the causes and risk factors. Several patients mentioned hormonal causes - pregnancy, menopause, endometriosis and oral contraception - as risk factors. Many patients associated cystitis with sexual intercourse. Hereditary factors were also mentioned. Patients also identified stress and fatigue, post-voiding residual urine, insufficient hydration. They wished for written explanations.	13Q1 12Q1 4Q1, 4Q3 16Q1, 26Q1, 20Q1, 14Q1 22Q1, 26Q2 1Q1, 1Q2, 28Q3, 6Q1	Patients need a clear definition and understanding of RC, UTI and colonisation, and causes thereof, with clear, written, illustrated information.
IMPACT ON DAILY LIFE	Patients described intense pain and anxiety interfering with their social, professional, family, and sexual life. A burning sensation upon voiding and urinary frequency were particularly invalidating and resulted in social isolation: home confinement, interference with work or having to take sick leave. Patients also complained of a major impact on their sexual activity, leading to abstinence during episodes, but also to reduced sexual activity at other times.	10Q1, 10Q2, 27Q2, 19Q1 1Q1, 16Q2 19Q2	The link with hygiene, diet, hormonal status (vaginal dryness) should be explained and accompanied with a diagram illustrating anatomical details.
COPING STRATEGIES	Few patients resorted to analgesics. Preventative measures regarding hygiene and diet, particularly increased fluid intake, were usually known but unevenly implemented, though some wished for more information on the subject. Many patients resorted to various forms of cranberry preparations. Half of them had a back-up prescription for antibiotics provided by their physician.	28Q3, 23Q4, 24Q1, 6Q2	Patients should be encouraged to increase their fluid intake and resort to analgesics, and should be provided with a back-up prescription of antibiotics in anticipation of future episodes

INVESTIGATIONS	Several patients had undergone various investigations (ultrasound examination, urinary tract scan, cystoscopy…), others wished for further testing or specialist advice. One patient confused Urine Test and Cervical swab.	19Q3, 24Q2 14Q3	Patients need a definition of urine microscopy and culture The relevance of urine dipstick test and urine culture for the management strategy of RC should be explained.
ANTIMICROBIAL THERAPY AND POSSIBLE ALTERNATIVES	Various antibiotic treatment strategies were used: fluoroquinolones, fosfomycin-trometamol, cotrimoxazole, nitrofurantoine, amoxicillin, with frequent self-medication, mainly with FT but also nitrofurantoine or cotrimoxazole leftovers from a previous infection. Patients considered there should be alternatives to antibiotics. They were concerned that antibiotics would harm their health, result in adverse events, and lead to emergence of bacterial resistance.	17Q2, 14Q6	Patients need to be reminded of indications for antibiotic therapy and preferential compounds according to type of RC. A short explanation on bacterial resistance should be given, as well as advice on non-antibiotic strategies.
VIEWS ON PHYSICIANS' APPROACH	Patients resented the constraint of repeated visits to the GP, who was often difficult to reach immediately. Several wished to self-manage their infection and requested back-up prescriptions for urine culture and single dose FT treatment. Lack of anticipation on the part of physicians led to patients performing a urine culture without a prescription (so were not reimbursed) and to self-medication. Patients complained of lack of information, empathy and support, investigations and follow-up. Some were fatalistic, accepting their condition as inevitable (referring to female family members and friends with the same problems). Antibiotics were considered over-prescribed and banal, and conducive to neglecting investigations into causes and risk factors. Women wished for information regarding diet and hygiene measures. They also wished for alternatives. Some tried « natural » approaches, i.e. phytotherapy or aromatherapy, despite their cost.	14Q5, 1Q2, 20Q1 18Q1 11Q2	Patients require clear, written management advice, and should be informed on how and when to self-treat and be provided with back-up prescriptions accordingly. The relevance and timeliness of investigations should be explained, and guidelines for an investigation strategy for simple cystitis and for cystitis at risk for complications A multidisciplinary approach and a yearly dedicated medical consultation should be made available.

DISCUSSION

This qualitative survey of women's needs and expectations regarding recurring RC has revealed their need to understand and self-manage their condition. Such patient empowerment is indeed increasingly favoured insofar as women are aware of those situations which might require a physician's intervention. Avoiding unnecessary consultations and antibiotic prescriptions thanks to an information leaflet specifying both prevention and management is a major objective which has been advocated namely through a National Action Plan in the UK to "raise public awareness to encourage self-care and reduce expectations of antibiotics" [20]. Unlike the present study, the qualitative study conducted in England involved both patients and healthcare providers and was based on focus groups, rather than face-to-face interviews, with a comparable number of patients and a similar approach in seeking patients' opinion on informing a leaflet [14].

1. Strengths and limitations

1.1. Strengths

This qualitative study in the form of individual interviews revealed the expectations and needs of patients suffering from RC, as well as their opinions and attitudes. The method provided the opportunity for an in-depth approach of the subject, thanks to the conversational character of the interviews which were able to overcome any embarrassment these might have caused. The semi-structured interview guide contained open questions that allowed to adjust the interview as it progressed. It was tested and found suitable after two pilot-interviews.

The various recruitment approaches resulted in a diverse and complementary theoretical sample, with a substantial number of respondents with varied characteristics, regarding age, number of years with the condition, age when it began, educational level.

To reduce loss of information to a minimum, each interview was followed by immediate debriefing. Thematic analysis was optimal thanks to the use of N-Vivo software.

1.2. Limitations

Participants' response was subject to their level of comprehension and motivation and the time they could allow for the interview. As in all qualitative face-to-face surveys, adjusting to the patient introduces an inevitable bias linked to the interaction between patient and interviewer.

Physicians' involvement was lower than expected as only five of all 31 contacted GPs recruited patients. This may be because physicians omitted or forgot to inform patients, or patients refused to participate.

Several patients' profession was related to healthcare, as information on the study and contact details were provided in healthcare facilities, and also due to snowball sampling. This may have translated into heightened health-related awareness of their condition, and thus stronger support for the proposed intervention.

Lastly, qualitative thematic analysis and interpretation of results necessarily imply a degree of subjectivity on the part of the researcher. Co-authors were involved in every step of the analysis.

2. Interpretation of findings in the light of published research

2.1. Patients' knowledge of the condition, its causes and risk factors

Confusion regarding the difference between cystitis and urinary colonisation could explain patients' inadequate strategies, such as resorting to antibiotics because of smelly urine. Few patients had any idea of the origin of their condition. Indeed, the physiopathology of recurrent cystitis remains obscure and multifactorial. In the case of relapsing RC, the possible presence of intracellular uropathogenic E coli within the bladder epithelium could interfere with an effective immune response and give rise to re-emergence of infection from this reservoir [21, 22], which may require reconsidering treatment approaches.

Several patients mentioned hormonal causes. Oestrogen insufficiency has been described as a causative factor [23, 24]. The SPILF suggests local oestrogen therapy after menopause if approved by the gynaecologist [9]. Oestrogen insufficiency results in decreased Lactobacillus vaginal colonisation and E. coli proliferation, and a study of local prophylactic treatment with probiotics shows encouraging results [25]. In the present study, none of the patients took topical oestrogens and only one took probiotics.

Some patients mentioned hereditary factors, and a history of UTI in mothers has been noted by infectious disease specialists, suggesting possible genetic susceptibility to infection [26], although this may also be related to behavioural factors within families [27, 28]. The high frequency of RC upon initiation of sexual activity is described in the literature [28]. However, stress, fatigue and apprehension of further episodes were also identified as risk factors, as well as bowel dysfunction, as identified in an ongoing prospective study conducted in our area [29].

2.2 Impact on daily life

Social isolation, sexual abstinence during episodes, but also reduced sexual activity at other times were mentioned and have also been described in an Italian study [5].

The major psychological impact, namely anxiety, resulting both from the RC episodes themselves (but which could also be a possible cause) and from the lack of adequate management, emphasizes the need for a multidisciplinary approach, taking the stress factor into [30].

2.3 Patients' coping strategies

The variety of strategies to cope with RC point to a wish by many patients to avoid antibiotics and to self-manage their condition: herbal medicine, aromatherapy... The importance of increasing fluid intake was widely known, if not sufficiently applied. Although many patients resorted to various forms of cranberry preparations, these have not been evaluated in terms of effectiveness, while French recommendations advise a minimum daily dose of 36mg proanthocyanidin [31, 32]. Back-up antibiotic prescriptions, often mentioned in this survey, have been advocated, along with guidance as to their appropriate use [33].

2.4 Investigations

While urine culture was performed too often for simple RC, dipstick tests were infrequent despite recommendations by the French language society for infectious diseases. [9]. However, the cost of dipstick tests is not endorsed by the National health insurance, which limits their use. Another inappropriate approach was to treat urinary colonisation revealed by an unnecessary follow-up urine microbiology and culture after a clinically effective antibiotic course, which should not lead to further antimicrobial prescription.

2.5 Antimicrobial therapy and possible alternatives

Although a wish to avoid antibiotics was expressed, these were used by many patients, especially FT due to the convenience of a single dose, but also inappropriate use of other compounds, whether self-administered or inadequately prescribed by a physician. Such variable coping measures when confronting initial signs of cystitis highlight the need for standardized approaches since the stated treatment strategies did not conform with recommendations: self-medication with fluoroquinolones, systematic urine culture , secondary adaptation of antibiotic treatment to susceptibility test results for uncomplicated RC; regular empirical antibiotic treatment for potentially complicated RC, with a single, thus suboptimal, FT dose; nitrofurantoïne as antibiotic prophylaxis, which is strictly contra-indicated according to French guidelines [**Error! Bookmark not defined.**, 9, 10, **Error! Bookmark not defined.**]. Many non-antibiotic options for RC have been explored [34]. Treatment strategies have been evolving in Scandinavian countries and in Germany, where pain killers/ non-steroid anti-inflammatory drugs (NSAIDs) can be offered for treating cystitis with mild/moderate symptoms in a watch and wait approach although their efficacy remains controversial [13, 35, 36]. Phytotherapy has been shown to be effective [37, 38]. French guidelines state that topical oestrogens can be beneficial to menopaused women [39], while, according to a Spanish study, prevention with D-Mannose significantly decreased

the frequency of UTI [31, 40]. Immunotherapy using a vaccine based on a bacterial extract is currently being tested [41]. Lastly, among the various approaches aiming to alleviate pain and stress, hypnosis could prove useful: it has been shown to alleviate symptoms in irritable bowel syndrome and to reduce the need for analgesics during surgical procedures 42. Preliminary results of its use in RC are promising (Ongoing HYpnocyst Protocol by the same author, unpublished data).

2.5. Patients' views on physicians' approach

The discrepancy between symptom intensity and the reputedly benign character of RC stands out as a frustrating situation whereby the condition is not seriously considered, although patients' distress has recently been acknowledged [43].

The lack of physicians' and society's understanding regarding RC contrasts with the major impact of the condition on patients' activities, perception and degree of anxiety. Ignorance of the cause of RC, cost of antibiotic alternatives, lack of investigation or of conclusive results thereof led patients to adopt a fatalistic attitude. This was noted by Italian authors who concluded to the "cost of resignation" related to physicians' lack of involvement [5]. Certain patients even expressed surprise at being questioned regarding their opinions on their management of RC.

Patients' request for more autonomy has been addressed in France with a strategy put forward in 2014, targeting selected, educated women with no risk factor, subject to twice-yearly re-assessment: this consists in self-treatment thanks to a delayed prescription, following a (non-reimbursed) dipstick test to confirm cystitis [5]. A recent qualitative survey conducted in the United Kingdom pointed to the need for addressing physicians' knowledge and skill gaps on UTI in women under the age of 65 years, including non-pharmaceutical recommendations for self-care [44].

Lastly, the request for more thorough, multidisciplinary management relying on various strategies is not in line with recommendations put forward by the SPILF for uncomplicated RC in 2014 [5] : in non-menopausal women with a normal pelvic and urethral clinical examination, no further investigation is systematically required. In other situations, for women at risk for complications, management should be decided by a multidisciplinary team. Few women (25%) had consulted a urologist or a gynaecologist, while infectious disease specialist advice was very rarely sought.

Clarification of this trajectory should result in more standardized approaches and reduce patients' anxiety.

3. Implications

3.1. Information leaflet

Based on the requests put forward by the interviewees, an information leaflet should be made available and include the following items to meet the needs and expectations of patients with RC:

- A reminder of the definitions
- Description of the known causes and risk factors of RC supported by a diagram and information on the usefulness and timeliness of urinalysis, dipstick test and urine microscopy and culture
- Procedure to be followed when first signs of cystitis appear
- Role of antimicrobial treatment and preferred compounds
- Summary of possible non-antibiotic treatments
- Clear suggested strategy for initial investigations/specialist referral

Such an information leaflet can be considered as a means of patient empowerment, as recommended by the French Language Society for Infectious Diseases (SPILF) in 2014 and which has still not been put into practice. It can contribute to patient education, aiming to involve patients in their healthcare and quality of life, while reducing inappropriate antibiotic use.

The effectiveness of information leaflets has been demonstrated in various contexts, namely regarding paediatric antibiotic prescriptions when coupled with GP online training [45]. A patient-clinician shared decision-making leaflet was developed in the UK that addressed the consultation barriers and promoted patient empowerment, with both leaflet and corresponding explanations delivered by the physician [46].

Although the use of such a leaflet will depend on the physician's wish to grant patients more autonomy and on the time available for dialogue, this may prove beneficial for both in the long run. Patients would have a clear, handy and relevant resource which would contribute to reduce their anxiety by addressing several of their queries and describe the procedure to follow in case of cystitis. For previously selected and educated patients provided with back-up of urine microbiology and culture and/or antibiotics, the leaflet would increase autonomy. A printed resource facilitates memorisation and assimilation. Clear and explicit definitions can eliminate any confusion and thus prevent inadequate treatment. A diagram can help understand the links between risk factors and hygiene and dietary measures to adopt. Improved understanding should lead to better adherence to the suggested management strategy. A summary of various non-antibiotic treatments, whether validated or not, can meet patients' request, describe how each should be administered and allow patients to test their respective effectiveness. Lastly, its use would contribute to improve to harmonize the currently highly disparate management approaches reported by patients.

Such an approach reflects most patients' demands. The leaflet (Appendix 3) could thus contribute to train physicians from various specialties in good clinical practice. This could even be complemented with a specific resource for physicians.

Assessment of this resource on a wider scale is now necessary, by distributing it to the RésO GPs and their patients, to confirm its relevance and consequently offer it to all women suffering from RC.

Figures and legends:

Figure 1: patient flowchart

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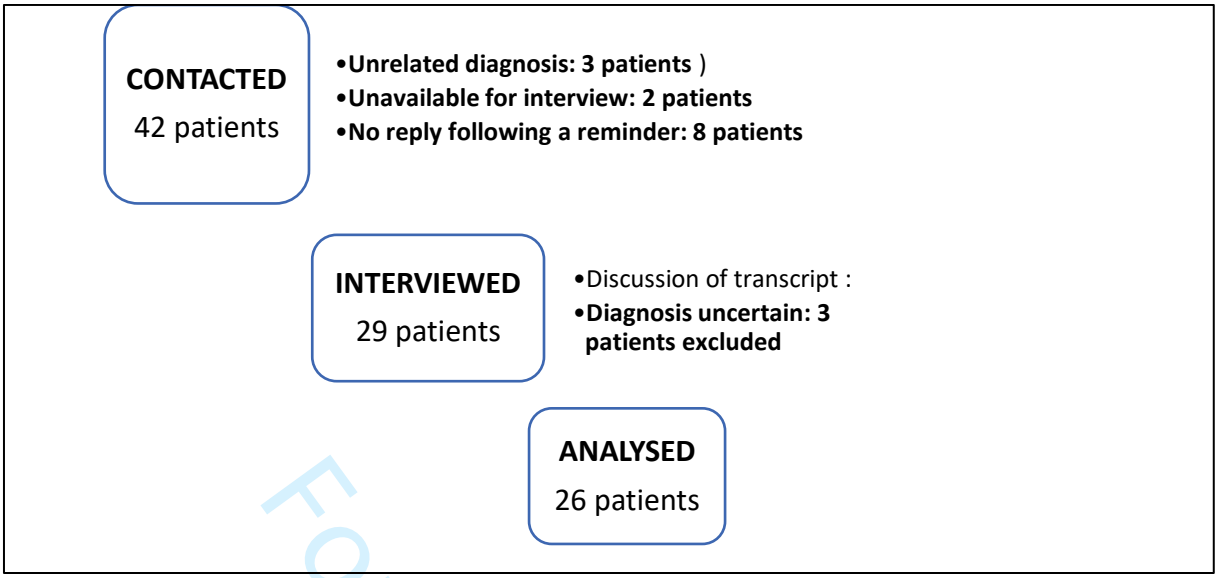


Figure 1 : Patient Flowchart

APPENDIX 1: INTERVIEW GUIDE

Interview guide for exploring the needs and expectations of women suffering from recurrent cystitis

Recurrent cystitis is a frequent complaint among women, its management is highly variable and needs to be improved.

Our interview aims to better understand the needs and expectations of these woemn to develop and information leaflet intended to provide them with accurate explanations of the causes of these recurring infections and the means of addressing them.

Thank you for participating.

Questions are deliberately « open » so that your personal experience can be recorded as completely as possible in vew of improving this information leaflet.

Your answers will be recorded and later analysed anonymously of course.

Question 1

Tell me about your latest episode of cystitis

Question 2

How long have you been suffering from recurring cystitis? In what way does the problem affect your daily life? What bothers you most?

Question 3

How do you explain your episodes of cystitis?

Question 4

What do you do to prevent or treat an episode of cystitis?

Question 5

What information have you been given by your physician(s) and how?

Question 6

What information have you obtained from other sources? What other information would you wish to have, and how would you wish to have it?

Question 7

What do you think about the way your recurrent cystitis is managed? How would you like it to be managed?

Quantitative questionnaire

Age

Educational level:

Social/professional category: Farmers / Agricultural employees / Industrial and commercial employers / Professionals and senior managers / Middle management / Employees / Workers / Service personnel / Others

Area of residence:

Urban / semi-rural / rural

Age at initial episodes of cystitis:

Physician consulted for recurring cystitis:
General practitioner / gynaecologist / urologist / infectious disease specialist/ other

Past medical history:
Gynaecological:
Urological:
Digestive system:
Immunosuppression, smoking:

Family history of recurring cystitis:

Other:

Would you be willing to read the information leaflet developed on the basis of all the comments collected during this survey; and eventually share your opinion with us during a brief telephone interview?

APPENDIX 2 PATIENTS QUOTES

N°	Interview	Quote
1Q1	1	« it's really related to stress, at least, that's my feeling »
1Q2		"So, yes, I have problems because when I pee, my bladder doesn't empty itself"
1Q3		« I try to get the doctor to write me a prescription I can keep. But they don't always do it… they say: « you must do an urine culture beforehand » But when it happens, I need to take the antibiotic quickly to avoid the pain. Admittedly, I haven't often done the test, to be honest! When it happens, I tend to rush to call the doctor and ask: "I've already been to the pharmacy and… can I have the prescription? » ». "I think it would be good to have a prescription, even for a urine culture, or to be able, from the susceptibility test, to find the antibiotic I need."
4Q1	4	« I met women much older than me, who also had recurring cystitis, they don't even know why they have this! It makes your life hell, you know! »
4Q2		« Well, I can't carry out my usual activities, I can't go shopping because I know I'll need to pee, and it burns, it's horrible! »
4Q3		"Why do we get so many RC episodes?".
6Q1	6	"I think the best thing would be to have a little booklet explaining because we don't have time to discuss it when we visit the GP."
6Q2		"nobody tells you to do tests, or… ummm, it's really NOT NORMAL to take antibiotics every 6 months! »
6Q3		"'This is what you should avoid, this is what you should rather do, this is when you should see your doctor', …that wouldn't be bad! "
7Q1	7	« I asked for further investigations because I get very tired taking antibiotics every month. So, at one point I said maybe we should look a bit deeper since I'd had episodes of cystitis but also of pyelonephritis. So, there I think it's also perhaps because the infection wasn't properly cured. So that's why I asked the doctor – I often change my GP – and I was sent to see a urologist ".
7Q2		« Since when do you have recurring cystitis? Since my pregnancies."
10Q1	10	« It's awful, because you're stuck at home
10Q2		«Well, the worst thing is to have to go to the toilet all the time and… NOT TO PEE!
10Q3		That's the worst, because you pee ONE DROP, and that drop, its… AWFUL! It burns, burns, burns !!! »
11Q1	11	"I don't go to the doctor's because I know antibiotics will be prescribed. If there was a follow up, we could discuss it each time and see if there's something else."
11Q2		« There's no follow-up. Although we get this regularly… »
12Q1	12	"So I'd really like to know why… what is cystitis? What's going on in the vagina? …and why does it start again each time?"
13Q1	13	. "Because I don't always have this burning sensation. Sometimes, it's only turbid and smelly urine. So, in that case, if I've run out of FT, then I take herbal teas."
14Q1	14	"… I'd like to know, is there a link with contraception or not? Are there means of contraception that favour cystitis, or not?"
14Q2		« after sexual intercourse, there's often a beginning of urinary tract infection"
14Q3		«since I'd told her I'd had a few episodes of cystitis during the year, the gynaecologist did a cervical swab."
14Q4		« Well … prefer, hum… perhaps not, but to think "I'm trying something else and if it doesn't work, resort to antibiotics".
14Q5		"Because in my view, antibiotics are really effective … it's a bit like a bomb, setting off suddenly, acting quickly! And that way, just using it when it's needed, if prior treatment hasn't worked. » (Int 14)

14Q6 **14Q7** **14Q8** **14Q9** **14Q10** **14Q11**		*« Isn't there something else that would be just as effective? Because taking antibiotics straight away, you see, always taking antibiotics, I don't know if that's really… good! Doesn't it generate … I don't know… resistance too in bacteria that…can cause cystitis? So, wouldn't there be other ways (and that takes us back to prevention), that would avoid taking antibiotics every time? »* *« Well, for a start, to know if I've properly identified all the causes that can lead to cystitis, because maybe there are things that I do every day that I'm unaware of and that can contribute to cystitis. »* *« To make matters worse, doctors are always jam-packed, so you need to wait a week to treat cystitis, It's a bit LONG!!! And just to get an antibiotic prescription that I can go and ask several times from the pharmacist. It's not very realistic in case of cystitis which occurs quite suddenly and can be treated very quickly, but that must be done right away! »* *« So that's rather a nuisance, the fact that there's no follow-up, for instance when you go to the GP and you've already been several times because of cystitis… you really get the impression that it stays in the file, because for the doctors, it's a bit anecdotal… They're going to ask if our pain in the arm (if you came once for that), if that's over now, etc., but for cystitis, even if you've been five times for that, they're not bothered... it's not something that I feel is important for them. » (Int 14)* *« Even at work, when you say, "I can't come, I've got cystitis", well, people don't understand, they tend to consider it trivial, it's not serious; even the doctors! »* *"Written yes, I think, with drawings it's important also, to understand the links with the anatomy and to know how it works."*
16Q1 **16Q2**	**16**	*"So I had it in fact during each of my pregnancies, practically every month"* *Because when I get it, generally we avoid intercourse because … it hurts too much!* *« In fact, the only information I have is the one I was given as a child. My parents were very careful so I was often told 'you don't drink enough, you should go to the toilet more often, that kind of thing. In fact, that's the only information I have about urinary tract infection, because recently I didn't have another one. That's why I can't identify the cause any more. »* *Or… perhaps there are other reasons, so I'd really like them to be identified,*
17Q1 **17Q2**	**17**	*« OK, usually I don't sit down, but, often, I still clean the toilet! But I think that even if you don't sit down and you're above it… maybe if there's really a bacterium there, one that's too strong, maybe as I have a weakness, maybe… » (17)* *« If it's too strong, or if it's in the evening (and if I think I can't wait till the next day) I take either my FT, or an antibiotic that I have at home. » (Int 17)*
18Q1 **18Q2** **18Q3**	**18**	*« Yes! Really… it's dealt with on the spot with a urine culture and an antibiotic, but nothing's done over the long term in fact! So, they should try to see with the gynaecologist if there's something wrong or send me to get tests which I've never done, although I've been having cystitis for over 30 years! » (Int 18)* *"Well, I'd like to know why"* *"What I'd like, is that it weren't a condition that's taken lightly!"*
19Q1 **19Q2** **19Q3**	**19**	*"There were times when I couldn't even go to work"* *"We can't have intercourse anymore because it's too painful."* *"I'd had an ultrasound examination of the bladder, to see if there was anything…But there was nothing."*

20Q1	***20***	*"Because I've had endometriosis, in fact, for a long time, and, well, the uterus is very near, the ovaries too and I think maybe with age and the course of the disease, today, maybe there's possibly something wrong with the bladder"*
20Q2		*« I'd like to be able to take the antibiotic myself, without having to go to the doctor and have the same test done over and over again every six or eight weeks, when I know the result perfectly well… I'm quite capable of telling the difference, it's been so long! And it's so constraining! I really feel I'm always going there to ask for the same thing, and my doctor always gives me the same answer: Cipro, urine test »(Int 20)*
20Q3		*« I have the feeling that cystitis is really considered a trivial complaint, but for me it's detrimental and important. If you say: 'I can't come to work, I've got cystitis', people don't understand, It's not serious, even for the doctors! »*
		« Besides paying for the visit during which, anyway, she's not even going to examine me, since I go in, I tell her « I've got a tummy ache, I pee three drops, I have to go every 10 minutes, it burns… », –"Yes, OK, here you are: Prescription… that's it!". » (Int 20)
22Q1	***22***	*"I know it's frequent after sexual intercourse »*
22Q2		*« All the doctors said is cranberries, drink a lot, take care when wiping, washing, choose appropriate underwear, avoid tight jeans… I tried to change all that a bit. It didn't do anything. Cranberry, I did that, it didn't work. Ah yes, they also said to use special mineral water so that the urine wasn't acid, well I still get it..."*
23Q1	***23***	*« Since I get this regularly, I always have a prescription, I have dipstick tests at home, so I always do that … But generally, I know I have it! So, it's usually positive…I always have urine test containers in advance because the lab gives them to me. » (Int 23)*
23Q2		*« On the contrary, we can work hand in hand, to have a wider scope, saying "OK, conventional medicine doesn't work with you. Apparently, we can't find the cause, nor an effective treatment."*
23Q3		*« I think medical practice should be more open to natural therapies »*
		« Couldn't a naturopath suggest something else? But then those treatments are not covered by the health insurance. So, it's difficult for people who don't have the means. »
23Q4		*« I often drink cranberry juice, I buy packets of cranberry, I eat dried cranberries, even though the taste isn't necessarily…especially the juice, it's acid! »*
24Q1	***24***	*« If I can bear it, I'm not going to go and have a dipstick test or urine culture, I'll stick to cranberries, water, cotton underwear and that's it. I only take antibiotics when I don't feel well."*
24Q2		*« Perhaps there's something else that might explain cystitis, I didn't have an ultrasound … would an ultrasound examination show something, I don't know if a malformation of the urinary tract or something that could explain cystitis recurring like this? »*
25Q1	***25***	*"So what information did you get from your doctor(s) and how?" "None at all. Sorry! "*
25Q2		*« I'd like to be given a guideline! »*
		« In my case, management was alright since, every time, my cystitis went away. However, considering overall management, … maybe that's what was missing: proper treatment but also proper information. The type of management I would like? real medium- and long-term support, that would be it. »
25Q3		*« As there's never been a urine culture done, it's always been dipstick tests … »*
25Q4		*« I mean… I don't go to the doctor's, because I know what I'll automatically get antibiotics, so, hum… So, if there's a follow-up, afterwards, we can talk about it each time and see if there's something else… »*
26Q1	***26***	*"Just after menopause, that's true."*
26Q2		*"A hereditary factor, family, you see? It's possible, because my mother had it too."*

27Q1	***27***	*« Yes, I saw Dr A…who prescribed a weekly dose of FT for 6 months… It worked perfectly for about 7 months, and then it started again! »*
27Q2		*« I always have this fear, when I go somewhere, I always take my FT dose with me. »*
		"I take cranberry… I try to drink regularly."
28Q1	***28***	*«I had taken antibiotics for cystitis, it was AUGMENTIN… Well, for a start, the taste was horrible. And even with probiotics, I got diarrhoea. And this time I got thrush, with lots of mouth ulcers, and that was due to CIPRO! …So, yes, if I can avoid taking them, perhaps.»*
28Q2		*"Besides, I had the baby at the time, which didn't help my libido!"*
28Q3		*"… Well, I admit it, it's true that I don't drink enough."*

APPENDIX 3:

INFORMATION LEAFLET FOR PATIENTS WITH RECURRENT CYSTITIS

WHAT IS CYSTITIS?

Cystitis or lower urinary tract infection is a bladder inflammation caused by bacteria. The main symptoms include a burning sensation when passing urine, urgency to urinate (pollakiuria), and sometimes blood in the urine (hematuria). **Recurrent cystitis** is usually defined as four episodes of bladder infection within the previous 12 months.

A **urine dipstick test** is the first step in guiding the diagnosis when leukocytes and/or nitrites are detected.

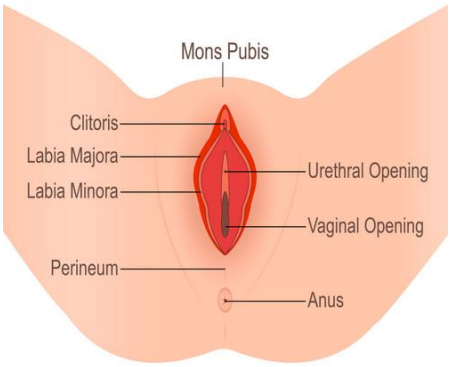
Urine culture can be performed in order to identify the bacteria involved and their antibiotic susceptibility.

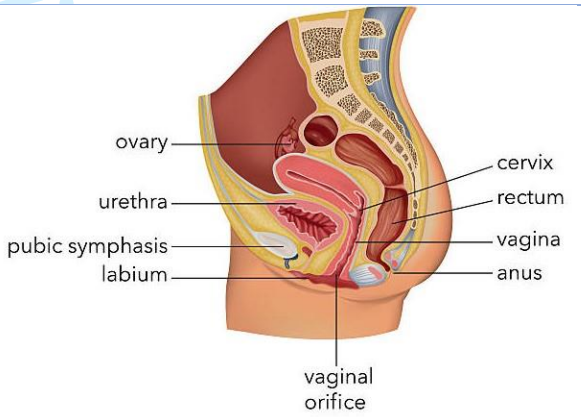
WHAT IS THE DIFFERENCE WITH URINARY TRACT COLONIZATION? WHAT ARE THE OTHER TYPES OF URINARY TRACT INFECTION?

If your urine is cloudy and/or foul-smelling but you do not experience any discomfort, it is therefore not cystitis but **urinary tract colonization.** There are bacteria in the urine, however they do not cause any infection. In such cases, you don't need to take an antibiotic but should simply increase your fluid intake.

Cystitis refers to an infection of the bladder, while **pyelonephritis** refers to an infection of the kidneys. Common symptoms of pyelonephritis include fever and/or chills and/or back pain. The infection must be rapidly treated with a different antibiotic than the one recommended for the treatment of cystitis.

WHAT CAUSES CYSTITIS? HOW CAN I PREVENT IT?





Bacteria present on the **perineum** (from the digestive tract and vaginal flora) can enter the bladder through the urethra. To prevent these bacteria from going into the bladder and multiplying, you can use the following tips:

- Drink 1,5 L of water each day so as to urinate every 3 hours during daytime, *avoid bladder irritants (coffee, tea, tobacco, alcohol…)*
- Do not delay going to the toilet, do not void in a standing or crouching position, *urinate after sexual intercourse*
- *Wipe front to back, avoid diarrhoea or constipation*
- Maintain good intimate hygiene: external wash only, once a day, using a neutral pH soap Symptomatic treatment of vaginal dryness if necessary (estriol cream, hyaluronic acid)
- *Apply vaseline to the meatus after urination or before activities that promote infection*

Propositions in italics are still under evaluation

WHAT SHOUD I DO IF CYSTITIS SYMPTOMS APPEAR?[1]

IN ORDER TO AVOID ANTIBIOTICS:

- Increase hydration to 3L per day[2] (forced diuresis)
- Relieve pain with:
  Phloroglucinol
  Ibuprofen[2]

IF NO IMPROVEMENT WITHIN 48 hours

SIMPLE RECURRENT CYSTITIS….

Do a urine dipstick test[3]

Then self administer[4] : Fosfomycin Trometamol **OR** Pivmecillinam

… OR WITH RISK OF COMPLICATIONS

Try to wait for the urine culture and antibiotic susceptibility test results[4] to choose the most suitable antibiotic with your doctor, **OTHERWISE** Fosfomycin Trometamol **OR** Nitrofurantoin

In 40 % of cases, antibiotics are not necessary for cure. They act directly on the normal bacterial flora (microbiota) and may have adverse effects, e.g. fungal infection (thrush) or diarrhoea. Their use also increases the likelihood of bacterial resistance to antibiotics[5].

If your cystitis episodes keep occurring very frequently (> 1 / month), or are specifically related to sexual intercourse, you need to discuss with your physician whether you should take a **prophylactic antibiotic treatment**, i.e. an extended antibiotic course to prevent cystitis (Fosfomycin Trometamol 1 sachet/week or Trimethoprim 1 pill a week or 2hours before/after sexual intercourse, as prescribed by your doctor).

…WHAT ABOUT NON-ANTIBIOTIC TREATMENTS?

- Phytotherapy :
  - cranberries if infection due to *E. Coli*: 36 mg/d of proanthocyanidins, during 3 to 6 months
  - *Other: treatment of the episode with Busserole[6], Heather, or Hibiscus*
- Prevention or treatment of the episode using D-Mannose if E. Coli infection
- Treatment of the episode with Aromatherapy[6]: essential oils of thyme, cinnamon, tea tree, savory
- Relaxation and pain management techniques : sophrology, yoga, hypnosis
- Vaccines: oral route or vaginal suppository unavailable in France (available in Switzerland or Belgium)

WHICH FURTHER EXAMINATIONS SHOULD BE CARRIED OUT?

If the urological or the gynaecological examination results are normal, **no further investigation will be systematically performed** except for menopausal women and/or women with specific medical histories. For all other cases, management should be discussed by a **multidisciplinary team** including an infectious diseases specialist, and conclusions communicated to the general practitioner.

[1]Subject to your general practitioner's review, at least twice a year. Should treatment failure occur, contact your doctor
[2]In the absence of medical contraindication: check with your doctor
[3]After 4 to 6 episodes of cystitis, you should have a urine culture to look for antibiotic resistance
[4]Talk to your doctor about delayed prescribing of urine culture and/or antibiotics according to your situation
[5]This is why Fluoroquinolones (Oflocet® Ciflox®) and third generation Cephalosporins (Oroken®, Rocéphine®) are not recommended[6]Contraindicated in case of pregnancy and breastfeeding

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Recurrent cystitis: patients' needs, expectations, and contribution to developing an information leaflet.

A qualitative study

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ABSTRACT

Objectives. Recurring cystitis (RC) is a common complaint among women. It has a significant impact on patients' quality of life. The physical discomfort and psychological distress related to RC are rarely addressed and women's needs in terms of information and advice have not been sufficiently explored, particularly in France in spite of their frequent episodes of RC. This study aimed to assess women's needs and expectations in view of developing a patient information leaflet to help them understand and better cope with their condition, thus offering them more autonomy and empowering them to self-manage whenever possible.

Method: qualitative study using recorded semi-structured interviews with patients suffering from RC.

Setting: interviews conducted with women suffering from RC in Corsica, France

Participants: Twenty-six patients interviewed between 01/2018 and 04/2018.

Results: knowledge of the condition was heterogeneous, but most women reported a major impact on daily life, a high level of anxiety, various management strategies and wished to avoid taking antibiotics, preferring alternative approaches. Patients complained of a lack of understanding and sympathy on the part of physicians and society and wished for more autonomy with delayed/back-up prescriptions, a multidisciplinary follow-up and, most of all, appropriate information.

Conclusion: The information leaflet should improve patients' knowledge and capacity for self-care, contribute to standardize practice and limit inappropriate antibiotic use.

Key words: recurrent cystitis, patient involvement, patient information leaflet, inappropriate medication, qualitative research.

Strengths and limitations

- This qualitative study, in the form of individual interviews, facilitated the expression of the expectations, needs, opinions and attitudes of patients suffering from recurrent cystitis.
- The conversational character of the interviews, which were able to overcome any embarrassment these might have caused, provided the opportunity for an in-depth approach of the subject.
- The various recruitment approaches resulted in a diverse and complementary theoretical sample, with a substantial number of respondents with varied characteristics.
- Participants' response was subject to their level of comprehension and motivation and the time they could allow for the interview.
- Physicians' involvement was lower than expected as only five of all 31 contacted GPs recruited patients.

Introduction

Cystitis is an extremely frequent complaint, one out of two women developing an episode over her lifetime [1]. It is a benign condition generally treated with antibiotics prescribed by the primary care physician.

Recurring cystitis (RC) is defined as the occurrence of at least four episodes of cystitis over a 12-month period, according to the French Language Society for Infectious Diseases (SPILF) [2] Although the prevalence rate of RC among the female population is not known, some studies on small cohorts of patients suggest it may be quite high [3, 4, 5]. Many women complain of the major impact of the condition on their daily life, as pain and urinary frequency can be invalidating, as well as on their sexual activity [6]. The significant psychological consequences, which are dominated by anxiety, have rarely been explored [7].

According to the French National Agency for Medicines and Health Products Safety (ANSM), urinary tract infections (UTI) currently rank third among ambulatory antibiotic prescriptions in France [8]. Choice of antimicrobial agents and duration of treatment both appear inappropriate: fluroquinolone and third generation cephalosporin prescriptions and treatment duration are excessive [9] and do not take either the epidemiology of antimicrobial-resistant bacteria nor the impact on the gut microbiota into account, and thus do not comply with recommendations [2, 10]. In some countries, treatment is

discussed with patients and alternatives to antimicrobial treatment are offered which have not shown an increased rate of complications or recurrence compared to patients treated with antibiotics. [11, 12, 13]. Such an approach should be made more broadly available to women with RC and with no risk of complications. The UK National Action Plan aims to prevent the need for antimicrobials and improve the publics' infection prevention behaviours. Indeed, the primary objective of a recent qualitative study conducted in the UK was to explore patients' needs on provision of self-care, which could reduce consultations and unnecessary antibiotic use. An information leaflet was developed to this end [14]. In France, the needs and expectations of patients suffering from RC have not been evaluated.

The ReSO-InfectiO PACA EST includes a group of healthcare institutions, laboratories, and health authorities in the Provence Alpes Côte d'Azur (PACA) region in South-Eastern France and aims to conduct research and harmonize the management of infectious diseases across the area. Infectious diseases physicians of the RéSO InfectiO PACA EST, coordinated by infectious diseases specialists at Nice University Hospital, consulting women referred for RC, conducted a survey of trigger factors, care pathways, and management [15]. This showed that women wished for more autonomy and treatment options. To this end, a qualitative survey was conducted among women with RC to inform the contents of an information leaflet intended to improve patients' knowledge and to help them manage their condition.

Methods

Qualitative semi-structured interviews were undertaken by a single researcher trained in qualitative research methods, with a purposive sample of female patients with a definite diagnosis of RC, i.e. at least three episodes of cystitis over 12 consecutive months, over 18 years of age, with no cognitive impairment [16].

Geographic study setting: the Ajaccio area conurbation in Corsica (CAPA).

Patients were recruited via their community-based general practitioner, gynaecologist or urologist as well as via hospital-based physicians. Recruitment was subsequently extended to include patients attending medical laboratories (where information describing the study was delivered through leaflets posted in waiting rooms), pharmacists, and via social networks. A snowball effect was produced as recruited patients had contacts with women with similar complaints. Recruitment continued until content saturation was achieved, as observed through immediate de-briefing and ongoing data analysis [17, 18, 19]. Indeed, data saturation is considered to be reached when there is enough

information to replicate the study, when the ability to obtain additional new information has been attained, and when further coding is no longer feasible [20].

Interview

The interview guide (Appendix 1) included a brief introduction, a qualitative section with seven neutral, open-ended questions that followed a guiding thread with the possibility of using topical probes if necessary, and a quantitative section with socio-demographic (age, educational level, socio-professional category, area of residence) and medical details related to RC (attending physician, age at start of RC, main past or current medical conditions). The interview guide was initially tested on two patients and proved satisfactory. No further alteration was required.

Data collection

Recorded Interviews were conducted and recorded according to patients' availability and in any quiet location they chose by a single trained researcher (LB). The aims of the study and the interviewing procedure were explained, and patients provided written informed consent to participate.

Data analysis

Each recorded interview was transcribed verbatim by a single trained secretary, with as many details as possible, both verbal and non-verbal. A de-briefing procedure by the researcher (LB) took place immediately following each interview to record the overall impression and identify the main ideas put forward by the patients and was shared with co-authors (PT, VM). This allowed to identify the point when theoretical data saturation was reached after discussion and agreement from all researchers, *i.e*. no new ideas arose, and discontinue recruitment [1618,19]

Inductive thematic analysis [1618] was performed using NVivo© software. This included 6 stages: getting acquainted with the content of the interview (familiarisation), followed by initial coding where codes were approved by all researchers after discussion, identification of overarching themes, grouping of themes or categories of ideas, exploration of links and interaction between themes, description and supporting quotations, according to an iterative procedure [18,20]. On an on-going basis, this data analysis procedure was discussed among all the co-authors at all the different stages to reach agreement and conducted in accordance with their comments.

Each category was summarized in the results section and illustrated with relevant quotes (Appendix 2). At the end of the results section, the implications derived from these results were illustrated in a table intended to be used as a basis for developing the information leaflet (Appendix 3).

Patient and public involvement statement

Patients or members of the public were not directly involved in the design and planning of this study.

Ethical approval was not required according to Article R1121-1-1 of French Public Health Code.

RESULTS

Quantitative results

Participants

A breakdown of patient inclusion is illustrated in the flowchart shown in Figure 1

Patient characteristics are shown in Table 1.

Table 1: Patient characteristics

Mean age	42 years (range 18 – 79),
Educational level:	
• High school or less	6
• Some college or tech school	10
• Bachelor's degree or higher	10 (of which 5 registered nurses)
Work status	
• employed	19
• retired	5
• jobless	2
Mean age of initial occurrence	30 years (Range: 16 – 70 years)
Mean duration of complaint	13 years (Range: 1 – 31 years)
TYPE OF RECURRING CYSTITIS	
Simple	20
At risk for complication	6

Among the stated risk factors, many women mentioned insufficient hydration, sexual intercourse, pregnancy and parturition, withheld micturition, constipation, and stress.

Physicians

Among the 53 physicians contacted, 50 agreed to participate in recruiting patients (33 community-based practitioners: 31 GPs, 2 gynaecologists, and 17 hospital-based practitioners: 9 Accident and Emergency physicians, 4 gynaecologists, 2 urologists, and 2 infectious disease specialists).

Interviews

The interviews were conducted between January 30th, 2018, and April 3rd, 2018. Their mean duration was 22 minutes (range 9-39 minutes). Sixteen interviews took place in a medical setting, 6 in patients' home, 3 in patients' workplace and 1 in a coffee shop.

Recruitment

Among the 26 patients interviewed, 8 had been recruited via their physician (mainly GPs), 5 via leaflets, 7 via Facebook and 6 through snowball sampling.

Qualitative results

Results of patient interviews are detailed in Table 2.

Table 2: Summary of results and implications (Patient quotes are listed in Appendix 2)

THEME	KEY FINDINGS	QUOTES	IMPLICATIONS
KNOWLEDGE OF THE CONDITION, ITS CAUSES AND RISK FACTORS	Patients were confused regarding the difference between cystitis and urinary colonisation: they had queries regarding the link between smelly urine and infection, requesting a definition of cystitis, an explanation of the causes and risk factors. Several patients mentioned hormonal causes - pregnancy, menopause, endometriosis and oral contraception - as risk factors. Many patients associated cystitis with sexual intercourse. Hereditary factors were also mentioned. Patients also identified stress and fatigue, post-voiding residual urine, insufficient hydration. They wished for written explanations.	13Q1 12Q1 4Q1, 4Q3 16Q1, 26Q1, 20Q1, 14Q1 22Q1, 26Q2 1Q1, 1Q2, 28Q3, 6Q1	Patients need a clear definition and understanding of RC, UTI and colonisation, and causes thereof, with clear, written, illustrated information.
IMPACT ON DAILY LIFE	Patients described intense pain and anxiety interfering with their social, professional, family, and sexual life. A burning sensation upon voiding and urinary frequency were particularly invalidating and resulted in social isolation: home confinement, interference with work or having to take sick leave. Patients also complained of a major impact on their sexual activity, leading to abstinence during episodes, but also to reduced sexual activity at other times.	10Q1, 10Q2, 27Q2, 19Q1 1Q1, 16Q2 19Q2	The link with hygiene, diet, hormonal status (vaginal dryness) should be explained and accompanied with a diagram illustrating anatomical details.
COPING STRATEGIES	Few patients resorted to analgesics. Preventative measures regarding hygiene and diet, particularly increased fluid intake, were usually known but unevenly implemented, though some wished for more information on the subject. Many patients resorted to various forms of cranberry preparations. Half of them had a back-up prescription for antibiotics provided by their physician.	28Q3, 23Q4, 24Q1, 6Q2	Patients should be encouraged to increase their fluid intake and resort to analgesics, and should be provided with a back-up prescription of antibiotics in anticipation of future episodes

INVESTIGATIONS	Several patients had undergone various investigations (ultrasound examination, urinary tract scan, cystoscopy…), others wished for further testing or specialist advice. One patient confused Urine Test and Cervical swab.	19Q3, 24Q2 14Q3	Patients need a definition of urine microscopy and culture The relevance of urine dipstick test and urine culture for the management strategy of RC should be explained.
ANTIMICROBIAL THERAPY AND POSSIBLE ALTERNATIVES	Various antibiotic treatment strategies were used: fluoroquinolones, fosfomycin-trometamol, cotrimoxazole, nitrofurantoine, amoxicillin, with frequent self-medication, mainly with FT but also nitrofurantoine or cotrimoxazole leftovers from a previous infection. Patients considered there should be alternatives to antibiotics. They were concerned that antibiotics would harm their health, result in adverse events, and lead to emergence of bacterial resistance.	17Q2, 14Q6	Patients need to be reminded of indications for antibiotic therapy and preferential compounds according to type of RC. A short explanation on bacterial resistance should be given, as well as advice on non-antibiotic strategies.
VIEWS ON PHYSICIANS' APPROACH	Patients resented the constraint of repeated visits to the GP, who was often difficult to reach immediately. Several wished to self-manage their infection and requested back-up prescriptions for urine culture and single dose FT treatment. Lack of anticipation on the part of physicians led to patients performing a urine culture without a prescription (so were not reimbursed) and to self-medication. Patients complained of lack of information, empathy and support, investigations and follow-up. Some were fatalistic, accepting their condition as inevitable (referring to female family members and friends with the same problems). Antibiotics were considered over-prescribed and banal, and conducive to neglecting investigations into causes and risk factors. Women wished for information regarding diet and hygiene measures. They also wished for alternatives. Some tried « natural » approaches, i.e. phytotherapy or aromatherapy, despite their cost.	14Q5, 1Q2, 20Q1 18Q1 11Q2	Patients require clear, written management advice, and should be informed on how and when to self-treat and be provided with back-up prescriptions accordingly. The relevance and timeliness of investigations should be explained, and guidelines for an investigation strategy for simple cystitis and for cystitis at risk for complications A multidisciplinary approach and a yearly dedicated medical consultation should be made available.

DISCUSSION

This qualitative survey of women's needs and expectations regarding recurring RC has revealed their need to understand and self-manage their condition. Such patient empowerment is indeed increasingly favoured insofar as women are aware of those situations which might require a physician's intervention. Avoiding unnecessary consultations and antibiotic prescriptions thanks to an information leaflet specifying both prevention and management is a major objective which has been advocated namely through a National Action Plan in the UK to "raise public awareness to encourage self-care and reduce expectations of antibiotics" [21]. Unlike the present study, the qualitative study conducted in England involved both patients and healthcare providers and was based on focus groups, rather than face-to-face interviews, with a comparable number of patients and a similar approach in seeking patients' opinion on informing a leaflet [14].

1. Strengths and limitations

1.1. Strengths

This qualitative study in the form of individual interviews revealed the expectations and needs of patients suffering from RC, as well as their opinions and attitudes. The method provided the opportunity for an in-depth approach of the subject, thanks to the conversational character of the interviews which were able to overcome any embarrassment these might have caused. The semi-structured interview guide contained open questions that allowed to adjust the interview as it progressed. It was tested and found suitable after two pilot-interviews.

The various recruitment approaches resulted in a diverse and complementary theoretical sample, with a substantial number of respondents with varied characteristics, regarding age, number of years with the condition, age when it began, educational level.

To reduce loss of information to a minimum, each interview was followed by immediate debriefing. Thematic analysis was optimal thanks to the use of N-Vivo software.

1.2. Limitations

Participants' response was subject to their level of comprehension and motivation and the time they could allow for the interview. As in all qualitative face-to-face surveys, adjusting to the patient introduces an inevitable bias linked to the interaction between patient and interviewer.

Physicians' involvement was lower than expected as only five of all 31 contacted GPs recruited patients. This may be because physicians omitted or forgot to inform patients, or patients refused to participate.

Several patients' profession was related to healthcare, as information on the study and contact details were provided in healthcare facilities, and also due to snowball sampling. This may have translated into heightened health-related awareness of their condition, and thus stronger support for the proposed intervention.

Lastly, qualitative thematic analysis and interpretation of results necessarily imply a degree of subjectivity on the part of the researcher. Co-authors were involved in every step of the analysis.

2. Interpretation of findings in the light of published research

2.1. Patients' knowledge of the condition, its causes and risk factors

Confusion regarding the difference between cystitis and urinary colonisation could explain patients' inadequate strategies, such as resorting to antibiotics because of smelly urine. Few patients had any idea of the origin of their condition. Indeed, the physiopathology of recurrent cystitis remains obscure and multifactorial. In the case of relapsing RC, the possible presence of intracellular uropathogenic E coli within the bladder epithelium could interfere with an effective immune response and give rise to re-emergence of infection from this reservoir [22, 23], which may require reconsidering treatment approaches.

Several patients mentioned hormonal causes. Oestrogen insufficiency has been described as a causative factor [24, 25]. The SPILF suggests local oestrogen therapy after menopause if approved by the gynaecologist [2]. Oestrogen insufficiency results in decreased Lactobacillus vaginal colonisation and E. coli proliferation, and a study of local prophylactic treatment with probiotics shows encouraging results [26]. In the present study, none of the patients took topical oestrogens and only one took probiotics.

Some patients mentioned hereditary factors, and a history of UTI in mothers has been noted by infectious disease specialists, suggesting possible genetic susceptibility to infection [27], although this may also be related to behavioural factors within families [28, 29]. The high frequency of RC upon initiation of sexual activity is described in the literature [29]. However, stress, fatigue and apprehension of further episodes were also identified as risk factors, as well as bowel dysfunction, as identified in an ongoing prospective study conducted in our area [30].

2.2 Impact on daily life

Social isolation, sexual abstinence during episodes, but also reduced sexual activity at other times were mentioned and have also been described in an Italian study [6].

The major psychological impact, namely anxiety, resulting both from the RC episodes themselves (but which could also be a possible cause) and from the lack of adequate management, emphasizes the need for a multidisciplinary approach, taking the stress factor into [31].

2.3 Patients' coping strategies

The variety of strategies to cope with RC point to a wish by many patients to avoid antibiotics and to self-manage their condition: herbal medicine, aromatherapy... The importance of increasing fluid intake was widely known, if not sufficiently applied. Although many patients resorted to various forms of cranberry preparations, these have not been evaluated in terms of effectiveness, while French recommendations advise a minimum daily dose of 36mg proanthocyanidin [32, 33]. Back-up antibiotic prescriptions, often mentioned in this survey, have been advocated, along with guidance as to their appropriate use [34].

2.4 Investigations

While urine culture was performed too often for simple RC, dipstick tests were infrequent despite recommendations by the French language society for infectious diseases. [**Error! Bookmark not defined.**]. However, the cost of dipstick tests is not endorsed by the National health insurance, which limits their use. Another inappropriate approach was to treat urinary colonisation revealed by an unnecessary follow-up urine microbiology and culture after a clinically effective antibiotic course, which should not lead to further antimicrobial prescription.

2.5 Antimicrobial therapy and possible alternatives

Although a wish to avoid antibiotics was expressed, these were used by many patients, especially FT due to the convenience of a single dose, but also inappropriate use of other compounds, whether self-administered or inadequately prescribed by a physician. Such variable coping measures when confronting initial signs of cystitis highlight the need for standardized approaches since the stated treatment strategies did not conform with recommendations: self-medication with fluoroquinolones, systematic urine culture , secondary adaptation of antibiotic treatment to susceptibility test results for uncomplicated RC; regular empirical antibiotic treatment for potentially complicated RC, with a single, thus suboptimal, FT dose; nitrofurantoïne as antibiotic prophylaxis, which is strictly contra-indicated according to French guidelines [2, **Error! Bookmark not defined.**, **Error! Bookmark not defined.**, **Error! Bookmark not defined.**]. Many non-antibiotic options for RC have been explored [35]. Treatment strategies have been evolving in Scandinavian countries and in Germany, where pain killers/ non-steroid anti-inflammatory drugs (NSAIDs) can be offered for treating cystitis with mild/moderate symptoms in a watch and wait approach although their efficacy remains controversial [13, 36, 37]. Phytotherapy has been shown to be effective [38, 39]. French guidelines state that topical oestrogens can be beneficial to menopaused women [40], while, according to a Spanish study, prevention with D-

Mannose significantly decreased the frequency of UTI [32, 41]. Immunotherapy using a vaccine based on a bacterial extract is currently being tested [42]. Lastly, among the various approaches aiming to alleviate pain and stress, hypnosis could prove useful: it has been shown to alleviate symptoms in irritable bowel syndrome and to reduce the need for analgesics during surgical procedures [43]. Preliminary results of its use in RC are promising (Ongoing HYpnocyst Protocol by the same author, unpublished data).

2.5. Patients' views on physicians' approach

The discrepancy between symptom intensity and the reputedly benign character of RC stands out as a frustrating situation whereby the condition is not seriously considered, although patients' distress has recently been acknowledged [44].

The lack of physicians' and society's understanding regarding RC contrasts with the major impact of the condition on patients' activities, perception and degree of anxiety. Ignorance of the cause of RC, cost of antibiotic alternatives, lack of investigation or of conclusive results thereof led patients to adopt a fatalistic attitude. This was noted by Italian authors who concluded to the "cost of resignation" related to physicians' lack of involvement [6]. Certain patients even expressed surprise at being questioned regarding their opinions on their management of RC.

Patients' request for more autonomy has been addressed in France with a strategy put forward in 2014, targeting selected, educated women with no risk factor, subject to twice-yearly re-assessment: this consists in self-treatment thanks to a delayed prescription, following a (non-reimbursed) dipstick test to confirm cystitis [2]. A recent qualitative survey conducted in the United Kingdom pointed to the need for addressing physicians' knowledge and skill gaps on UTI in women under the age of 65 years, including non-pharmaceutical recommendations for self-care [45].

Lastly, the request for more thorough, multidisciplinary management relying on various strategies is not in line with recommendations put forward by the SPILF for uncomplicated RC in 2014 [2]: in non-menopausal women with a normal pelvic and urethral clinical examination, no further investigation is systematically required. In other situations, for women at risk for complications, management should be decided by a multidisciplinary team. Few women (25%) had consulted a urologist or a gynaecologist, while infectious disease specialist advice was very rarely sought.

Clarification of this trajectory should result in more standardized approaches and reduce patients' anxiety.

3. Implications

3.1. Information leaflet

Based on the requests put forward by the interviewees, an information leaflet should be made available and include the following items to meet the needs and expectations of patients with RC:

- A reminder of the definitions
- Description of the known causes and risk factors of RC supported by a diagram and information on the usefulness and timeliness of urinalysis, dipstick test and urine microscopy and culture
- Procedure to be followed when first signs of cystitis appear
- Role of antimicrobial treatment and preferred compounds
- Summary of possible non-antibiotic treatments
- Clear suggested strategy for initial investigations/specialist referral

Such an information leaflet can be considered as a means of patient empowerment, as recommended by the French Language Society for Infectious Diseases (SPILF) in 2014 and which has still not been put into practice. It can contribute to patient education, aiming to involve patients in their healthcare and quality of life, while reducing inappropriate antibiotic use.

The effectiveness of information leaflets has been demonstrated in various contexts, namely regarding paediatric antibiotic prescriptions when coupled with GP online training [46]. A patient-clinician shared decision-making leaflet was developed in the UK that addressed the consultation barriers and promoted patient empowerment, with both leaflet and corresponding explanations delivered by the physician [47].

Although the use of such a leaflet will depend on the physician's wish to grant patients more autonomy and on the time available for dialogue, this may prove beneficial for both in the long run. Patients would have a clear, handy and relevant resource which would contribute to reduce their anxiety by addressing several of their queries and describe the procedure to follow in case of cystitis. For previously selected and educated patients provided with back-up of urine microbiology and culture and/or antibiotics, the leaflet would increase autonomy. A printed resource facilitates memorisation and assimilation. Clear and explicit definitions can eliminate any confusion and thus prevent inadequate treatment. A diagram can help understand the links between risk factors and hygiene and dietary measures to adopt. Improved understanding should lead to better adherence to the suggested management strategy. A summary of various non-antibiotic treatments, whether validated or not, can meet patients' request, describe how each should be administered and allow patients to test their respective effectiveness. Lastly, its use would contribute to improve to harmonize the currently highly disparate management approaches reported by patients.

Such an approach reflects most patients' demands. The leaflet (Appendix 3) could thus contribute to train physicians from various specialties in good clinical practice. This could even be complemented with a specific resource for physicians.

Assessment of this resource on a wider scale is now necessary, by distributing it to the RésO GPs and their patients, to confirm its relevance and consequently offer it to all women suffering from RC.

Figures and legends:

Figure 1: patient flowchart

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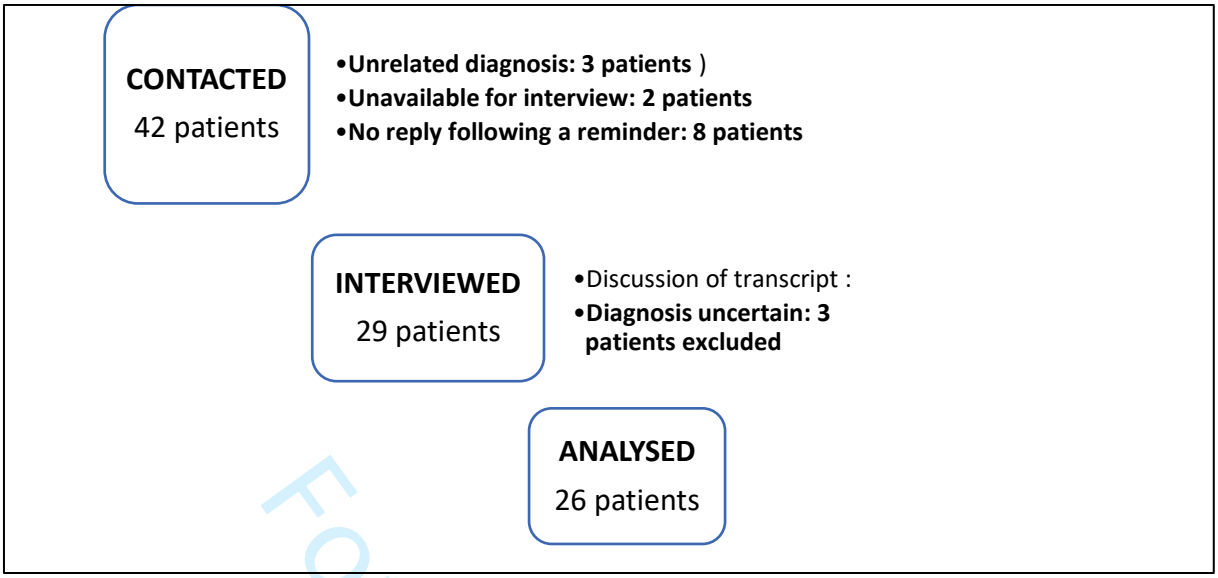


Figure 1 : Patient Flowchart

APPENDIX 1: INTERVIEW GUIDE

Interview guide for exploring the needs and expectations of women suffering from recurrent cystitis

Recurrent cystitis is a frequent complaint among women, its management is highly variable and needs to be improved.

Our interview aims to better understand the needs and expectations of these woemn to develop and information leaflet intended to provide them with accurate explanations of the causes of these recurring infections and the means of addressing them.

Thank you for participating.

Questions are deliberately « open » so that your personal experience can be recorded as completely as possible in vew of improving this information leaflet.

Your answers will be recorded and later analysed anonymously of course.

Question 1

Tell me about your latest episode of cystitis

Question 2

How long have you been suffering from recurring cystitis? In what way does the problem affect your daily life? What bothers you most?

Question 3

How do you explain your episodes of cystitis?

Question 4

What do you do to prevent or treat an episode of cystitis?

Question 5

What information have you been given by your physician(s) and how?

Question 6

What information have you obtained from other sources? What other information would you wish to have, and how would you wish to have it?

Question 7

What do you think about the way your recurrent cystitis is managed? How would you like it to be managed?

Quantitative questionnaire

Age

Educational level:

Social/professional category: Farmers / Agricultural employees / Industrial and commercial employers / Professionals and senior managers / Middle management / Employees / Workers / Service personnel / Others

Area of residence:

Urban / semi-rural / rural

Age at initial episodes of cystitis:

Physician consulted for recurring cystitis:
General practitioner / gynaecologist / urologist / infectious disease specialist/ other

Past medical history:
Gynaecological:
Urological:
Digestive system:
Immunosuppression, smoking:

Family history of recurring cystitis:

Other:

Would you be willing to read the information leaflet developed on the basis of all the comments collected during this survey; and eventually share your opinion with us during a brief telephone interview?

APPENDIX 2 PATIENTS QUOTES

N°	Interview	Quote
1Q1	1	« it's really related to stress, at least, that's my feeling »
1Q2		"So, yes, I have problems because when I pee, my bladder doesn't empty itself"
1Q3		« I try to get the doctor to write me a prescription I can keep. But they don't always do it… they say: « you must do an urine culture beforehand » But when it happens, I need to take the antibiotic quickly to avoid the pain. Admittedly, I haven't often done the test, to be honest! When it happens, I tend to rush to call the doctor and ask: "I've already been to the pharmacy and… can I have the prescription? » ». "I think it would be good to have a prescription, even for a urine culture, or to be able, from the susceptibility test, to find the antibiotic I need."
4Q1	4	« I met women much older than me, who also had recurring cystitis, they don't even know why they have this! It makes your life hell, you know! »
4Q2		« Well, I can't carry out my usual activities, I can't go shopping because I know I'll need to pee, and it burns, it's horrible! »
4Q3		"Why do we get so many RC episodes?".
6Q1	6	"I think the best thing would be to have a little booklet explaining because we don't have time to discuss it when we visit the GP."
6Q2		"nobody tells you to do tests, or… ummm, it's really NOT NORMAL to take antibiotics every 6 months! »
6Q3		"'This is what you should avoid, this is what you should rather do, this is when you should see your doctor', …that wouldn't be bad! "
7Q1	7	« I asked for further investigations because I get very tired taking antibiotics every month. So, at one point I said maybe we should look a bit deeper since I'd had episodes of cystitis but also of pyelonephritis. So, there I think it's also perhaps because the infection wasn't properly cured. So that's why I asked the doctor – I often change my GP – and I was sent to see a urologist ".
7Q2		« Since when do you have recurring cystitis? Since my pregnancies."
10Q1	10	« It's awful, because you're stuck at home
10Q2		«Well, the worst thing is to have to go to the toilet all the time and… NOT TO PEE!
10Q3		That's the worst, because you pee ONE DROP, and that drop, its… AWFUL! It burns, burns, burns !!! »
11Q1	11	"I don't go to the doctor's because I know antibiotics will be prescribed. If there was a follow up, we could discuss it each time and see if there's something else."
11Q2		« There's no follow-up. Although we get this regularly… »
12Q1	12	"So I'd really like to know why… what is cystitis? What's going on in the vagina? …and why does it start again each time?"
13Q1	13	. "Because I don't always have this burning sensation. Sometimes, it's only turbid and smelly urine. So, in that case, if I've run out of FT, then I take herbal teas."
14Q1	14	"… I'd like to know, is there a link with contraception or not? Are there means of contraception that favour cystitis, or not?"
14Q2		« after sexual intercourse, there's often a beginning of urinary tract infection"
14Q3		«since I'd told her I'd had a few episodes of cystitis during the year, the gynaecologist did a cervical swab."
14Q4		« Well … prefer, hum… perhaps not, but to think "I'm trying something else and if it doesn't work, resort to antibiotics".
14Q5		"Because in my view, antibiotics are really effective … it's a bit like a bomb, setting off suddenly, acting quickly! And that way, just using it when it's needed, if prior treatment hasn't worked. » (Int 14)

14Q6 **14Q7** **14Q8** **14Q9** **14Q10** **14Q11**		*« Isn't there something else that would be just as effective? Because taking antibiotics straight away, you see, always taking antibiotics, I don't know if that's really… good! Doesn't it generate … I don't know… resistance too in bacteria that…can cause cystitis? So, wouldn't there be other ways (and that takes us back to prevention), that would avoid taking antibiotics every time? »* *« Well, for a start, to know if I've properly identified all the causes that can lead to cystitis, because maybe there are things that I do every day that I'm unaware of and that can contribute to cystitis. »* *« To make matters worse, doctors are always jam-packed, so you need to wait a week to treat cystitis, It's a bit LONG!!! And just to get an antibiotic prescription that I can go and ask several times from the pharmacist. It's not very realistic in case of cystitis which occurs quite suddenly and can be treated very quickly, but that must be done right away! »* *« So that's rather a nuisance, the fact that there's no follow-up, for instance when you go to the GP and you've already been several times because of cystitis… you really get the impression that it stays in the file, because for the doctors, it's a bit anecdotal… They're going to ask if our pain in the arm (if you came once for that), if that's over now, etc., but for cystitis, even if you've been five times for that, they're not bothered... it's not something that I feel is important for them. » (Int 14)* *« Even at work, when you say, "I can't come, I've got cystitis", well, people don't understand, they tend to consider it trivial, it's not serious; even the doctors! »* *"Written yes, I think, with drawings it's important also, to understand the links with the anatomy and to know how it works."*
16Q1 **16Q2**	**16**	*"So I had it in fact during each of my pregnancies, practically every month"* *Because when I get it, generally we avoid intercourse because … it hurts too much!* *« In fact, the only information I have is the one I was given as a child. My parents were very careful so I was often told 'you don't drink enough, you should go to the toilet more often, that kind of thing. In fact, that's the only information I have about urinary tract infection, because recently I didn't have another one. That's why I can't identify the cause any more. »* *Or… perhaps there are other reasons, so I'd really like them to be identified,*
17Q1 **17Q2**	**17**	*« OK, usually I don't sit down, but, often, I still clean the toilet! But I think that even if you don't sit down and you're above it… maybe if there's really a bacterium there, one that's too strong, maybe as I have a weakness, maybe… » (17)* *« If it's too strong, or if it's in the evening (and if I think I can't wait till the next day) I take either my FT, or an antibiotic that I have at home. » (Int 17)*
18Q1 **18Q2** **18Q3**	**18**	*« Yes! Really… it's dealt with on the spot with a urine culture and an antibiotic, but nothing's done over the long term in fact! So, they should try to see with the gynaecologist if there's something wrong or send me to get tests which I've never done, although I've been having cystitis for over 30 years! » (Int 18)* *"Well, I'd like to know why"* *"What I'd like, is that it weren't a condition that's taken lightly!"*
19Q1 **19Q2** **19Q3**	**19**	*"There were times when I couldn't even go to work"* *"We can't have intercourse anymore because it's too painful."* *"I'd had an ultrasound examination of the bladder, to see if there was anything…But there was nothing."*

20Q1	***20***	*"Because I've had endometriosis, in fact, for a long time, and, well, the uterus is very near, the ovaries too and I think maybe with age and the course of the disease, today, maybe there's possibly something wrong with the bladder"*
20Q2		*« I'd like to be able to take the antibiotic myself, without having to go to the doctor and have the same test done over and over again every six or eight weeks, when I know the result perfectly well… I'm quite capable of telling the difference, it's been so long! And it's so constraining! I really feel I'm always going there to ask for the same thing, and my doctor always gives me the same answer: Cipro, urine test »(Int 20)*
20Q3		*« I have the feeling that cystitis is really considered a trivial complaint, but for me it's detrimental and important. If you say: 'I can't come to work, I've got cystitis', people don't understand, It's not serious, even for the doctors! »*
		« Besides paying for the visit during which, anyway, she's not even going to examine me, since I go in, I tell her « I've got a tummy ache, I pee three drops, I have to go every 10 minutes, it burns… », –"Yes, OK, here you are: Prescription… that's it!". » (Int 20)
22Q1	***22***	*"I know it's frequent after sexual intercourse »*
22Q2		*« All the doctors said is cranberries, drink a lot, take care when wiping, washing, choose appropriate underwear, avoid tight jeans… I tried to change all that a bit. It didn't do anything. Cranberry, I did that, it didn't work. Ah yes, they also said to use special mineral water so that the urine wasn't acid, well I still get it..."*
23Q1	***23***	*« Since I get this regularly, I always have a prescription, I have dipstick tests at home, so I always do that … But generally, I know I have it! So, it's usually positive…I always have urine test containers in advance because the lab gives them to me. » (Int 23)*
23Q2		*« On the contrary, we can work hand in hand, to have a wider scope, saying "OK, conventional medicine doesn't work with you. Apparently, we can't find the cause, nor an effective treatment."*
23Q3		*« I think medical practice should be more open to natural therapies »*
		« Couldn't a naturopath suggest something else? But then those treatments are not covered by the health insurance. So, it's difficult for people who don't have the means. »
23Q4		*« I often drink cranberry juice, I buy packets of cranberry, I eat dried cranberries, even though the taste isn't necessarily…especially the juice, it's acid! »*
24Q1	***24***	*« If I can bear it, I'm not going to go and have a dipstick test or urine culture, I'll stick to cranberries, water, cotton underwear and that's it. I only take antibiotics when I don't feel well."*
24Q2		*« Perhaps there's something else that might explain cystitis, I didn't have an ultrasound … would an ultrasound examination show something, I don't know if a malformation of the urinary tract or something that could explain cystitis recurring like this? »*
25Q1	***25***	*"So what information did you get from your doctor(s) and how?" "None at all. Sorry! "*
25Q2		*« I'd like to be given a guideline! »*
		« In my case, management was alright since, every time, my cystitis went away. However, considering overall management, … maybe that's what was missing: proper treatment but also proper information. The type of management I would like? real medium- and long-term support, that would be it. »
25Q3		*« As there's never been a urine culture done, it's always been dipstick tests … »*
25Q4		*« I mean… I don't go to the doctor's, because I know what I'll automatically get antibiotics, so, hum… So, if there's a follow-up, afterwards, we can talk about it each time and see if there's something else… »*
26Q1	***26***	*"Just after menopause, that's true."*
26Q2		*"A hereditary factor, family, you see? It's possible, because my mother had it too."*

27Q1	***27***	*« Yes, I saw Dr A…who prescribed a weekly dose of FT for 6 months… It worked perfectly for about 7 months, and then it started again! »*
27Q2		*« I always have this fear, when I go somewhere, I always take my FT dose with me. »*
		"I take cranberry… I try to drink regularly."
28Q1	***28***	*«I had taken antibiotics for cystitis, it was AUGMENTIN… Well, for a start, the taste was horrible. And even with probiotics, I got diarrhoea. And this time I got thrush, with lots of mouth ulcers, and that was due to CIPRO! …So, yes, if I can avoid taking them, perhaps.»*
28Q2		*"Besides, I had the baby at the time, which didn't help my libido!"*
28Q3		*"… Well, I admit it, it's true that I don't drink enough."*

APPENDIX 3:

INFORMATION LEAFLET FOR PATIENTS WITH RECURRENT CYSTITIS

WHAT IS CYSTITIS?

Cystitis or lower urinary tract infection is a bladder inflammation caused by bacteria. The main symptoms include a burning sensation when passing urine, urgency to urinate (pollakiuria), and sometimes blood in the urine (hematuria). **Recurrent cystitis** is usually defined as four episodes of bladder infection within the previous 12 months.

A **urine dipstick test** is the first step in guiding the diagnosis when leukocytes and/or nitrites are detected.

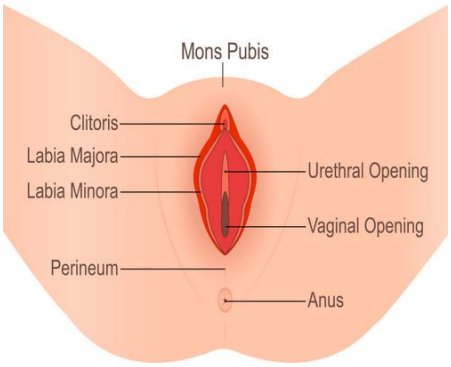
Urine culture can be performed in order to identify the bacteria involved and their antibiotic susceptibility.

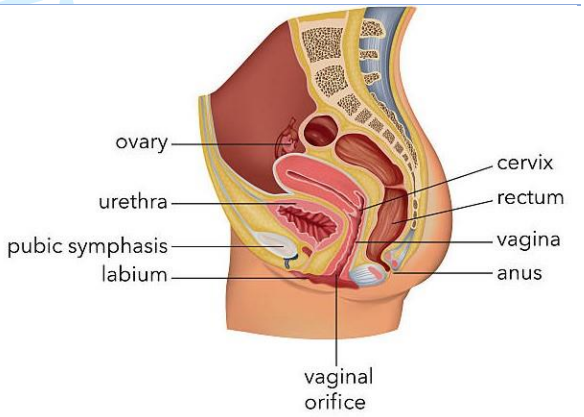
WHAT IS THE DIFFERENCE WITH URINARY TRACT COLONIZATION? WHAT ARE THE OTHER TYPES OF URINARY TRACT INFECTION?

If your urine is cloudy and/or foul-smelling but you do not experience any discomfort, it is therefore not cystitis but **urinary tract colonization.** There are bacteria in the urine, however they do not cause any infection. In such cases, you don't need to take an antibiotic but should simply increase your fluid intake.

Cystitis refers to an infection of the bladder, while **pyelonephritis** refers to an infection of the kidneys. Common symptoms of pyelonephritis include fever and/or chills and/or back pain. The infection must be rapidly treated with a different antibiotic than the one recommended for the treatment of cystitis.

WHAT CAUSES CYSTITIS? HOW CAN I PREVENT IT?





Bacteria present on the **perineum** (from the digestive tract and vaginal flora) can enter the bladder through the urethra. To prevent these bacteria from going into the bladder and multiplying, you can use the following tips:

- Drink 1,5 L of water each day so as to urinate every 3 hours during daytime, *avoid bladder irritants (coffee, tea, tobacco, alcohol…)*
- Do not delay going to the toilet, do not void in a standing or crouching position, *urinate after sexual intercourse*
- *Wipe front to back, avoid diarrhoea or constipation*
- Maintain good intimate hygiene: external wash only, once a day, using a neutral pH soap Symptomatic treatment of vaginal dryness if necessary (estriol cream, hyaluronic acid)
- *Apply vaseline to the meatus after urination or before activities that promote infection*

Propositions in italics are still under evaluation

WHAT SHOUD I DO IF CYSTITIS SYMPTOMS APPEAR?[1]

IN ORDER TO AVOID ANTIBIOTICS:

- Increase hydration to 3L per day[2] (forced diuresis)
- Relieve pain with:
  Phloroglucinol
  Ibuprofen[2]

IF NO IMPROVEMENT WITHIN 48 hours

SIMPLE RECURRENT CYSTITIS….

Do a urine dipstick test[3]

Then self administer[4] : Fosfomycin Trometamol **OR** Pivmecillinam

… OR WITH RISK OF COMPLICATIONS

Try to wait for the urine culture and antibiotic susceptibility test results[4] to choose the most suitable antibiotic with your doctor, **OTHERWISE** Fosfomycin Trometamol **OR** Nitrofurantoin

In 40 % of cases, antibiotics are not necessary for cure. They act directly on the normal bacterial flora (microbiota) and may have adverse effects, e.g. fungal infection (thrush) or diarrhoea. Their use also increases the likelihood of bacterial resistance to antibiotics[5].

If your cystitis episodes keep occurring very frequently (> 1 / month), or are specifically related to sexual intercourse, you need to discuss with your physician whether you should take a **prophylactic antibiotic treatment**, i.e. an extended antibiotic course to prevent cystitis (Fosfomycin Trometamol 1 sachet/week or Trimethoprim 1 pill a week or 2hours before/after sexual intercourse, as prescribed by your doctor).

…WHAT ABOUT NON-ANTIBIOTIC TREATMENTS?

- Phytotherapy :
  - cranberries if infection due to *E. Coli*: 36 mg/d of proanthocyanidins, during 3 to 6 months
  - *Other: treatment of the episode with Busserole[6], Heather, or Hibiscus*
- Prevention or treatment of the episode using D-Mannose if E. Coli infection
- Treatment of the episode with Aromatherapy[6]: essential oils of thyme, cinnamon, tea tree, savory
- Relaxation and pain management techniques : sophrology, yoga, hypnosis
- Vaccines: oral route or vaginal suppository unavailable in France (available in Switzerland or Belgium)

WHICH FURTHER EXAMINATIONS SHOULD BE CARRIED OUT?

If the urological or the gynaecological examination results are normal, **no further investigation will be systematically performed** except for menopausal women and/or women with specific medical histories. For all other cases, management should be discussed by a **multidisciplinary team** including an infectious diseases specialist, and conclusions communicated to the general practitioner.

[1]Subject to your general practitioner's review, at least twice a year. Should treatment failure occur, contact your doctor
[2]In the absence of medical contraindication: check with your doctor
[3]After 4 to 6 episodes of cystitis, you should have a urine culture to look for antibiotic resistance
[4]Talk to your doctor about delayed prescribing of urine culture and/or antibiotics according to your situation
[5]This is why Fluoroquinolones (Oflocet® Ciflox®) and third generation Cephalosporins (Oroken®, Rocéphine®) are not recommended[6]Contraindicated in case of pregnancy and breastfeeding