Protocols for the Management of Urinary Tract Infections during Pregnancy

A guide for community pharmacists
This booklet was compiled by Katya Busuttil as part of a dissertation carried out for the partial fulfilment of the requirements of the course leading to the Degree of Masters of Pharmacy.

This study was carried out under the supervision of Professor Lilian M Azzopardi, Head of Department, Department of Pharmacy, University of Malta.

Protocols were adapted from previous projects entitled ‘Treatment Protocols in Pregnancy’ by Antonella Aquilina in 2004, and ‘Treatment Protocols in Pregnancy’ by Roberta Fenech in 2008.

The contents of this booklet have been validated by a panel of experts, namely:
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University of Malta
Women are at risk of developing urinary tract infections which are normally uncomplicated and easy to treat. The risk of developing a urinary infection is increased during pregnancy and serious complications may ensue.

As part of her project leading to the degree of Masters of Pharmacy, Katya Busuttil has participated in the research project which we are conducting in the development and implementation of protocols in pharmacy care. Following on earlier work conducted, Katya is now presenting a concise protocol that can be used by community pharmacists in differentiating symptoms of nocturia, increased frequency and urinary urgency that are common in pregnancy from symptoms of urinary tract infections. She has captured recommendations on the use of antibacterial agents for urinary tract infections in pregnant women. Of particular value are the Referral Forms that have been devised. These are intended to support communication between community pharmacists and physicians.

This booklet is part of a research study and we look forward to feedback from clinicians and pharmacists to support the development of evidence-based tools that can be used in the day-to-day practice of documented pharmacist interventions.

Professor Lilian M. Azzopardi
Head, Department of Pharmacy
University of Malta
Acknowledgements

I would like to express my deep gratitude and sincere appreciation to all who have shared my journey in the making of this booklet.

First and foremost, I would like to thank God; I could never have done this without the faith I have in You. Special thanks go to Professor Lilian M. Azzopardi, Professor Anthony Serracino-Inglott, Dr Maurice Zarb Adami and Dr Claire Shoemake from the Department of Pharmacy for suggesting the title of the project and for their encouragement, advice and guidance throughout.

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Sincere thanks also go to pharmacists Louise Grech, Francesca Buttigieg, Chantel Ellul, Ryan Sacco and general practitioner Dr Mario Rizzo Naudi for their utmost support and care throughout.

Lastly, I would like to thank my family, particularly my mother, my brother and my father, the best daddy, the greatest love and the most extraordinary blessing in my life, Frederick for his patience and Adrian, a treasured friend.

Thank you everyone.
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How to use this booklet

This booklet includes a set of protocols and important guidelines that may be used by community pharmacists for the management of UTIs during pregnancy. They should be considered as guidelines and should not replace the pharmacist’s clinical judgement. The following steps indicate the way to use this booklet;

**Step 1:** Choose either the Prescription protocol flowchart or the Non-Prescription protocol flowchart.

For the Prescription protocol, a confirmed diagnosis of UTI during pregnancy is assumed. For the Non-prescription protocol continue with the following steps;

**Step 2:** Assess the presenting sign/s and symptom/s and history of UTI and decide if referral is necessary or not.

**Step 3:** If referral is necessary, complete *Referral form A* by filling applicable parts (*Appendix 2*) and exit the protocol.

**Step 4:** If referral is not necessary, continue with the protocol, while giving appropriate advice and information at each stage to the patient.

**Step 5:** If patient remains symptomatic on follow-up visit, complete *Referral form D* (*Appendix 2*).

**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>b.d.-</td>
<td>twice times daily</td>
</tr>
<tr>
<td>t.d.s.-</td>
<td>three times daily</td>
</tr>
<tr>
<td>q.d.s.-</td>
<td>four times daily</td>
</tr>
<tr>
<td>UTI-</td>
<td>urinary tract infection</td>
</tr>
<tr>
<td>PMR-</td>
<td>Patient Medication Record</td>
</tr>
<tr>
<td>G6PD-</td>
<td>Glucose-6-phosphate dehydrogenase</td>
</tr>
<tr>
<td>FDA-</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>CNS-</td>
<td>central nervous system</td>
</tr>
<tr>
<td>GI-</td>
<td>gastro-intestinal</td>
</tr>
<tr>
<td>mg-</td>
<td>milligrams</td>
</tr>
<tr>
<td>pgs-</td>
<td>pages</td>
</tr>
</tbody>
</table>
Interpretation of shapes

- **Data box**: Represents patient data
- **Action or process box**: Used when pharmacist is required to perform an action
- **Terminator**: Used when it is time to exit the protocol
- **Decision box**: Used when a decision made by pharmacist leads to different paths
- **Connection between one page and another**: Used when the flowchart continues on a new page

Note: The outer colour of certain shapes in the flowcharts refer the pharmacist to read further information required for the proper management of the condition. This information could be found in the booklet after the flowcharts (pgs. 10-23).
Non-Prescription Protocol

1. Pregnant woman presents with complaints suggestive of UTI

2. Document patient identity (PMR- Appendix 3)

3. Assess
   - Risk of complicated UTI,
   - History of UTI,
   - Symptoms and signs to identify need for referral

4. Referral necessary?
   - YES
   - Go to boxes 9,10,11,12
   - NO

5. Fill up applicable part/s of Referral Form A (Appendix 2) and exit protocol.

6. Any factor/s that could interfere with this test?
   - YES
   - Counsel patient on the collection of urine using the midstream clean-catch technique for urine dipstick test. Look out for any factor/s that could interfere with this test (pgs. 14,15)
   - NO

7. Perform urine dipstick test and interpret the result. When reading test, wait for the time recommended by the manufacturer

8. Go to boxes 9,10,11,12
From Box 8

9. All negative nitrite leukocyte protein blood
   - 13. UTI very unlikely

10. Positive nitrite +/- leukocyte +/- protein +/- blood
   - 14. Probable UTI

11. Negative nitrite Positive leukocyte +/- protein +/- blood
   - 15. UTI or other condition

12. Negative nitrite Negative leukocyte Positive protein or blood

17. Repeat urine dipstick test using another sample of midstream urine specimen within 24 hours
   - 18. Result all negative nitrite leukocyte protein?

   YES
   - 19. Advice on implementation of lifestyle modifications and encourage patient for follow-up

   NO
   - 20. Patient still complains of symptoms after implementation of lifestyle modifications?

     YES
     - 21. Complete Referral Form D (Appendix 2) and exit protocol.

     NO
     - 22. Advice on maintaining of lifestyle modifications to prevent future recurrences

Give pregnant patient appropriate advice and information at each stage.
Prescription Protocol

Pregnant patient presents with a prescription for an antibiotic for the treatment of UTI.

Document patient identity

(PMR- Appendix 3)

Check and report to the prescriber if (Complete Referral Form B (Appendix 2))
- Patient is allergic to the drug
- Drug is teratogenic
- Any possible interaction with other drugs

Dispense medication/s and record dispensing (PMR- Appendix 3). Advice pregnant patient on
- Dose and dosage regimen
- Duration of treatment
- Any side-effects to look out for

Arrange follow-up appointment with the patient for urine dipstick test after treatment is completed and then monthly for the remainder of the pregnancy.

The **presentation** of symptoms and signs varies depending on whether the pregnant patient has a lower tract (cystitis), or an upper tract (pyelonephritis) infection (**Table A**).

**Cystitis** - characterised by the presence of symptoms such as dysuria, urinary urgency, urinary frequency, nocturia, haematuria and suprapubic discomfort in afebrile women.

**Pyelonephritis** - defined as significant bacteriuria in the presence of systemic illness and symptoms such as flank or renal angle pain, pyrexia, chills, nausea and vomiting.

(McCormick et al., 2008; Schnarr and Smaill, 2008)

**Table A: Symptoms and signs**

<table>
<thead>
<tr>
<th>Symptoms and signs</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysuria</td>
<td>-Common symptoms and signs encountered during pregnancy.</td>
</tr>
<tr>
<td>Nocturia</td>
<td>-If mild or ≤ 2 symptoms and signs - perform urine dipstick test to identify occurrence of UTI.</td>
</tr>
<tr>
<td>Urinary frequency</td>
<td>-Prompt <strong>immediate referral</strong> if (complete <strong>Referral form A</strong> (<em>Appendix 2</em>));</td>
</tr>
<tr>
<td>Urinary urgency</td>
<td>-≥ 1 symptoms and signs accompanied by <strong>warning symptoms</strong> such as <strong>flank or renal angle pain</strong>, <strong>chills</strong>, <strong>fever</strong> and <strong>nausea and vomiting</strong>: possibility of <strong>pyelonephritis</strong></td>
</tr>
<tr>
<td>Suprapubic discomfort</td>
<td>-Severe or ≥ 3 symptoms and signs without vaginal discharge and/or irritation since the probability of UTI raises in this scenario.</td>
</tr>
</tbody>
</table>

| Flank or renal angle pain | -Probability of UTI and probability of pyelonephritis unknown. |
| Chills                  | -Refer pregnant patient **immediately** (complete **Referral form A** (*Appendix 2*)) - need for **urine culture** to establish diagnosis. |
| Fever                   | |

(Delzell and Lefevre, 2000; McCormick et al., 2008)

(British National Formulary, No.61, 2011)

Advice and information following a UTI

Give pregnant patient information and advice about the following:

- **Preventive treatment** - The possibility of a UTI recurring (see note below) and the importance of being cautious and seeking prompt treatment from a healthcare professional
- **Recognising symptoms quickly** - The nature of and reason for UTIs

**Recurrent infections**

Even with appropriate treatment, the pregnant patient may experience a reinfection of the urinary tract from the rectal reservoir. UTIs recur in approximately 4 to 5 percent of pregnancies. A single dose or daily suppression with cephalexin or nitrofurantoin in patients with recurrent UTIs is effective preventive therapy. A **postpartum urologic evaluation** may be necessary in patients with recurrent infections because they are more likely to have structural abnormalities of the renal system or in patients who have a recurrent UTI while on suppressive antibiotic therapy.

(National Institue for Health and Clinical Excellence, No. 54, 2007)
Lifestyle modifications to prevent UTIs

Although not well studied, several preventive measures for the prevention of bacteriuria during pregnancy have been suggested by healthcare professionals. Many of these methods have not been proven to be clinically effective. However, if signs and symptoms suggestive of UTI are present, these methods may be worth trying, since they do not pose harm to patients.

Advice on preventive treatment of UTIs

- Drink plenty of water daily and avoid drinks such as soft drinks and fruit juices.
- Empty the bladder fully when urinating.
- Do not delay urinating when the need arises.
- Wipe from front to back to prevent bacteria from entering the vagina or urethra.
- Avoid irritation of the vagina with feminine products such as sprays or douches.

(Cimerville et al., 2005) (Patel, 2007) (Jepson and Craig, 2008; Stapleford AE et al., 2012)

Cranberry juice

There is some evidence that cranberry juice may prevent UTIs, particularly for women with recurrent UTIs. However, recent randomized controlled study suggests that cranberry juice did not significantly reduce UTI risk compared with placebo. It is not clear what is the optimum dosage or method of administration (e.g. juice, tablets or capsules).

Vaginal discharge and/or vaginal irritation

- Refer pregnant patient immediately (complete Referral form A (Appendix 2) - need for pelvic examination (including cervical cultures when appropriate) and urine culture to establish diagnosis; patient is more likely to have vaginitis.

Nausea and vomiting

- Refer pregnant patient immediately (complete Referral form A (Appendix 2) if nausea and vomiting accompanied by ≥ 1 of the following symptoms and signs: dysuria, nocturia, urinary frequency, urinary urgency, suprapubic discomfort, fever or chills, chest pain, severe abdominal pain, CNS symptoms, hypotension and severe dehydration.
- Need for urine culture to establish diagnosis.

(Aquilina, 2004; Bent et al., 2002; Fenech, 2008; Scorza et al., 2007)

Complicated and history of UTI

In pregnant patients with risk factors for a complicated UTI including patients with a functional or anatomic abnormality of the urinary tract and patients with a history of
- polycystic renal disease,
- nephrolithiasis,
- neurogenic bladder,
- recent urinary tract instrumentation,
- diabetes mellitus

and/or pregnant patients with a history of UTI during previous pregnancies; a urine culture with initial empirical treatment is recommended, therefore pharmacist should prompt immediate referral (complete Referral form A (Appendix 2)).

(Bent et al., 2002; Delzell and Lefevre, 2000; McCormick et al., 2008)
Urine analysis

**Urine dipstick testing** is a useful rapid screening method for diagnosing or excluding infection. **Nitrite** and **leukocyte esterase** are the most specific parameters whereas **blood** and **protein** are not specific for infection. The interpretation of the physical properties from general examination of urine are shown in Table B, while Tables C (a), (b), (c) (d) and (e) show details about the important parameters a pharmacist should look for when testing urine for the possibility of a UTI.

(Simerville et al., 2005)

**Table B: General examination of urine: Physical properties**

<table>
<thead>
<tr>
<th>Colour</th>
<th>-Colour of normal urine varies with its concentration, from deep yellow to almost clear. -Often, changes in urine colour are a result of certain factors; therefore pharmacists should rule out this possibility (Table D).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odour</td>
<td>-Patients with UTIs often have urine with an offensive smell. -The presence of malodorous urine does not indicate the presence of infection and does not negate the need for testing.</td>
</tr>
<tr>
<td>Sediment and cloudiness</td>
<td>-Presence of sediment/cloudiness is not always associated with infection and a test is not automatically indicated.</td>
</tr>
</tbody>
</table>

(Panesar, 2009, Simerville et al., 2005)

**Table C: Parameters that might indicate a UTI**

**Table C (a): Blood**

- Presence of blood in urine suggests serious renal or urological disease or/ and UTI. **Negative Result** - Patients at risk should be tested regularly to ensure that intermittent bleeding is detected. **Positive Result** - Follow-up will depend upon the results from other tests.

(Aquilina, 2004; Fenech, 2008; Panesar, 2009, Simerville et al., 2005)
Table C (b): Nitrite

<table>
<thead>
<tr>
<th>Negative Result</th>
<th>Positive Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Normally indicates absence of Gram negative bacteria.</td>
<td>Confirmation of UTI.</td>
</tr>
<tr>
<td>- Always view negative result test in light of other test results.</td>
<td></td>
</tr>
</tbody>
</table>

(Aquilina, 2004; Fenech, 2008; Panesar, 2009, Simerville et al., 2005)

Table C (c): Protein

<table>
<thead>
<tr>
<th>Negative Result</th>
<th>Positive Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>- The reagent strip is more sensitive to albumin, so a negative result does not rule out presence of globulins, haemoglobin.</td>
<td>- Needs confirmation.</td>
</tr>
<tr>
<td>- Persistent positive results indicate renal disease, UTI, hypertension, pre-eclampsia, congestive heart failure.</td>
<td>- Check nitrite, blood and leukocyte test results.</td>
</tr>
</tbody>
</table>

(Aquilina, 2004; Fenech, 2008; Panesar, 2009, Simerville et al., 2005)
**Table C (d): Leukocytes**

| Presence of leukocytes in urine indicates a bladder or renal infection. | **Negative Result** | -Where positive symptoms are present; result should be confirmed by follow-up testing e.g. microscopy, culture, etc.  
-Note blood and protein results. |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Result</td>
<td>Indicator of UTI</td>
<td></td>
</tr>
</tbody>
</table>

(Aquilina, 2004; Fenech, 2008; Panesar, 2009, Simerville et al., 2005)

**Table C (e): pH**

| Average urine is slightly acidic, usually within the pH range of 5-6, but can vary from pH 4.8-8.5. | **Alkaline (> 8)** | -Might indicate UTI.  
-Check using nitrite/leukocyte/protein/blood test results. |
|---|---|---|
| Strongly acidic (<4) | -May indicate uncontrolled diabetes/dehydration.  
-Check glucose and ketone test results. |

(Aquilina, 2004; Fenech, 2008; Panesar, 2009, Simerville et al., 2005)

**Table D: Foods and diseases that can change the colour of urine**

<table>
<thead>
<tr>
<th>Colour of Urine</th>
<th>Foods</th>
<th>Disease/s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orange</td>
<td>Vitamin C, carrots</td>
<td>Dehydration</td>
</tr>
<tr>
<td>Red/pink</td>
<td>Blackberries, rhubarb</td>
<td>Haematuria</td>
</tr>
<tr>
<td>Blue/green</td>
<td>Asparagus</td>
<td>Pseudomonal UTI</td>
</tr>
<tr>
<td>Dark brown</td>
<td>Fava beans, rhubarb, aloe</td>
<td>Liver disorders (accompanied by yellow skin and pale stools); myoglobin; renal disorders that affect the kidney’s ability to excrete fluid and waste materials</td>
</tr>
</tbody>
</table>

(Panesar, 2009, Simerville et al., 2005)
**False-positive and false-negative results**

**False-positive** and **false-negative** results are not unusual with dipstick urine test (Table E). Therefore, where positive symptoms and signs of UTI are positive and urine dipstick test results do not indicate an infection, it is recommended to **repeat this test within 24 hours**.

(Simerville et al., 2005)

<table>
<thead>
<tr>
<th>Dipstick test</th>
<th>False-Positive</th>
<th>False-Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>pH</strong></td>
<td>Acidic urine: ingestion of proteins &amp; acidic foods. Alkaline urine: diet high in citrate, antiepileptic drugs, aged urine sample</td>
<td>Not applicable</td>
</tr>
<tr>
<td><strong>Leukocytes</strong></td>
<td>Contamination from container</td>
<td>Elevated specific gravity, glycosuria, ketonuria, proteinuria, ascorbic acid, cephalexin, nitrofurantoin</td>
</tr>
<tr>
<td><strong>Nitrite</strong></td>
<td>Contamination from container, insufficient dietary nitrate, lack of incubation time in bladder</td>
<td>Elevated specific gravity, pH &lt; 6, vitamin C, elevated urobilinogen levels</td>
</tr>
<tr>
<td><strong>Blood</strong></td>
<td>Dehydration, exercise, contamination from container</td>
<td>Elevated specific gravity, pH &lt; 5.1, proteinuria, vitamin C, exposure of dipstick to air</td>
</tr>
<tr>
<td><strong>Protein</strong></td>
<td>Alkaline or concentrated urine, phenazopyridine</td>
<td>Acidic or diluted urine, primary protein is not albumin</td>
</tr>
</tbody>
</table>

Indication of a UTI

Immediate referral is recommended if urine dipstick test indicates an infection since empirical antimicrobial treatment will need to be initiated as soon as possible. Effective treatment significantly reduce the incidence of pyelonephritis, premature delivery and low birthweight.

(Bent et al., 2002; Simerville et al., 2005)

Advice on urine collection using the midstream clean-catch technique

Give pregnant patient advice to
- Use a container provided specifically for urine collection
- Wash hands before collecting the sample with soap and water
- Remove the lid of the collection container and place it with the inner surface up, making sure one do not touch the inside of the lid or the container
- Urinate a small amount into the toilet for a few seconds, then pause and advice not to collect any of the sample
- Continue urinating into the collection container until enough urine has been collected
- Finish urinating into the toilet
- Carefully replace the lid and return the container for testing
- Store the sample in a refrigerator if the sample is not being tested immediately (see note below).

(Simerville et al., 2005)

Preserving the urine sample

Urine samples should be tested immediately after collection to prevent false results. If immediate testing is not possible, the sample should be refrigerated and allowed to return to room temperature before testing.

(National Institute for Health and Clinical Excellence, No. 54, 2007)
Advice on urine collection using the midstream clean catch technique

Give pregnant patient advice to -

Use a container provided specifically for urine collection -

Wash hands before collecting the sample with soap and water -

Remove the lid of the collection container and place it with the inner surface up, making sure one do not touch the inside of the lid or the container -

Urinate a small amount into the toilet for a few seconds, then pause – advice not to collect any of the sample -

Continue urinating into the collection container until enough urine has been collected -

Finish urinating into the toilet -

Carefully replace the lid and return the container for testing -

Store the sample in a refrigerator if the sample is not being tested immediately (see note below).

Indication of a UTI

Immediate referral is recommended if urine dipstick test indicates an infection since empirical antimicrobial treatment will need to be initiated as soon as possible. Effective treatment significantly reduce the incidence of pyelonephritis, premature delivery and low birthweight. (Bent et al., 2002; Simerville et al., 2005)

Preserving the urine sample

Urine samples should be tested immediately after collection to prevent false results. If immediate testing is not possible, the sample should be refrigerated and allowed to return to room temperature before testing. (National Institue for Health and Clinical Excellence, No. 54, 2007)

Treatment

There is no clear consensus in the literature on either the choice of antibiotic or the duration of therapy and as a result, practice is more likely guided by national patterns of practice than by evidence from clinical trials. (Schnarr and Smaill, 2008)

Urine alkanising agents

Urine alkanising agents have been popular for the treatment of women with urinary symptoms but the benefits of such treatments have not been established and there are particular concerns with regard to hypernatraemia and the use of sodium citrate in pregnancy. The general advice is to avoid these preparations. (McCormick et al., 2008)

Preferred antibiotics for the treatment of UTIs during pregnancy

Drugs which have been extensively used in pregnancy and appear to be frequently safe should be prescribed in preference to new or untried drugs. The smallest effective dose should be used (Table F and Table G). (British National Formulary, No.61, 2011)

Note: It is recommended in the literature that pregnant patients who have a UTI should be treated with an appropriate antibiotic therapy for a period of 7 to 10 days because of the risks associated with recurrence. Some studies have recommended shorter courses of treatment; even single-day therapy. Conflicting evidence remains as to whether pregnant patients should be treated with shorter courses of antibiotics. (Delzell and Lefevre, 2000; Lee et al., 2008)
### Table F: Penicillins

<table>
<thead>
<tr>
<th>Example of an Active Ingredient</th>
<th>Co-amoxiclav</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA Category</td>
<td>B</td>
</tr>
<tr>
<td>Recommended dose and dosage regimen of co-amoxiclav</td>
<td>250 mg/125 mg t.d.s. (amoxicillin 250mg, clavulanic acid 125mg)</td>
</tr>
<tr>
<td>Caution</td>
<td>History of allergy</td>
</tr>
</tbody>
</table>
| Contra-indications             | • Penicillin hypersensitivity  
• History of penicillin associated jaundice or hepatic dysfunction |
| Drug-antibiotic interaction/s  | • Allopurinol  
• Muscle Relaxants |
| Potential adverse fetal and maternal effects of penicillins | **Fetal effects**  
None known, but **fetal hypersensitivity** is a theoretical risk | **Maternal effects**  
Hypersensitivity reactions  
Hematological toxicity  
Renal toxicity  
CNS toxicity  
GI toxicity |
| Common side-effects            | • Nausea  
• Vomiting  
• Diarrhoea  
• Abdominal discomfort |
| Notes                          | -The use of **amoxicillin** is discouraged due to increasing resistance leading to treatment failure, therefore amoxicillin is no longer considered an optimal choice for treatment of UTI during pregnancy. |

(British National Formulary, No.61, 2011; Delzell and Lefevre, 2000)
Table G: Cephalosporins

<table>
<thead>
<tr>
<th>Example of an Active Ingredient</th>
<th>Cefalexin</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA Category</td>
<td>B</td>
</tr>
<tr>
<td>Recommended dose and dosage regimen of cefalexin</td>
<td>250-500 mg t.d.s.</td>
</tr>
<tr>
<td>Caution</td>
<td>Sensitivity to beta-lactam antibacterials</td>
</tr>
<tr>
<td>Contra-indications</td>
<td>Cephalosporin hypersensitivity</td>
</tr>
</tbody>
</table>
| Drug-antibiotic interaction/s   | • Antacids  
|                                 | • H₂ antagonists |
| Potential adverse fetal and maternal effects of cephalosporins | **Fetal effects**  
|                                 | Testicular toxicity*  
|                                 | **Maternal effects**  
|                                 | Bleeding dyscrasia*  
|                                 | GI disorders  
|                                 | Hematological toxicity  
|                                 | Hepatic toxicity  
|                                 | Hypersensitivity reactions  
|                                 | Renal toxicity  |

*Animal studies only; has not been reported in humans

Common side-effects | See under Co-amoxiclav

Notes
- Cefalexin is a **first-generation** cephalosporin. It is effective against most urinary pathogens.
- **Second-generation** cephalosporins are not as well absorbed orally as the first-generation cephalosporins, have a greater incidence of GI adverse effects, thus they should only be used where specifically indicated.
- **Third-generation** cephalosporins generally require parenteral administration and are reserved for use in secondary care for serious infections.

(British National Formulary, No.61, 2011: Delzell and Lefevre, 2000)
Antibiotics to be used with caution for the treatment of UTIs during pregnancy

<table>
<thead>
<tr>
<th>Table H: Nitrofurans</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Example of an Active Ingredient</strong></td>
</tr>
<tr>
<td><strong>FDA Category</strong></td>
</tr>
<tr>
<td><strong>Recommended dose and dosage regimen of nitrofurantoin</strong></td>
</tr>
</tbody>
</table>
| **Caution** | • Anaemia  

  • Diabetes mellitus  

  • Electrolyte imbalance  

  • Vitamin B and folate deficiency |
| **Contra-indications** | • Nitrofurans hypersensitivity  

  • G6PD deficiency  

  • Teratogenic risk in third trimester |
| **Drug-antibiotic interaction/s** | • Antacids |
| **Potential adverse fetal and maternal effects of nitrofurantoin** | **Fetal effects**  

  May produce neonatal haemolysis in a G6PD-deficient infant if used at term  

| **Maternal effects** | Hemolytic anemia in women with G6PD deficiency |
| **Common side-effects** | See under Co-amoxiclav; anorexia, acute and chronic pulmonary reactions. |
| **Notes** | Avoid at term |

(British National Formulary, No.61, 2011; Mallia Azzopardi et al., 2004)

Advice on treatment

Give pregnant women information and advice about the need for treatment, the importance of completing treatment and any side-effect/s to look out for.
Urine dipstick testing is a useful rapid screening method for diagnosing or excluding infection. Nitrite and leukocyte esterase are the most specific parameters whereas blood and protein are not specific for infection. The interpretation of the physical properties from general examination of urine are shown in Table B, while Tables C(a), (b), (c), (d) and (e) show details about the important parameters a pharmacist should look for when testing urine for the possibility of a UTI.

- **Colour**
  - Colour of normal urine varies with its concentration, from deep yellow to almost clear.
  - Often, changes in urine colour are a result of certain factors; therefore pharmacists should rule out this possibility (Table D).

- **Odour**
  - Patients with UTIs often have urine with an offensive smell.
  - The presence of malodorous urine does not indicate the presence of infection and does not negate the need for testing.

- **Sediment and cloudiness**
  - Presence of sediment/cloudiness is not always associated with infection and a test is not automatically indicated.

(British National Formulary, No.61, 2011)

### Table I: Contraindicated drugs not to be used during pregnancy

<table>
<thead>
<tr>
<th>Drug or class of drug</th>
<th>FDA Category</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co-trimoxazole</td>
<td>C</td>
<td>Teratogenic risk in first trimester (trimethoprim is a folate antagonist) unless combined with folic acid 1mg/day. Neonatal haemolysis and methaemoglobinemia in third trimester; fear of increased risk of kernicterus in neonates appears to be unfounded.</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>D</td>
<td>Effects on skeletal development have been documented when tetracyclines have been used in the first trimester of pregnancy in animal studies. Administration during the second or third trimester may cause discoloration of the child’s teeth and maternal hepatotoxicity has been reported with large parenteral doses.</td>
</tr>
<tr>
<td>Quinolones</td>
<td>C</td>
<td>Have been shown to cause arthropathy in animal studies; safer alternatives are available.</td>
</tr>
</tbody>
</table>

(British National Formulary, No.61, 2011)
Lifestyle modifications to prevent UTIs

Although not well studied, several preventive measures for the prevention of bacteriuria during pregnancy have been suggested by health care professionals. Many of these methods have not been proven to be clinically effective. However, if signs and symptoms suggestive of UTI are present, these methods may be worth trying, since they do not pose harm to patients.

(Simerville et al., 2005)

Advice on preventive treatment of UTIs

Give pregnant patient advice to
- Drink plenty of water daily and avoid drinks such as soft drinks and fruit juices.
- Empty the bladder fully when urinating.
- Do not delay urinating when the need arises.
- Wipe from front to back to prevent bacteria from entering the vagina or urethra.
- Avoid irritation of the vagina with feminine products such as sprays or douches.

(Patel, 2007)

Cranberry juice

There is some evidence that cranberry juice may prevent UTIs, particularly for women with recurrent UTIs. However, recent randomized controlled study suggests that cranberry juice did not significantly reduce UTI risk compared with placebo. It is not clear what is the optimum dosage or method of administration (e.g. juice, tablets or capsules).

(Jepson and Craig, 2008; Stapletin AE et al., 2012)
Assess the symptoms and signs

The presentation of symptoms and signs varies depending on whether the pregnant patient has a lower tract (cystitis), or an upper tract (pyelonephritis) infection (Table A).

**Cystitis** - characterised by the presence of symptoms such as dysuria, urinary urgency, urinary frequency, nocturia, haematuria and suprapubic discomfort in afebrile women.

**Pyelonephritis** - defined as significant bacteriuria in the presence of systemic illness and symptoms such as flank or renal angle pain, pyrexia, chills, nausea and vomiting.

Symptoms and signs

- Dysuria
- Nocturia
- Urinary frequency
- Urinary urgency
- Suprapubic discomfort

Common symptoms and signs encountered during pregnancy.

If mild or <2 symptoms and signs - perform urine dipstick test to identify occurrence of UTI.

Prompt immediate referral if (complete Referral form A (Appendix 2); >1 symptoms and signs accompanied by warning symptoms such as flank or renal angle pain, chills, fever and nausea and vomiting: possibility of pyelonephritis.

- Flank or renal angle pain
- Chills
- Fever

Probability of UTI and probability of pyelonephritis unknown.

Refer pregnant patient immediately (complete Referral form A (Appendix 2)) - need for urine culture to establish diagnosis.

(McCormick et al., 2008; Schnarr and Smaill, 2008)

<table>
<thead>
<tr>
<th>Table A: Symptoms and signs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

Follow-up

After finishing the antibiotic therapy indicated by the prescriber, the pharmacist should give a **follow-up appointment** to the pregnant woman. A dipstick urine test is encouraged after treatment of the primary infection to ensure response and then **monthly** for the remainder of the pregnancy to monitor for **recurrence**.

(British National Formulary, No.61, 2011)

**Advice and information following a UTI**

Give pregnant patient information and advice about the following:
- Preventive treatment
- The possibility of a UTI recurring (see **note below**) and the importance of being cautious and seeking prompt treatment from a healthcare professional
- Recognising symptoms quickly
- The nature of and reason for UTIs

(National Institute for Health and Clinical Excellence, No. 54, 2007)

**Recurrent infections**

Even with appropriate treatment, the pregnant patient may experience a reinfection of the urinary tract from the rectal reservoir. **UTIs recur** in approximately **4 to 5 percent of pregnancies**. A single dose or daily suppression with cephalexin or nitrofurantoin in patients with recurrent UTIs is effective preventive therapy. A **postpartum urologic evaluation** may be necessary in patients with recurrent infections because they are more likely to have **structural abnormalities** of the renal system or in patients who have a recurrent UTI while on suppressive antibiotic therapy.

(Delzell and Lefevre, 2000; McCormick et al., 2008)
Appendix 1: The FDA Category Interpretation

The FDA has established five categories (A, B, C, D, and X) to indicate a drug's potential for causing teratogenicity (Table J). The FDA categories are intended to guide drug choice before fetal exposure.

(Einarson et al., 2010)

Table J: Current FDA Categorisation for Drug use during pregnancy

<table>
<thead>
<tr>
<th>Category</th>
<th>Summary of the FDA Category Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Controlled studies in pregnant women show no risk to the fetus in any trimester of pregnancy and the possibility of fetal harm appears remote.</td>
</tr>
<tr>
<td>B</td>
<td>No evidence of risk in pregnant women - Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women or in the absence of adequate human studies, animal studies show no fetal risk. The chance of fetal harm is remote, but remains a possibility.</td>
</tr>
<tr>
<td>C</td>
<td>Risk can not be ruled out - Adequate, well-controlled human studies are lacking, and studies in animals have revealed adverse effects on the fetus or there are no controlled studies in pregnant women or animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.</td>
</tr>
<tr>
<td>D</td>
<td>Positive evidence of risk - There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., the drug may be acceptable if needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).</td>
</tr>
<tr>
<td>X</td>
<td>Contraindicated in pregnancy - Studies in animals or humans have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit.</td>
</tr>
</tbody>
</table>

(Einarson et al., 2010)
Appendix 2: Referral Forms

Referral Form A
(for pregnant patients)

Date ______________________
Dear Dr. __________________
Name of patient ________________________________
Week of gestation _____________________________

PART A:
This patient presented with the following signs and/or symptoms and we thought it was best to refer her to you:
_____________________________________________________________________
_____________________________________________________________________
_____________________________________________________________________
or

PART B:
This patient presented with the following signs and/or symptoms and stated that she had a previous history of urinary tract infection. We thought it was best to refer her to you:
_____________________________________________________________________
_____________________________________________________________________
_____________________________________________________________________
or

PART C:
This patient presented with the following signs and/or symptoms. The following factor/s was identified that can cause false negatives or false positive results using the test strips mentioned for dipstick urine testing. We thought it was best to refer her to you:

Signs and/or Symptoms:_________________________________________________
Factor/s:_____________________________________________________________
Test Strips:   ___________________________________________________________

If you have any questions about this patient do not hesitate to call us at:
_____________________________________________________________________

Sincerely,
________________________________
(Pharmacist)
Date ______________________
Dear Dr ___________________
Name of patient _______________________________
Week of gestation ______________________________

This patient presented with the following signs and/or symptoms:
_____________________________________________________________________
_____________________________________________________________________
_____________________________________________________________________

After explaining to the patient the correct method of how to collect a midstream sample of urine, a dipstick urine test was performed on a morning, fresh sample of urine.
Test strips used for urine dipstick test: _________________________________

<table>
<thead>
<tr>
<th>PART A: 1st test performed: Results obtained;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrite</td>
</tr>
<tr>
<td>Leukocytes</td>
</tr>
<tr>
<td>Protein</td>
</tr>
<tr>
<td>Blood</td>
</tr>
<tr>
<td>Urine pH</td>
</tr>
</tbody>
</table>

or

<table>
<thead>
<tr>
<th>PART B: 1st test performed: Results obtained;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrite</td>
</tr>
<tr>
<td>Leukocytes</td>
</tr>
<tr>
<td>Protein</td>
</tr>
<tr>
<td>Blood</td>
</tr>
<tr>
<td>Urine pH</td>
</tr>
</tbody>
</table>

(continue...)
2nd test performed: Repeat sampling of another midstream urine specimen within 24 hours of carrying out the first test- which had given a negative result. Results obtained:

<table>
<thead>
<tr>
<th>Nitrite</th>
<th>Leukocytes</th>
<th>Protein</th>
<th>Blood</th>
<th>Urine pH</th>
</tr>
</thead>
</table>

After interpretation of these results, we thought it was best to refer her to you.

If you have any questions about this patient do not hesitate to call us at:

_____________________________________________________________________

Sincerely,

________________________________
(Pharmacist)

---

**Referral Form C**

*(for pregnant patients)*

Date ______________________
Dear Dr ___________________
Name of patient _______________________________
Week of gestation _____________________________

<table>
<thead>
<tr>
<th>Date of dispensing</th>
<th>Medication name</th>
<th>Dosage Strength, dosage form</th>
<th>Dosage regimen</th>
<th>Duration</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

The above medication was prescribed for the patient. However : (continue...)
PART A:
This drug is found to be teratogenic. Evidence-based information from:
______________________________________________________________

or

PART B:
This drug can cause an interaction since patient is also on

Medication/s name: _______________________

Strength: ________________________________

Dosage form: ____________________________

Dosage regimen: ________________________

Duration: ______________________________

Indication/s: ____________________________

or

PART C: The patient is stating that she is allergic to the drug prescribed

We thought it was best to refer her to you.

If you have any questions about this patient do not hesitate to call us at:
______________________________________________________________

Sincerely,
________________________________
(Pharmacist)

Referral Form D  
(for pregnant patients)

Date ______________________
Dear Dr. ___________________
Name of patient _______________________________
Week of gestation _____________________________

PART A:
This patient presented with the following signs and/or symptoms on __/__/____ (date)

_____________________________________________________________________
_____________________________________________________________________
_____________________________________________________________________

Dipstick urine testing was performed on __/__/____ (date) and repeated using another fresh sample of midstream urine specimen within 24 hours. Both tests had given a negative result.

The patient was adviced on the implementation of lifestyle modifications and was given a follow-up appointment on __/__/____ (date). Patient still complaints of the following signs and/or symptoms;

_____________________________________________________________________
_____________________________________________________________________
_____________________________________________________________________

We thought it was best to refer her to you:

If you have any questions about this patient do not hesitate to call us at:

________________________________

Sincerely,

________________________________

(Pharmacist)
Appendix 3: Patient Medication Record (PMR)

Patient Name: ___________________
I.D. Number: ____________________
Age: ___________________________
Week of gestation: _______________

Presenting complaint:
_____________________________________________________________________
_____________________________________________________________________
_____________________________________________________________________

History of UTI:
_____________________________________________________________________
_____________________________________________________________________
_____________________________________________________________________

Current treatment:
_____________________________________________________________________
_____________________________________________________________________
_____________________________________________________________________

<table>
<thead>
<tr>
<th>Date</th>
<th>Medication name</th>
<th>Dosage strength, dosage form</th>
<th>Dosage regimen</th>
<th>Duration</th>
<th>Specific Advice</th>
<th>Follow-up date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Any drug and/or food allergies: _______________________________________
_____________________________________________________________________
_____________________________________________________________________

Women are at risk of developing urinary tract infections which are normally uncomplicated and easy to treat. The risk of developing a urinary infection is increased during pregnancy and serious complications may ensue.

As part of her project leading to the degree of Masters of Pharmacy, Katya Busuttil has participated in the research project which we are conducting in the development and implementation of protocols in pharmacy care. Following on earlier work conducted, Katya is now presenting a concise protocol that can be used by community pharmacists in differentiating symptoms of nocturia, increased frequency and urinary urgency that are common in pregnancy from symptoms of urinary tract infections. She has captured recommendations on the use of antibacterial agents for urinary tract infections in pregnant women. Of particular value are the Referral Forms that have been devised. These are intended to support communication between community pharmacists and physicians.

This booklet is part of a research study and we look forward to feedback from clinicians and pharmacists to support the development of evidence-based tools that can be used in the day-to-day practice of documented pharmacist interventions.

Professor Lilian M. Azzopardi
Head, Department of Pharmacy
University of Malta

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### Appendix 4: Antibiotics available locally

#### Antibiotics used for the treatment of UTIs during pregnancy available locally according to the Malta Medicines Authority July 2011.

#### Key:
- **Trade Name**
- (active ingredient/s, dose/s)
- **Pharmaceutical form**
- **Licence Holder name**

#### Penicillins

<table>
<thead>
<tr>
<th>Key</th>
<th>Trade Name</th>
<th>(active ingredient/s, dose/s)</th>
<th>Pharmaceutical form</th>
<th>Licence Holder name</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Augmentin® (amoxicillin (as trihydrate) 250mg; 500mg; 875mg, clavulanic acid 125mg)</td>
<td>Film-coated tablets</td>
<td>Glaxo SmithKline Ireland Ltd.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Augmentin-Duo 400/57® (amoxicillin (as trihydrate) 400mg/5ml, clavulanic acid 57mg/5ml)</td>
<td>Powder for Oral Suspension</td>
<td>Smithkline Beecham PLC.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clavomid® (amoxicillin 250mg; 500mg, clavulanic acid 125mg)</td>
<td>Film-coated tablets</td>
<td>Remedica Ltd.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Co-Amoxiclav Aurobindo Film-Coated Tablets® (amoxicillin (as trihydrate) 875mg, potassium clavulanate 125mg), Film-Coated tablets</td>
<td>Amoxicillin/Clavulanic Acid Aurobindo Powder for Oral Suspension® (amoxicillin (as trihydrate) 125mg/5ml; 250mg/5ml, clavulanic acid (as potassium clavulanate) 31.25mg/5ml; 62.5mg/5ml), Powder for oral suspension</td>
<td>Aurobindo Pharma (Malta) Ltd.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Co-Amoxiclav Coated Tablets® (amoxicillin 250mg; 500mg, clavulanic acid 125mg)</td>
<td>Coated tablets</td>
<td>Sandoz Pharmaceuticals DD.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Co-Amoxiclav Tablets BP 250-125mg® (amoxicillin 250mg, clavulanic acid 125mg)</td>
<td>Film-coated tablets</td>
<td>Generics UK Ltd.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Forcid® (amoxicillin 500mg; 875mg, clavulanic acid 125mg)</td>
<td>Tablets/tablets for oral suspension</td>
<td>Astellas Pharma.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fungentin® (amoxicillin (as trihydrate) 500mg, clavulanic acid (as potassium clavulanate) 125 mg), Film-coated tablets</td>
<td>Fungentin® (amoxicillin (as trihydrate) 125mg/5ml; 250mg/5ml, clavulanic acid (as potassium clavulanate) 31.25/5ml; 62.5mg/5ml), Powder for Oral Suspension</td>
<td>Elpen Pharmaceutical Co. Inc.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moxiclav® (amoxicillin 250mg; 500mg; 875mg, clavulanic acid 125mg), Film-coated tablets</td>
<td>Moxiclav 156.25mg/5ml® (amoxicillin 125mg/5ml, clavulanic acid 31.25mg/5ml), Powder for Oral Suspension</td>
<td>Medochemie Ltd.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moxiclav Forte 312.5mg/5ml® (amoxicillin 250mg/5ml, clavulanic acid 62.5mg/5ml), Powder for Oral Suspension</td>
<td>Noprilam® (amoxicillin 500mg; 875mg, clavulanic acid 125mg), Tablets</td>
<td>Bial - Portela &amp; C S.A.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Noprilam DT 400® (amoxicillin 400mg/5ml, clavulanic acid 57mg/5ml), Powder for Oral Suspension</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Nitrofurans

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Description</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macroldantin Capsules® (nitrofurantoin 50mg; 100mg)</td>
<td>Hard capsules</td>
<td>Goldshield Pharmaceuticals Ltd., Alfred Gera &amp; Sons Ltd.</td>
</tr>
</tbody>
</table>

### Cephalosporins

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Description</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceclor MR tablets® (cefaclor (as monohydrate) 375mg; 500mg; 750mg)</td>
<td>Modified Release Tablets</td>
<td>Phadisco Ltd.</td>
</tr>
<tr>
<td>Ceclor® (cefaclor (as monohydrate) 125mg/5ml; 250mg/5ml)</td>
<td>Granules for Oral Suspension</td>
<td>Phadisco Ltd.</td>
</tr>
<tr>
<td>Cefuroxime 250mg tablets® (cefoxime (as axetil) 250mg)</td>
<td>Tablet, coated tablets</td>
<td>Sandoz Pharmaceuticals DD</td>
</tr>
<tr>
<td>Cefuroxime Aurobindo Tablets® (cefoxime (as axetil) 125mg; 250mg; 500mg)</td>
<td>Tablets</td>
<td>Aurobindo Pharma (Malta) Ltd.</td>
</tr>
<tr>
<td>Cefuroxime Axetil Actavis® (cefoxime (as axetil) 250mg; 500mg)</td>
<td>Film-coated tablets</td>
<td>Actavis Group PTC ehf.</td>
</tr>
<tr>
<td>Ceporex® (cefalexin 125mg/5ml)</td>
<td>Granules for Oral suspension</td>
<td>P &amp; D Pharmaceuticals Ltd</td>
</tr>
<tr>
<td>Eurocefix 500mg® (cefaclor (as monohydrate) 500mg), Hard capsules</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eurocefix 250mg/5ml granules for oral suspension® (cefaclor (as monohydrate) 250mg/5ml)</td>
<td>Granules for Oral Suspension</td>
<td>Alta Care Laboratoires s.r.l</td>
</tr>
<tr>
<td>Keflex Capsules® (cefaclor 500mg)</td>
<td>Capsules</td>
<td>Phadisco Ltd.</td>
</tr>
<tr>
<td>Medolexin 250® (cefalexin 250mg)</td>
<td>Capsules</td>
<td>Medochemie Ltd</td>
</tr>
<tr>
<td>Orelox tablets® (cefpodoxime (as proxetil) 100mg, 200mg)</td>
<td>Film-coated tablets</td>
<td>Aventis Pharma AEBE</td>
</tr>
<tr>
<td>Performer® (cefaclor (as monohydrate) 250mg/5ml)</td>
<td>Granules for Oral Suspension</td>
<td>Vecchi &amp; C. PIAM s.a.p.a.</td>
</tr>
<tr>
<td>Zinnat Granules for Oral Suspension® (cefoxime (as axetil) 125mg/5ml; 250mg/5ml)</td>
<td>Granules for oral suspension</td>
<td>Glaxo SmithKline Ireland Ltd.</td>
</tr>
<tr>
<td>Zinnat Tablets® (cefoxime (as axetil) 250mg; 500mg)</td>
<td>Film-coated tablets</td>
<td>Glaxo Wellcome UK Ltd., NeoFarma Ltd., Medicem Ltd., AlphaFarma Ltd.</td>
</tr>
</tbody>
</table>

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References


