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PART 1 | IMAGING IN CLINICAL PRACTICE

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These are the imaging pictures of a man who is 65 years, working as a constructor for years.
He was presenting with progressive shortness of breath with left sided chest pain. There was a mild non-productive cough, and significant weight loss.
He was a heavy smoker, quitted 6 months ago, and has hypertension well controlled with 20 mg lisinopril per a day.

Q1: What are the chest x ray and CT chest findings?
Q2: What are the differential Diagnosis?
Q3: What is the best diagnostic test to prove the diagnosis?

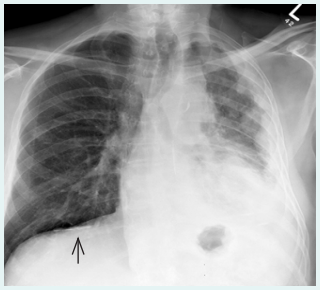

Figure 1: Chest X ray

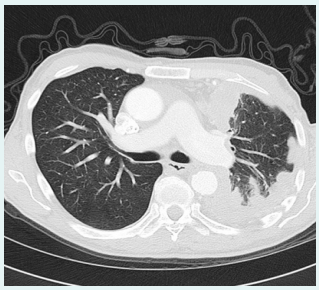

Figure 2: CT Scan of the chest Mediastinal window

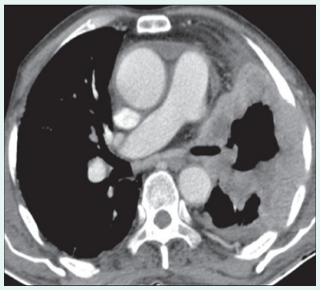

Figure 3: CT Scan of the chest Lung Window

ANSWER OF Q1:

Findings on chest X-Ray (Figure 1): There is a lobulated pleural based mass along the lateral chest wall on the left side with another large pleural based mediastinal mass. Volume loss is apparent on the same side; evident by mediastinal and tracheal shift to the ipsilateral side. The mass is extending into the main fissures. There are calcified plaques seen on the basal pleura covering the diaphragms, more visible on the right side (**black arrow**). The mass can be easily differentiated form an intrapulmonary tumours by forming an obtuse angle with the pleural surface while in case of intra-pulmomnary mass it should form an acute angle with the pleural surface.

Findings on CT scan : The mass is encasing the whole lung and extending into the fissures with a mediastinal mass evident on a ***mediastinal window*** (Figure 2), the mass is also showing a hypodense central areas due to necrosis; however, no invasion of the chest wall is seen, which if present favours a metastatic disease process instead. ***Lung window*** (Figure 3) shows how the tumour is encasing the lung and resulting in volume loss.

ANSWER OF Q3:

Thoracoscopic biopsy is diagnostic in 98 % of cases.
Thoracocentesis alone is diagnostic in 26 % of cases, while thoracocentesis with closed pleural biopsy is diagnostic in 39 % of cases.
As the above case has no pleural effusion so the best diagnostic test is thoracoscopic biopsy.

ANSWER OF Q2:

Secondary malignant lesions:
1. Metastasis: The most common primary tumours that causes pleural nodules are adenocarcinoma of lung (40%), Breast (20%), intestinal tumour (including pancreas) and gynaecological tumours (ovarian and uterus). Usually such lesions are associated with pleural effusion.
2. Thymoma: It is a rare cause, usually occur due to direct invasion.

Primary malignant tumour:
1. Mesothelioma: presented as irregular lobulated mass encasing the lung and associated with volume loss.
2. Lymphoma: is a rare, may present as thickening and / or pleura nodules. It is associated with pleural effusion and involvement of lymph nodes.
3. Sarcoma: It is a very rare cause presents as discrete masses or thickening .

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Screening Test

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A screening test is a test used to identify apparently healthy people who may be at an increased risk to develop a disease or condition (figure 1).[1] The goal of screening tests is for detection of disease as early as possible and before being clinically apparent in order to decrease morbidity and mortality.

Screening tests are not considered diagnostic but are used to identify a subset of the population who should have additional testing to determine the presence or absence of a disease.[2]

Types of screening:[3] There are different types of screening; each with specific aims:

1. Mass screening aims at screening the whole population (or subset) e.g. screening of women for carcinoma of the breast.
2. Multiple or multiphasic screening uses several screening tests at the same time to screen for many diseases[4] e.g. screening campaigns for detection of hypertension, diabetes mellitus, and hypercholesterolaemia in a community.
3. Targeted screening of groups with specific exposures, e.g. workers in lead battery factories are often used in environmental and occupational health.
4. Case-finding or opportunistic screening is aimed at patients who consult a health practitioner for some other purpose.

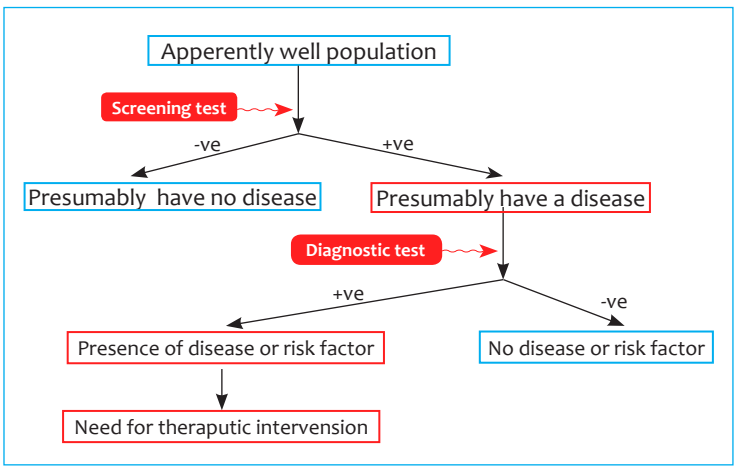

Figure 1: Schematic presentation of the use of screening tests

Criteria for ideal screening process: The Wilson's criteria for screening emphasise the important features of any screening programme, as follows:

1) The condition should be an important health problem. 2) Natural history of a disease should be understood. 3) A disease should have a recognisable latent or early symptomatic stage. 4) The test used should be easy to perform and interpret, acceptable, accurate, reliable, sensitive and specific. 5) There should be an accepted treatment recognised for the disease. 6) Treatment should be more effective if started early. 7) There should be a policy on who should be treated. 8) Diagnosis and treatment should be cost-effective. 9) Case-finding should be a continuous process.[5]

Criteria for evaluating a screening test:

Validity (accuracy): Ability of a test to detect who does and does not have the disease. This is made through measurements of *Sensitivity* and *Specificity*.

Yield: Amount of disease detected in the population, relative to the effort. It depends on the prevalence of disease and the positive and negative predictive values.

Reliability (precision): ability of a test to give consistent results when applied on the same person under the same conditions.

Validity of Screening Test (Accuracy):

Validity of a test is measured by sensitivity and specificity.

Sensitivity: The sensitivity of a clinical test refers to the ability of the test to correctly identify those patients with the disease. A test with 100% sensitivity correctly identifies all patients with the disease.

Table 1: 2x2 table for calculation of sensitivity and specificity

	Diseased	Disease Free	Total
Screen Positive	True positive (a)	False positive (b)	(a+b)
Screen Negative	False negative (c)	True negative (d)	(c+d)
Total	(a+c)	(b+d)	N

- Sensitivity = true positive/ true positive+ false negative = a/(a + c)
- Specificity = true negative/ false positive + true negative = d/(b + d)[6]
- Positive predictive value = true positive/ true positive+ false positive = a/(a + b)
- Negative predictive value = true negative/ false negative + true negative = d/(c + d)
- Prevalence of Disease = True disease (a+c)/ Total (N) × 100[7]

" Sensitivity means the ability of a test to identify correctly person who has the disease".

" Specificity means the ability of a test to exclude the presence of disease in a person".

Specificity: The specificity of a clinical test refers to the ability of the test to correctly identify those patients without the disease. Therefore, a test with 100% specificity correctly identifies all patients without the disease.

In order to calculate sensitivity and specificity of a test we need to conduct a cross sectional study. Then the data should be tabulated in 2x2 table as in table 1.

A cut-off point is a point in the range of results of a test that defines a normal from abnormal or diseased from non-diseased status.

It is a point separating false positive from false negative, hence determines sensitivity and specificity. The cut-off point is dynamic and can be set by the operator depending on his aim (see figure 2). If we move the point to the right we will increase specificity on expense of sensitivity i.e. decreasing false positive. Moving of the point to the left will increase the sensitivity on expense of specificity i.e. decreasing false negative.

Test with high false positive (high sensitivity) can detect wrongly more persons as having a disease while actually they are not. This per se will keep such patients in a state of axiety, and subjects them to unnecessary cost and burden of diagnostic intervention. Having high false negative will put people in danger of missing a disease and this would be of paramount loss if the disease is serious.

So moving cut-off point to this side or to the other is not without some adverse effects and in order to minimise them one should depend on the aim of the screening process.

There are many methods used to calculate a cut–off point of a tests: the classical method and the receiver operating characteristics (ROC).

The classical method is the easiest in which we apply the test on two groups of people. The first includes persons who have a disease, while the second one includes persons without a disease. Then for each group we calculate the mean±2SD and plot the results of the two groups graphically as in figure 2 . Area of intersection between the two curves is called cut-off period, and point on intersection between the curves would be the cut-off point. Intersected area on the left of the point is called false negative, while that on the right is the false positive.[8]

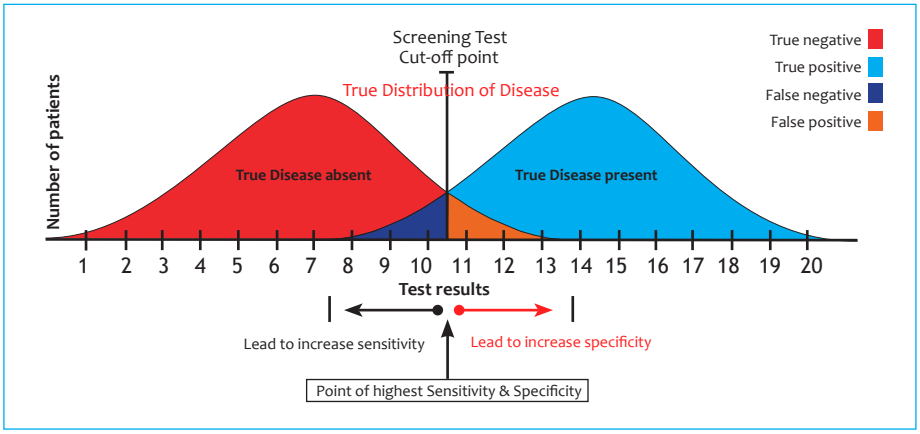

Figure 2: setting of Cut-off point by mean ±2SD showing how to change sensitivity and specificity[9]

Yield :

The yield of a screening service is measured by the number of cases identified whose prognosis is improved as a result of their early detection. Theoretically, the yields of screening may be improved by restricting it to high risk groups, as has been suggested in the screening of infants for developmental and other abnormalities. If uptake of a screening procedure is low then yield will be correspondingly limited. Ultimately the yields of a screening service have to be balanced against the costs, in terms of staff and facilities, of screening and making the confirmatory diagnoses. For breast cancer screening, it has been found that identifying one case requires examining 170 women by palpation and mammography and taking nine biopsy specimens.[10]

" Positive predictive value means the probability that a person with a positive result is truly has the disease".

" Negative predictive value means the probability that a person with a negative result is truly has no disease".

When evaluating the feasibility or the success of a screening program (yield), one should also consider the positive and negative predictive values. These are also computed from the same 2 x 2 contingency table, but the perspective is entirely different.

- ***Positive predictive value*** is the probability that subjects with a positive screening test truly have the disease.
- ***Negative predictive value*** is the probability that subjects with a negative screening test truly don't have the disease. (Table 1)

Positive predictive value of a test is very dependent on the prevalence of the disease in the population being tested. The higher the prevalence of a disease is in the population being screened, the higher is the positive predictive values (and the yield). Consequently, the primary means of increasing the yield of a screening program is to target the test to groups of people who are at higher risk of developing the disease.[11]

Limitations of screening

- Screening cannot offer a guarantee of protection.
- Presence of unavoidable false positive and false negative has bad impact on the community.[1]
- Detection of insignificant disease (information bias).
- Lead time (information bias): the systematic error of apparent increased survival from detecting disease in an early stage.
- Length (information bias): the systematic error from detecting disease with a long latency or pre-clinical period
- Referral/Volunteer bias (selection bias): the systematic error from detecting disease in persons who have a propensity to seek health care.[12]

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Single choice questions about this article are on the next page

Questions about Screening test

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Choose the most appropriate answer:

1. Screening test means :
- **(a)** Test used for the diagnosis of a disease.
- **(b)** Used to identify people how are in need for a medical intervention.
- **(c)** Applied on apparently normal people to detect a disease before being clinically apparent.
- **(d)** None of the above statement.

2. A new test for autism has been discovered. What term describes the proportion of patients with clinically confirmed autism who will be identified by the test?
- **(a)** Sensitivity
- **(b)** Specificity
- **(c)** Positive predictive value
- **(d)** Accuracy
- **(e)** Negative predictive value

3. If a diagnostic test for myocardial infarction is introduced. Which parameter will indicate the proportion of patients without an MI in whom the test will be negative?
- **(a)** Accuracy.
- **(b)** Negative predictive value.
- **(c)** Positive predictive value.
- **(d)** Sensitivity.
- **(e)** Specificity.

4. The best study design to measure sensitivity and specificity of a screening test is:
- **(a)** Cross section study.
- **(b)** Cohort study.
- **(c)** Retrospective study.
- **(d)** All of the above.

5. All the followings are criteria of an ideal test except:
- **(a)** Being accurate.
- **(b)** Sensitive but not necessarily specific.
- **(c)** Sensitive and specific.
- **(d)** Easy to perform and interpret.

6. When a test gives consistent results if applied on a same person under same circumstances it is called:
- **(a)** Specific.
- **(b)** Valid.
- **(c)** Precise.
- **(d)** Accurate.

7. Screening of smokers for bronchogenic carcinoma is an example of:
- **(a)** Mass screening.
- **(b)** Targeted or selective screening.
- **(c)** Multiphase screening .
- **(d)** None of the above.

8. If a test (x) can detect 85 persons to have the disease (y) out of 95 person how truly has disease (y). And the same test detects 84 normal persons to have negative result (no disease) out of 96 normal persons, the specificity of this test would be:
- **(a)** 89.4 %
- **(b)** 82.5 %
- **(c)** 83 %
- **(d)** 89.8 %

9. D dimer test is used in detection of pulmonary embolism, it is said to have high negative predictive value. Clinically this means:
- **(a)** If D dimer is negative then pulmonary embolism is very unlikely.
- **(b)** If D dimer is positive then pulmonary embolism is very possible diagnosis.
- **(c)** It has a high sensitivity.
- **(d)** None of the above.

10. When you want to detect a dangerous disease in a community which has an effective treatment going to change the morbidity and mortality, you need a test with:
- **(a)** High sensitivity.
- **(b)** High specificity.
- **(c)** High precision .
- **(d)** High negative predictive value.

11. All the statement are true about the yield of a test except:
- **(a)** It depends not only about the identification of a disease but also to ability to improve the disease outcome by treatment.
- **(b)** It can be measured by sensitivity and specificity.
- **(c)** Positive and negative predictive value should be considered.
- **(d)** Targeting high risk group is one mean of increasing the yield of a screening test.

12. Positive predictive value means:
- **(a)** The probability of truly having a disease in a person who has a positive result.
- **(b)** The ability of the test to detect person who truly has the disease.
- **(c)** The ability of a test to detect person who truly do not have a disease.
- **(d)** It is a good parameter to evaluate the validity of a screening test.

PART 3 | WHAT DO YOU KNOW ABOUT?

Asymptomatic Bacteriuria in Pregnancy

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Asymptomatic bacteriuria is not uncommon problem in general population; however, it has considerable importance during pregnancy. The following questions are based on some international guidelines and recommendations in a quest from the editorial board to promote your knowledge. Please try to answer the following questions, then you can see the results on page 110-111.

1. The usual quantitative definition of asymptomatic bacteriuria, or asymptomatic urinary infection is:

(a) (10^5 cfu/mL) in one urine specimen.
(b) (10^5 cfu/mL) in 2 consecutive urine specimens.
(c) (10^5 cfu/mL) in 3 consecutive urine specimens.
(d) None of the above.

2. All of the following about appropriate collection of urine specimen are true except:

(a) Washing hands and vagina before collection.
(b) Antibiotic should be withhold at least 3 days prior to the test.
(c) The collection begins after the urine has flowed for several seconds.
(d) Antiseptic should be use for cleaning of hands and urethral orifice.

3. Prevalence of asymptomatic bacteriuria in pregnant women in comparison to its prevalence in non pregnant women is:

(a) As the same.
(b) Higher.
(c) Lower.
(d) Controversial.

4. The gold standard test to screen asymptomatic bacteriuria in pregnancy is:

(a) General urine examination.
(b) General urine examination and urine culture.
(c) Urine culture at least once.
(d) Dipstick analysis and direct microscopy.

5. Asymptomatic bacteriuria during pregnancy increases the risk of pyelonephritis by:

(a) 20-30 folds.
(b) 30-40 folds.
(c) 10–20 folds.
(d) Less than 10 folds.

6. The most common pathogen associated with asymptomatic bacteriuria is:

(a) *E. coli.*
(b) *Neisseria gonorrhoea.*
(c) *Pseudomonas Aeruginosa.*
(d) *Group B streptococci.*

7. Most of the guidelines recommend screening of asymptomatic bacteriuria in pregnancy at:

(a) Late pregnancy.
(b) At any time during pregnancy.
(c) Early pregnancy.
(d) Not recommending a specific time for screening.

8. All of the following decisions about treatment of asymptomatic bacteriuria in pregnancy are true except:

(a) Pregnant women should be treated if the results are positive.
(b) The duration of antimicrobial therapy should be 3–7 days.
(c) Periodic screening for recurrent bacteriuria should be undertaken after therapy.
(d) Asymptomatic bacteriuria is a self limiting disease and needs no treatment.

9. Contributing risk factors associated with asymptomatic bacteriuria in pregnancy are:

(a) Low socioeconomic status.
(b) History of recurrent urinary tract infections.
(c) Diabetes and anatomical abnormalities of the urinary tract.
(d) All of the above.

10. Relation of pyuria to asymptomatic bacteriuria in pregnancy:

(a) In pregnancy, pyuria is a synonym to asymptomatic bacteriuria.
(b) Asymptomatic bacteriuria in pregnancy has never accompanied with pyuria.
(c) One fourth of pregnant women who have asymptomatic bacteriuria showed pyuria in their urine.
(d) Pyuria can be found in one- two third of pregnant women who have asymptomatic bacteriuria.

11. All of the following statements are true regarding drug treatment of asymptomatic bacteriuria in pregnancy except:

(a) Ampicillin or amoxicillin are good optimal choice for *E coli.*
(b) Tetracyclines, chloramphenicol, trimethoprim in the first trimester and sulfonamides in the third trimester should be avoided.
(c) Nitrofurantoin is safe and effective
(d) Macrolides are not first-line agents for UTI in pregnancy.

12. Asymptomatic bacteriuria in pregnant women is associated with the following complication:

(a) Preterm delivery and low birth weight.
(b) Antepartum haemorrhage.
(c) Gestational diabetes.
(d) None of the above.

13. Concerning asymptomatic bacteriuria for all other non-pregnant adult populations; all of the following statements are true except:

(a) Asymptomatic bacteriuria has not been shown to be harmful.
(b) Treatment of asymptomatic bacteriuria decreases the frequency of symptomatic infection or improves other outcomes.
(c) Screening for or treatment of asymptomatic bacteriuria is not appropriate and should be discouraged.
(d) Asymptomatic bacteriuria is common.

SCREENING TESTS

Answers of Questions on page 107

1. ***Correct answer is (c)***: screening test is used to detect a disease or a risk factor in apparently normal person before being clinically apparent; however, patient who identified by screening test should be subjected to more diagnostic tests or procedures.
2. ***Correct answer is (a)***: sensitivity is the proportion of patients with the disease who are labelled positive by the test.
3. ***Correct answer is (e)***: Specificity is the proportion of persons without the disease and tested negative by the test.
4. ***Correct answer is (a)***: cross sectional study is the most suitable design to measure sensitivity and specificity. Cohort and retrospective studies do not identify the disease in continuous interval; a condition which is very important in screening process.
5. ***Correct answer is (b)***: sensitivity and specificity are required in a test to be ideal, others are required criteria.
6. ***Correct answer is (c)***: this is the definition of precision (reliability)
7. ***Correct answer is (b)***: this is a good example of targeted screening.
8. ***Correct answer is (c)***: specificity means = true negative/ (true negative + false positive). i.e. 88/ (18+88) = 83 %.
9. ***Correct answer is (a)***: in clinical practice the benefit of having a test with high negative predictive value is to exclude the presence of the disease if the test is possible, so in patient suspected to have pulmonary embolism if D dimer is negative then the patient is unlikely to have pulmonary embolism.
10. ***Correct answer is (a)***: a test with a high sensitivity will detect all possible cases, and this is the required aim if we screen for a disease which has a treatment potentially affect morbidity and mortality in a positive way.
11. ***Correct answer is (b)***: all statements are for yield, while sensitivity and specificity are parameters of validity.
12. ***Correct answer is (a)***: positive predictive value is the probability of a person who identified by a test to be positive to really have a disease. It answers the usual question made by a person with positive test, what is the probability that I have really the disease?

ASYMPTOMATIC BACTERIURIA IN PREGNANCY

What should you know for your daily practice?

Asymptomatic bacteriuria in pregnancy

- Increases risk of pyelonephritis.
- Diagnosed by Quantitative culture.
- Search for it & treat it effectively.
- Fosfomycin and nitrofurantoin are safe.
- Amoxicillin and ampicillin are not optimum for treatment.

Answers of Questions on page 108-109

1. ***Correct answer is (b)***. Asymptomatic bacteriuria, or asymptomatic urinary infection, is an isolation of (10^5 cfu/mL) in a two consecutive appropriately collected urine specimen obtained from a person without symptoms or signs referable to urinary infection.[1,2]

2. ***Correct answer is (d).*** An appropriate collection of urine specimen is vital for the accuracy of urine culture. To achieve this the followings are needed: Pregnant women should withhold antibiotics for at least 3 days prior to the test. They should be advised to avoid frequent urination before the test as much as possible. Washing hands and area around the urethral orifice by soap and water is recommended and antiseptic should not be used. A woman should separate labial folds apart during urination. Discard the first few drops of urine then collect a mid stream urine. Collect, in a sterile container, about 60 ml of this "midstream" urine without stopping the flow; The first urine of the day is preferred because bacterial levels would be higher.[3]

3. ***Correct answer is (a).*** The prevalence of asymptomatic bacteriuria in pregnancy is variable in different studies. It ranges from (2-7 %). Guidelines agreed that the prevalence of asymptomatic bacteriuria in the pregnant women is as the same as in non-pregnant women.[1, 2]

4. ***Correct answer is (c).*** Because the performance of rapid urine screening tests in pregnancy is poor, quantitative culture remains the gold standard for diagnosis. Dipstick analysis and direct microscopy have poor positive and negative predictive values for detecting bacteriuria in asymptomatic patients. The optimal frequency of subsequent testing is uncertain.[1,2]

5. ***Correct answer is (a).*** Pregnant women identified to have asymptomatic bacteriuria in early pregnancy have an increased risk of developing pyelonephritis by 20–30 folds comparing to pregnant women who haven't. Also many comparative clinical trials have consistently reported that antimicrobial treatment of asymptomatic bacteriuria during pregnancy decreases the risk of subsequent pyelonephritis.[1]

6. ***Correct answer is (a).*** *E. coli* is the most common pathogen associated with asymptomatic bacteriuria, representing at least 80% of isolates. Other organisms include other gram negative bacteria and group B streptococci. These bacteria colonize the vaginal introitus and periurethral area. *Uropathogenic* gram negative bacteria possess specific virulent factors that enhance both colonization and invasion of the urinary tract; for example, the P-fimbriae of certain strains of *E. coli*. [4]

7. ***Correct answer is (c).*** Most of the guidelines agreed that pregnant women should be screened for asymptomatic bacteriuria during early pregnancy.[1,2, 5]

8. ***Correct answer is (d).*** Pregnant women should be treated if the results are positive. The duration of antimicrobial therapy should be 3–7 days. Periodic screening for recurrent bacteriuria should be undertaken after therapy.[1]

9. ***Correct answer is (d).*** The prevalence of asymptomatic bacteriuria is most closely related to socioeconomic status and is similar in both pregnant and non-pregnant women. Other contributing factors include a history of recurrent urinary tract infections, diabetes and anatomical abnormalities of the urinary tract.[1,2]

10. ***Correct answer is (d).*** Pyuria is evidence of inflammation in the genitourinary tract and is common in subjects with asymptomatic bacteriuria. It is present in 30–70% of pregnant women who has asymptomatic bacteriuria.[1]

11. ***Correct answer is (a).*** The resistance of *E. coli* to ampicillin and amoxicillin is 20-40%; accordingly, these agents are no longer considered optimal for treatment of UTIs caused by this organism. Fosfomycin, a phosphonic acid derivative, is useful in the treatment of uncomplicated UTIs caused by susceptible strains of *E. coli* and *Enterococcus species*. Fosfomycin is a category B agent in pregnancy (ie, fetal risk is not confirmed by human studies but has been shown in some animal studies). Some antibiotics should not be used during pregnancy, because of their effects on the fetus. These include tetracyclines, chloramphenicol, trimethoprim in the first trimester and sulfonamides in the third trimester. Nitrofurantoin is safe and effective. Macrolides are not first-line agents for UTI in pregnancy.[6]

12. ***Correct answer is (a).*** Women with asymptomatic bacteriuria are more likely to experience premature delivery and to have infants of low birth weight. Meta-analyses of cohort studies and randomised clinical trials also support the conclusion that antimicrobial treatment of asymptomatic bacteriuria decreases the frequency of low–birth weight infants and preterm delivery.[1,2]

13. ***Correct answer is (b).*** For all other adult populations, asymptomatic bacteriuria has not been shown to be harmful. Although persons with bacteriuria are at an increased risk of symptomatic urinary infection, treatment of asymptomatic bacteriuria does not decrease the frequency of symptomatic infection or improve other outcomes. Thus, in populations other than those for whom treatment has been documented to be beneficial, screening for or treatment of asymptomatic bacteriuria is not appropriate and should be discouraged.[1]

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