4.5 Antibacterial agents

Groups	Agents
Trimethoprim-sulphonamide combinations	Trimethoprim, co-trimoxazole, co-tetroxoprime (trimethoprim plus sulfametrol)
Fluoroquinolones[1,2]	
Group 1	Norfloxacin, pefloxacin
Group 2	Enoxacin, fleroxacin, lomefloxacin, ofloxacin, ciprofloxacin
Group 3	Levofloxacin
Group 4	Gatifloxacin, moxifloxacin
Macrolides	Erythromycin, roxithromycin, clarithromycin, azithromycin
Tetracyclines	Doxycycline, minocycline, tetracycline
Fosfomycin	Fosfomycin sodium, fosfomycin trometamol[3]
Nitrofuran[4]	Nitrofurantoin
Penicillins	
Benzylpenicillin	Penicillin G
Phenoxypenicillins	Penicillin V, propicillin, azidocillin
Isoxazolylpenicillins	Oxacillin, cloxacillin, dicloxacillin, flucloxacillin
Aminobenzylpenicillins[5]	Ampicillin, amoxycillin, bacampicillin
Aminopenicillins/BLI[6]	Ampicillin/sulbactam, amoxycillin/clavulanic acid7
Acylaminopenicillins	Mezlocillin, piperacillin
±BLI[6]	Piperacillin/tazobactam, sulbactam6
Cephalosporins[1]	
Group 1 (oral)	Cefalexin, cefadroxil, cefaclor
Group 2 (oral)	Loracarbef, cefuroxime axetile
Group 3 (oral)	Cefpodoxime proxetile, cefetamet pivoxil, ceftibuten, cefixime
Group 1 (parenteral)	Cefazolin
Group 2 (parenteral)	Cefamandole, cefuroxime, cefotiam
Group 3a (parenteral)	Cefodizime, cefotaxime, ceftriaxone
Group 3b (parenteral)	Cefoperazone, ceftazidime
Group 4 (parenteral)	Cefepime, cefpirome
Group 5 (parenteral)	Cefoxitin
Monobactams	Aztreonam
Carbapenems	Imipenem, meropenem, ertapenem
Aminoglycosides	Gentamicin, netilmicin, tobramycin, amikacin
Glycopeptides	Vancomycin, teicoplanin
Oxazolidones	Linezolid

[1]Classification according to the Paul Ehrlich Society for Chemotherapy [1-3].
[2]Only in adults, except pregnant and lactating women.
[3]Only in acute, uncomplicated cystitis as a single dose.
[4]Contraindicated in renal failure and in newborns.
[5]In cases of resistance, the pathogen is most likely to be a β-lactamase producer.
[6]BLIs can only be used in combination with b-lactam antibiotics.
[7]In solution, storage instability.

*4.5.1 **Penicillins***

Penicillin G and the oral penicillins, penicillin V, propicillin and azidocillin, have a high intrinsic activity against streptococci and pneumococci. However, the resistance rate of pneumococci may vary considerably between countries. In Germany, penicillin resistance in pneumococci is still < 1%. Because of their narrow spectrum of activity, these penicillins do not have any role in the treatment of urogenital infections.

4.5.1.1 Aminopenicillins

Aminopenicillins, e.g. ampicillin and amoxycillin, have a broader spectrum of activity. Apart from streptococci and pneumococci, they cover enterococci, Haemophilus influenzae, Haemophilus parainfluenzae, Listeria sp., E. coli, Pr. mirabilis, and Salmonella and Shigella sp. However, resistance may occur.

Aminopenicillins are sensitive to β-lactamases. They are therefore not sufficiently active against certain species, such as staphylococci, Moraxella catarrhalis, Bacteroides fragilis and many enterobacteria. This gap in the spectrum of activity can be closed by the use of a BLI (clavulanic acid, or sulbactam).

Amoxycillin/clavulanic acid and ampicillin/sulbactam are available on the market as fixed combinations. Indications for aminopenicillins and their combinations with a BLI are mild respiratory tract infections, UTIs, as well as infections of the skin and soft tissues.

4.5.1.2 Acylaminopenicillins

The acylaminopenicillins include apalcillin, azlocillin, mezlocillin and piperacillin. They are characterised by their high activity against enterococci, enterobacteria and Pseudomonas (weaker activity of mezlocillin). Acylaminopenicillins are hydrolysed by β-lactamases and are therefore active only against β-lactamase-producing strains of staphylococci, B. fragilis, and if used in combination with a BLI, some of the enterobacteria. The acylaminopenicillin/BLI combination provides a broad spectrum of activity and may be used for a large number of indications, including complicated UTIs and urosepsis. A selection of free combinations with sulbactam are available, or there is the fixed combination of tazobactam and piperacillin, which has the advantages of being easy to use and a well-documented database drawn from qualified clinical studies.

4.5.1.3 Isoxazolylpenicillins

Isoxazolylpenicillins are available as parenteral drugs with oxacillin and flucloxacillin, and have a narrow spectrum of activity. Their indications are limited to infections caused by S. aureus. Due to their suboptimal pharmacokinetic parameters, isoxazolylpenicillins are preferably used in milder infections of the skin and soft tissues, and of the ear, nose and throat area. They play no role in the treatment of UTIs, but may be used for staphylococcal abscesses in the genital area.

4.5.2 ***Parenteral cephalosporins***

According to the Paul Ehrlich Society for Chemotherapy [2], the parenteral cephalosporins have been classified into five groups, according to their spectrum of activity (Table 25).

Group 1 cephalosporins (e.g. cefazolin and cefazedone): They are very active against streptococci and staphylococci (including penicillin-G-resistant strains). They have only weak activity against Gram-negative microorganisms. Like all cephalosporins, cefazolin is not active against enterococci and MRSA and methicillin-resistant coagulase-negative staphylococci (MRSE).

Group 2 cephalosporins (e.g. cefuroxime, cefotiame and cefamandole): They exhibit markedly improved activity against Gram-negative pathogens and maintain high activity against staphylococci.

Group 3a cephalosporins: They have high activity against Gram-negative bacteria and less activity against staphylococci. They differ mainly in their pharmacokinetic characteristics.

Group 3b cephalosporins (e.g. ceftazidime and cefoperazone): They have added high anti-pseudomonal activity. However, the activity of cefoperazone against P. aeruginosa is markedly inferior to that of the other substances in this group.

Group 4 cephalosporins (e.g. cefepime and cefpirome): They have a comparable activity against Gram-negative bacteria, but are more stable against extended-spectrum β-lactamases, and a better activity against Gram-positive bacteria.

Group 5 cephalosporins: They are characterised by their anti-anaerobic activity. These cephalosporins have superior activity against Gram-negative bacteria compared with Group 1 and 2 cephalosporins, but most of them are weaker than Group 3 drugs. At present, cefoxitin is the only drug of that group available on the market in some countries.

Table 25: Classification of parenteral cephalosporins [3]

Group	Generic names	Features of the group
Group 1 (1st generation)	Cefazolin Cefazedone	• Active against Gram-positive and partly against Gram-negative bacteria • Stable against staphylococcal penicillinases • Unstable against β-lactamases of Gram-negative bacteria
Group 2 (2nd generation)	Cefuroxime Cefotiame Cefamandole	• Activity against Gram-positive bacteria good, but weaker than Group 1 • Activity against Gram-negative bacteria superior to that of Group 1 • Stable against staphylococcal penicillinases • Limited stability against β-lactamases of Gram-negative bacteria
Group 3a (3rd generation)	Cefotaxime Ceftriaxone Ceftizoxime Cefmenoxime Cefodizime	• Activity against Gram-negative bacteria clearly superior to that of Groups 1 and 2 • Stable against numerous β-lactamases of Gram-negative bacteria • Microbiologically less active against staphylococci
Group 3b (3rd generation)	Ceftazidime Cefoperazone	• Spectrum of antibacterial activity similar to that of Group 3a • Additional activity against P. aeruginosa
Group 4	Cefepime Cefpirome	• Spectrum of antibacterial activity similar to that of Group 3a • Additional activity against P. aeruginosa
Group 5	Cefoxitin	• Higher stability against beta-lactamases than Group 3b • With anti-anaerobic activity • Superior activity against Gram-negative bacteria than Group 1 and 2 • Weaker than Group 3

*4.5.3 **Oral cephalosporins***

Oral cephalosporins are classified into three groups, based on their spectrum of activity, according to the recommendations of the Paul Ehrlich Society for Chemotherapy [2] (Table 26).

Table 26: Classification of oral cephalosporins [2]

Oral cephalosporins	Drug names
Group 1	Cefalexin Cefadroxil Cefaclor
Group 2	Cefprozil Loracarbef Cefuroxime axetile
Group 3	Cefpodoxime proxetile Cefetamet pivoxile Ceftibuten Cefixime

Group 1 oral cephalosporins: Thes include cefalexin, cefadroxil and cefaclor. They are mainly active against Gram-positive cocci with limited activity against *H. influenzae* (cefaclor). Their main indications are skin and soft tissue infections and, with limitations, respiratory tract infections. Their activity against enterobacteria is limited, therefore, they can only be recommended for the treatment or prophylaxis of uncomplicated UTIs in children or pregnant women, for whom the use of other antibiotics is limited.

Group 2 oral cephalosporins: The activity of cefprozil against *S. aureus, Streptococcus pyogenes, Streptococcus pneumoniae, H. influenza* and *Mor. catarrhalis* is somewhat higher than that of cefaclor. However, cefprozil is less active than cefaclor against *E. coli, Klebsiella pneumoniae* and *Pr. mirabilis*.

Loracarbef is structurally close to cefaclor. In contrast to cefaclor, it is stable in solution, has better pharmacokinetics and a broader antibacterial spectrum. However, its activity against staphylococci is lower than that of cefaclor. The main indications are respiratory tract, skin and soft-tissue infections and uncomplicated UTIs.

Cefuroxime axetile has a higher β-lactamase stability and thus a broader spectrum than others in this group. It can be used mainly for bacterial infections of the upper (including otitis media) and lower respiratory tract, for skin and soft-tissue infections, and UTIs.

Group 3 oral cephalosporins: They have a higher activity and a broader spectrum against enterobacteria than group 2 cephalosporins. In contrast, their activity against Gram-positive bacteria is lower. Against staphylococci, the activity of cefpodoxime proxetil is intermediate, whereas cefetamet pivoxil, ceftibuten and cefixime are inactive.

The main indications for the oral cephalosporins of group 3 are complicated infections of the respiratory tract (provided that staphylococci can be excluded) and infections due to enterobacteria, e.g. UTIs or infections in immunocompromised patients. Group 3 oral cephalosporins are also suitable for oral switch therapy, i.e. when initial parenteral therapy (using a parenteral group 3a cephalosporin) needs to be continued orally. In addition, cefixime is licensed also for treatment of gonorrhoea.

4.5.4 ***Monobactams***

Among the monobactams, only aztreonam is available. It is active only against Gram-negative aerobes. In this respect, its spectrum and activity are similar to those of the parenteral group 3b cephalosporins.

4.5.5 ***Carbapenems***

Carbapenems are broad-spectrum antibiotics with good activity against Gram-positive and Gram-negative bacteria, including anaerobes. They are preferably used in the treatment of mixed infections and in the initial therapy of life-threatening diseases, including urosepsis. Imipenem/cilastatin, meropenem and doripenem are also active against P. aeruginosa. However, ertapenem is not active against P. aeruginosa. Ertapenem has a longer half-life than imipenem/cilastatin and meropenem, and is therefore, suitable for once-daily dosing.

4.5.6 ***Fluoroquinolones***

Non-fluorinated quinolones are no longer recommended because of their poor antibacterial activity. According to the Paul Ehrlich Society for Chemotherapy, the fluoroquinolones are classified into four groups, based on their spectrum of activity, their pharmacokinetics and indications (Table 27).

Table 27: Classification of fluoroquinolones, as modified according to the Paul Ehrlich Society for Chemotherapy [1]

Generic name	Trade name*/features of the group
Group 1	**Indications essentially limited to UTIs in some countries, e.g. Germany**
	Norfloxacin
	Pefloxacin**
Group 2	**Broad indications for systemic use**
	Enoxacin
	Fleroxacin***
	Lomefloxacin
	Ofloxacin
	Ciprofloxacin
Group 3	**Improved activity against Gram-positive and atypical pathogens**
	Levofloxacin
Group 4	**Improved activity against Gram-positive and atypical pathogens and anaerobes**
	Gatifloxacin
	Moxifloxacin

** Listed according to increasing in vitro activity (minimum inhibitory concentration) against indicative pathogens.*
*** In France and other countries, pefloxacin is also available for systemic use.*
**** Investigated in acute exacerbations of chronic bronchitis, UTIs, gonorrhoea and gastrointestinal infections.*

Group 1 fluoroquinolones: Indications for use are limited to UTIs in some countries, e.g. Germany. In France and some other countries, pefloxacin is also used for systemic oral and parenteral use. Norfloxacin is not available as parenteral antibiotic.

Group 2 fluoroquinolones: These include fluoroquinolones for systemic use with a broad spectrum of indications. These include infections of the urinary tract, respiratory tract, skin and soft tissues, bones and joints, as well as systemic infections and even sepsis. Group 2 fluoroquinolones exhibit good activity against enterobacteria and *H. influenzae*, with less activity against staphylococci, pneumococci, enterococci and atypical pathogens, e.g. *Chlamydia, Legionella* and *Mycoplasma* sp. Their activity against *P. aeruginosa* varies, with ciprofloxacin being most active in vitro. In addition, ciprofloxacin, ofloxacin and fleroxacin are also available for parenteral use.

Group 3 fluoroquinolones: The main difference in the spectra of activity of group 3 fluoroquinolones (levofloxacin) and group 4 fluoroquinolones (gatifloxacin and moxifloxacin) is that the former have a higher intrinsic activity against Gram-positive pathogens, such as staphylococci, streptococci, pneumococci and enterococci.

However, group 3 and group 4 fluoroquinolones have comparable activity against Gram-negative pathogens. In addition, they have improved activity against the so-called atypical pathogens, such as *Chlamydia, Mycoplasma* and *Legionella sp*. In addition, group 4 fluoroquinolones have improved anti-anaerobic activity.

The only group 3 fluoroquinolone available for parenteral use is levofloxacin; the left enantiomer of the ofloxacin racemate. The main indications for levofloxacin are respiratory tract infections, and, due to its high renal elimination rate, UTIs, as well as skin and soft-tissue infections.

Among group 4 fluoroquinolones, gatifloxacin (not on the market in Europe), moxifloxacin and trovafloxacin have been licensed. However, in June 1999, trovafloxacin was taken off the market because of severe side effects. Thus, to date, no parenteral fluoroquinolone of this group has been made available.

Apart from respiratory tract infections, these broad-spectrum fluoroquinolones are appropriate for treatment of skin, soft-tissue and intra-abdominal infections, and oral treatment of gynaecological infections. However, final judgement of their position in the treatment of these diseases is not yet possible. Gatifloxacin has the highest renal excretion (about 84%) after oral administration. It is therefore also the most suitable for the treatment of uncomplicated and complicated UTI. Urinary excretion of moxifloxacin after oral administration is only in the range of about 20%.

*4.5.7 **Co-trimoxazole***

The treatment of UTIs is the main indication for trimethoprim alone or in combination with a sulphonamide,

e.g. sulphamethoxazole. Trimethoprim with or without sulphamethoxazole can also be used for the prophylaxis of recurrent cystitis. The resistance rate against *E. coli* can vary between countries. It is therefore not recommended for empirical therapy of acute uncomplicated cystitis or pyelonephritis, when the resistance rate in the area is > 10-20% [4]. In complicated UTIs, co-trimoxazole should only be used in accordance with sensitivity testing. Trimethoprim, especially in combination with sulphamethoxazole, can lead to severe although rare adverse events, such as Lyell syndrome, Stevens-Johnson syndrome and pancytopenia.

4.5.8 ***Fosfomycin***

Fosfomycin is active against Gram-negative and Gram-positive bacteria. The sodium salt is only for parenteral use. Fosfomycin trometamol is licensed for single-dose (3 g) treatment of uncomplicated cystitis in women.

4.5.9 ***Nitrofurantoin***

The antibacterial activity of nitrofurantoin is limited to the urinary tract because of its low serum concentrations. It is active against *E. coli, Citrobacter* and most strains of *Klebsiella* and *Enterobacter*, whereas *Providencia* and *Serratia* are mostly resistant. *Proteus, P. aeruginosa* and *Acinetobacter* are almost always resistant. It is active against Gram-positive cocci, e.g. enterococci and staphylococci.

It is suitable only for the treatment or prophylaxis of uncomplicated UTIs. Short-term therapy for this indication has not been proven in sufficiently large studies. Little development of resistance has been observed over many years. Treatment can lead to severe, though rare adverse events, such as chronic desquamative interstitial pneumonia with fibrosis.

4.5.10 ***Macrolides***

Erythromycin is the only macrolide that is available for both oral and parenteral use. The newer macrolides, roxithromycin, clarithromycin and azithromycin, are better tolerated than erythromycin, but can only be administered orally. The macrolides have good activity against streptococci, pneumococci, *Bordetella pertussis*, and *Chlamydia, Mycoplasma* and *Legionella sp*. The macrolides are not active against Gram-negative rods, therefore, their use in the treatment of UTIs is limited to special indications, such as non-gonococcal urethritis due to *C. trachomatis*.

4.5.11 ***Tetracyclines***

The resistance against doxycycline and tetracycline of pneumococci, streptococci, H. influenzae and E. coli shows marked regional differences. Tetracyclines are therefore only suitable for initial empirical therapy if the local resistance situation is sufficiently well known and justifies their use. As a result of their high activity against the so-called atypical pathogens (Legionella, Chlamydia and Mycoplasma sp.), they may be used as alternative antibiotics in infections caused by these microorganisms, e.g. in non-gonococcal urethritis due to C. trachomatis.

4.5.12 ***Aminoglycosides***

Aminoglycosides are for parenteral use only. These drugs have a narrow therapeutic window. Their effective levels of activity are close to toxic borderline concentrations, making a strict therapeutic indication mandatory. With few exceptions (e.g. treatment of UTIs), aminoglycosides should only be used in combination with another appropriate antibiotic. Ideal partners are b-lactam antibiotics, because this combination has a marked synergistic effect against certain bacterial species. Streptomycin is one of the older aminoglycosides and is used only for the treatment of tuberculosis.

Newer aminoglycosides include netilmicin, gentamicin, tobramycin and amikacin. They have good activity against enterobacteria and Pseudomonas (especially tobramycin). Their activity against streptococci, anaerobes and H. influenzae is not satisfactory. Resistance data for tobramycin, gentamicin and netilmicin are almost identical, whereas the resistance situation is more favourable for amikacin against many enterobacteria.

4.5.13 ***Glycopeptides***

The glycopeptides vancomycin and teicoplanin are active against Gram-positive pathogens, i.e. staphylococci (including oxacillin-resistant strains), streptococci, enterococci, Clostridium difficile, diphtheria bacteria and Gram-positive aerobes. They are inactive against Gram-negative pathogens. Their use is indicated:

- In infections caused by the above-mentioned pathogens in case of allergy against all other suitable antibiotics.
- In infections caused by ampicillin-resistant enterococci or oxacillin-resistant staphylococci, or multiresistant corynebacteria.
- As an alternative, in oral form, to metronidazole for the treatment of pseudomembranous colitis. Due to the risk of selection of glycopeptide-resistant enterococci and staphylococci, the use of glycopeptides should be highly restricted. Similar to the aminoglycosides, glycopeptides have a

narrow therapeutic window.

4.5.14 ***Oxazolidinones***

The only substance of this group is linezolid, which can be administered parenterally and orally. It has good activity against Gram-positive cocci, such as staphylococci, including methicillin (oxacillin)-resistant strains, enterococci, including vancomycin-resistant strains, and streptococci.

4.6 CPSI

See reference [5]

NIH-Chronic Prostatitis Symptom Index (NIH-CPSI)

Pain or Discomfort

1. In the last week, have you experienced any pain or discomfort in the following areas?

	Yes	No
a. Area between rectum and testicles (perineum)	❑ 1	❑ 0
b. Testicles	❑ 1	❑ 0
c. Tip of penis	❑ 1	❑ 0
d. Below your waist, in your pubic or bladder area	❑ 1	❑ 0

2. In the last week, have you experienced:

	Yes	No
a. Pain or burning during urination	❑ 1	❑ 0
b. Pain or discomfort during or after sexual climax (ejaculation)?	❑ 1	❑ 0

3. How often have you had pain or discomfort in any of these areas over the last week?

❑ 0 Never
❑ 1 Rarely
❑ 2 Sometimes
❑ 3 Often
❑ 4 Usually
❑ 5 Always

4. Which number best describes your AVERAGE pain or discomfort on the days that you had it, over the last week?

❑ 0 ❑ 1 ❑ 2 ❑ 3 ❑ 4 ❑ 5 ❑ 6 ❑ 7 ❑ 8 ❑ 9 ❑ 10

NO PAIN **PAIN AS BAD AS YOU CAN IMAGINE**

Urination

5. How often have you had a sensation of not emptying your bladder completely after you finished urinating over the last week?

❑ 0 Not at all
❑ 1 Less than 1 time in 5
❑ 2 Less than half the time
❑ 3 About half the time
❑ 4 More than half the time
❑ 5 Almost always

6. How often have you had to urinate again less than two hours after you finished urinating, over the last week?

❑ 0 Not at all
❑ 1 Less than 1 time in 5
❑ 2 Less than half the time
❑ 3 About half the time
❑ 4 More than half the time
❑ 5 Almost always

Impact of Symptoms

7. How much have your symptoms kept you from doing the kinds of things you would usually do over the last week?

❑ 0 None
❑ 1 Only a little
❑ 2 Some
❑ 3 A lot

8. How much did you think about your symptoms, over the last week?

❑ 0 None
❑ 1 Only a little
❑ 2 Some
❑ 3 A lot

Quality of life

9. If you were to spend the rest of your life with your symptoms, just the way they have been during the last week, how would you feel about that?

❑ 0 Delighted
❑ 1 Pleased
❑ 2 Mostly satisfied
❑ 3 Mixed (about equally satisfied and dissatisfied)
❑ 4 Mostly dissatisfied
❑ 5 Unhappy
❑ 6 Terrible

Scoring the NIH-CPSI Prostatitis Symptom Index

Domain

Pain:

Total of items 1a,1b,1c,1d,2a,2b,3 and 4 = ___

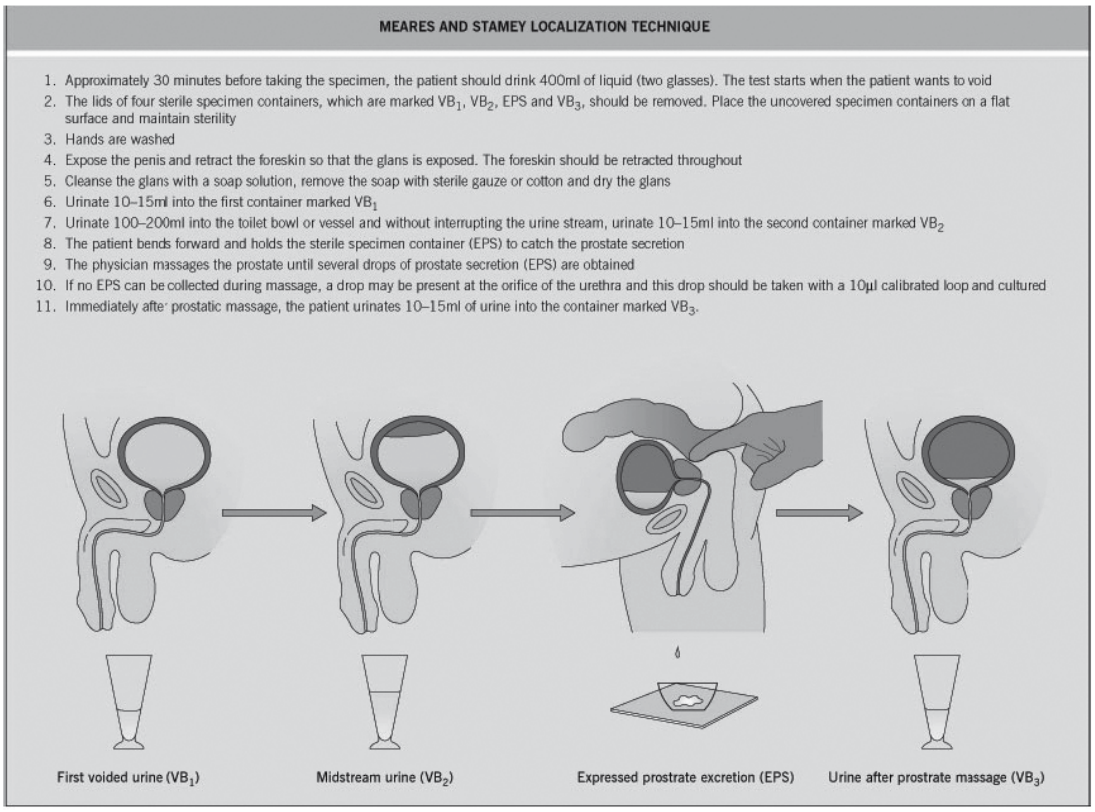
Urinary Symptoms:

Total of items 5 and 6 = ____

Quality of Life Impact:

Total of items 7,8, and 9 = ____

4.7 Meares & Stamey localisation technique*



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