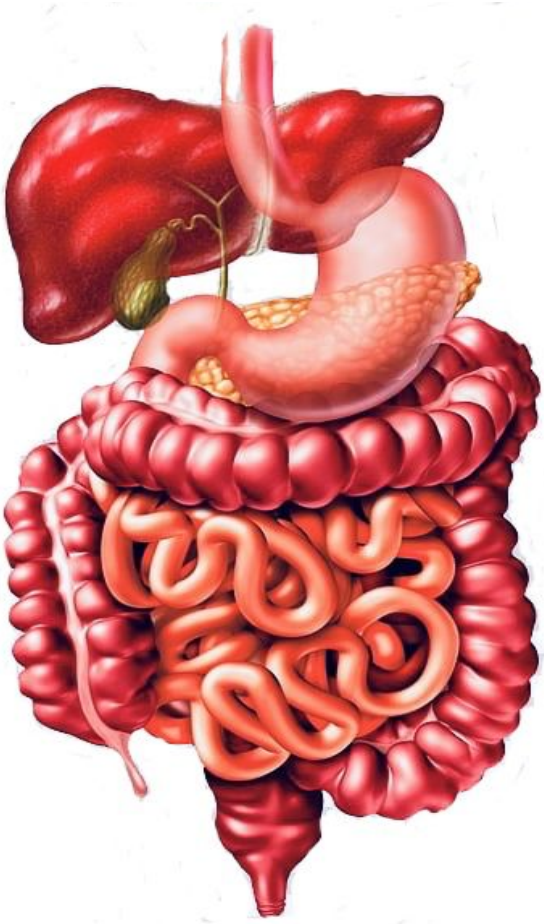
Last one!
Good luck!

MED437
KING SAUD UNIVERSITY

PATHOLOGY
TEAM 437

هذه المحاضرة هي تكريم لكل من يعمل ولا يكرّم،لكل من يعمل بالخفاء،لكل ايادي تدفعنا من ظهورنا لا نرى وجوه اصحابها



Pathology and Pathogenesis of Cholecystitis

Objectives:

- **Recognize the predisposing factors of gallstones and cholecystitis**
- **Describe the different types of cholecystitis**
- **Understand the pathogenesis of acute and chronic cholecystitis**

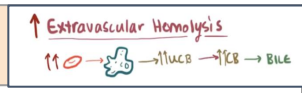
Disorders of the Gallbladder CHOLELITHIASIS (GALLSTONES) & it different types

Disorders of the Gallbladder CHOLELITHIASIS (GALLSTONES)

Character	Majority of gallstones (>80%) are "silent," and most individuals remain free of biliary pain or stone complications for decades.	
types 	1. **Cholesterol Stones** Most common	- about 80% are cholesterol stones - containing more than 50% of crystalline **cholesterol monohydrate**
	2. **Pigment Stones**	- composed predominantly of **bilirubin calcium salts (unconjugated bilirubin)** since they're made of calcium they'll be radio-opaque "can be seen in X-ray"
Age and gender	- The prevalence of gallstones increases throughout life. - The prevalence in women of all ages is about twice as high as in men. Cholesterol stone is more common in females because it's associated with estrogen	
Ethnic and geographic	Cholesterol gallstone prevalence approaches 50% to 75% in certain Native American populations (Pima, Hopi, and Navajo), seems to be related to biliary cholesterol hypersecretion.	
Heredity	A positive family history imparts increased risk, associated with impaired bile synthesis and secretion.	
Environment	-Estrogens increase hepatic cholesterol uptake and synthesis, leading to **excess biliary secretion of cholesterol**. (oral contraceptive use and with pregnancy).estrogen -Obesity, rapid weight loss, and treatment with the hypocholesterolemic agent are strongly associated with **increased biliary cholesterol secretion.** Rapid weight loss :Stasis in circulation and abnormality in motility ,affect metabolism	
Acquired disorders	Any condition in which **gallbladder motility is reduced** predisposes to gallstones, such as pregnancy, rapid weight loss, and spinal cord injury.	

Prevalence and Risk Factors of gallstones

Cholesterol Stones most common	**Pigment Stones**
- **Demography:** Northern Europe, North and South America, Native Americans, Mexican Americans - **Advancing age** - **Female sex hormones:** Associated with estrogen • Female gender • Oral contraceptives • Pregnancy - **Obesity and insulin resistance** - **Rapid weight** causes dehydration so effect motility causing stasis. - **Gallbladder stasis** - **Dyslipidemia syndromes** - **Inborn disorders of bile acid metabolism**	- **Demography:** Asian more than Western, rural more than urban -**Chronic hemolysis** (e.g., sickle cell anemia, hereditary spherocytosis) - **Biliary infection** - **Gastrointestinal disorders:** ileal disease (e.g., Crohn disease), ileal resection or bypass, cystic fibrosis with pancreatic insufficiency Hemolytic disorders and biliary infection leads to excessive production of unconjugated bilirubin. Anything increase the presence of bilirubin can cause pigmented stones



Cholesterol Stones & Pigment Stones

Pigment stones

Pathogenesis

Pathogenesis of pigment stones is based on the presence *in the biliary tract* of unconjugated bilirubin (which is poorly soluble in water) and precipitation of calcium bilirubin salts. Thus, infection of the biliary tract, as with

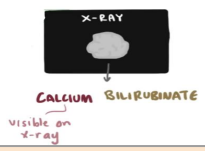
- Escherichia coli
- Ascaris lumbricoides
- by the **liver fluke** Opisthorchis sinensis

These infections secrete enzymes that affect conjugation

increases the likelihood of pigment stone formation. Chronic hemolytic conditions also promote formation of unconjugated bilirubin in the biliary tree.

Morphology

Pigment gallstones are **black and brown**. "**Black** pigment stones are found in **sterile** gallbladder. "**Brown**" pigment stones are found in **infected** intrahepatic or extrahepatic bile ducts. Both are soft and usually multiple. Brown stone are greasy. Because of calcium carbonates and phosphates, approximately 50% to 75% of black stones are radio-opaque.



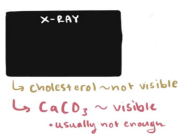
Cholesterol stones

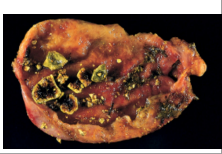
Pathogenesis

•Cholesterol is rendered soluble in bile by aggregation with water-soluble **bile salts** and water-insoluble **lecithins**, both of which act as **detergents**.
• When cholesterol concentrations exceed the solubilizing capacity of bile (supersaturation), cholesterol can no longer remain dispersed and nucleated into solid cholesterol monohydrate crystals.
•Cholesterol gallstone formation involves **three** simultaneous defects:
1.**Supersaturation of bile with cholesterol:** the result of hepatocellular hypersecretion of cholesterol.
2.**Gallbladder hypomotility.** It promotes nucleation typically around a calcium salt crystal nidus.
3.**Mucus hypersecretion in the gallbladder**: This traps the crystals, permitting their aggregation into stones.

Morphology

Cholesterol stones arise exclusively in the gallbladder and are composed of cholesterol ranging from 100% pure (which is rare) down to around 50%. pale yellow, round to ovoid to faceted, and have a finely granular, hard external surface. Stones composed largely of cholesterol are radiolucent only 10% to 20% are radio-opaque.

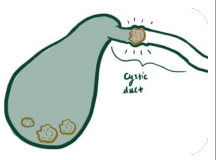




Cholesterolosis: An incidental finding, is **cholesterolosis**. Cholesterol hypersecretion by the liver promotes excessive accumulation of cholesterol esters within the lamina propria of the gallbladder. The mucosal surface is studded with minute yellow flecks, producing the "strawberry gallbladder" Not clinically important But just to mention it ممكن تشوفها احيانا

Clinical Features of Gallstones

70% to 80% of patients remain asymptomatic.
Symptoms: spasmodic or "colicky" يعني زي المغص right upper quadrant pain epigastric , which tends to be excruciating. It is usually due to obstruction of bile ducts by passing stones.
Nausea and vomiting ممكن تشوف



Complications

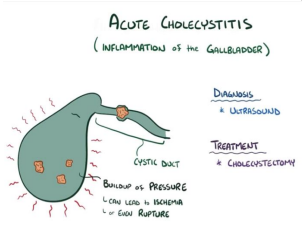
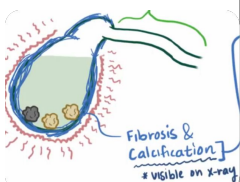
•include empyema, perforation, fistulae, inflammation of the biliary tree (cholangitis), pancreatitis, obstructive cholestasis and gallbladder carcinoma
•Obstructive cholestasis
— -The larger the calculi, the less likely they are to enter the cystic or common ducts to produce obstruction; it is the very small stones, or"gravel," that are the more dangerous. —
-Occasionally, a large stone may erode directly into an adjacent loop of small bowel, generating intestinal obstruction ("gallstone ileus").
•Gallbladder carcinoma:
— -The most important risk factor associated with gallbladder carcinoma is gallstones (cholelithiasis), which are present in 95% of cases

احفظ الأهم فالأقل اهمية
Pancreatitis is the most important complication,after that ascending cholangitis
Other complications are rare and late

Understand the pathogenesis of acute and chronic cholecystitis

CHOLECYSTITIS

— **Inflammation of the gallbladder may be acute, chronic, or acute superimposed on chronic. It almost always occurs in association with gallstones.**

	Acute	Chronic most common
General Information	• **Acute <u>calculous</u> cholecystitis** The most common type is an acute inflammation of the gallbladder, precipitated 90% of the time by obstruction of the neck or cystic duct. There will **not** be jaundice because it didn't reach the common bile duct. It is the **primary complication of gallstones** and the most common reason for emergency cholecystectomy. • **Acute <u>acalculous</u> cholecystitis** occurs in the **absence of gallstones**, generally in severely ill patient. Most cases of occur in the following circumstances: 1-the postoperative state after major, non biliary surgery 2-severe trauma (motor vehicle accidents, war injuries) 3-severe burns 4-multisystem organ failure Heart, lung or kidney failure 5-sepsis = Proliferating of bacteria in the blood تسمم الدم 6-prolonged intravenous hyperalimentation When there's no absorption of nutrition in the small bowel, the nutrition will come through the intravenous line 7-the postpartum state. After birth	• **Chronic cholecystitis** may be a sequel to repeated bouts of mild to severe acute cholecystitis, but in many instances, it develops in the apparent absence of antecedent attacks. • It is associated with cholelithiasis in over 90% of cases. This is the most common cause of cholecystectomy.
Pathogenesis	Acute calculous cholecystitis results from chemical irritation and inflammation of the obstructed gallbladder. These events occur in the absence of bacterial infection; only later in the course may bacterial contamination develop. The gallbladder **obstructed** by the stones in the cystic duct and then secondary **chemical** irritation (bile is very irritant substance) so if it stays within the mucosa for long time it could injure the mucosa and lead to **inflammatory** reaction	—
Clinical Features	• Progressive right upper quadrant or epigastric pain, frequently associated with mild **fever**, anorexia, tachycardia, sweating, and nausea and vomiting. These are manifestation of acute inflammation. The upper abdomen is tender. Most patients are free of jaundice • When the cystic duct is obstructed in acute calculous cholecystitis, patient present with remarkable sudden **severe upper abdominal pain radiating to right shoulder.** referring pain. This constitute an acute surgical emergency. • It may present with mild symptoms that resolve without medical intervention. • Clinical symptoms of acute **acalculous cholecystitis tend to be more insidious** (خفيفة), since symptoms are obscured by the underlying conditions precipitating the attacks. A higher proportion of patients have no symptoms referable to the gallbladder. The incidence of **gangrene and perforation is much higher** than in calculous cholecystitis because there's no symptoms so it may progress into gangrene 	• The symptoms of calculous chronic cholecystitis are similar to those of the acute form and range from biliary colic to indolent right upper quadrant pain and epigastric distress. • Patients often have **intolerance to fatty food**, belching and postprandial epigastric distress, sometimes include nausea and vomiting. They have abdominal pain <u>after</u> the fatty food. IMPORTANT in MCQ 

Understand the pathogenesis of acute and chronic cholecystitis

Morphology

Acute

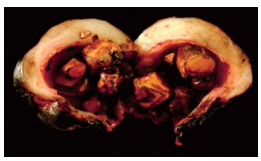
- In acute cholecystitis, the gallbladder is usually enlarged and tense, and bright red to green-black[1]. The serosal covering is frequently layered by fibrin and, in severe cases, by exudate. there will be acute inflammatory cells, mainly neutrophils.
- There are no morphologic differences between acute acalculous and calculous cholecystitis, except for the absence of macroscopic stones in the former. In the latter instance, an obstructing stone is usually present in the neck of the gallbladder or the cystic duct.
- The gallbladder lumen is filled with a cloudy or turbid bile that may contain fibrin and frank pus, as well as hemorrhage[2]. When the contained exudate is virtually pure pus, the condition is referred to as **empyema of the gallbladder**[3].like any acute inflammation
- In mild cases, the gallbladder wall is thickened, edematous, and hyperemic.
- In more severe cases, it is transformed into a green-black necrotic organ, termed **gangrenous cholecystitis**[4], with small-to-large perforations.

[1]: From the bile.
[2]: Secondary injury to the blood vessel wall itself especially small blood vessels lead to hemorrhage in the mucosa.
[3]: When the gallbladder is mainly PUS and in severe cases it occurs.
[4]: The blood supply to the gallbladder is **reduced** from the **edema**, the edema will press on the blood supply, so there will be **ischemia** and it will go **necrosis**.

Chronic

Morphology:

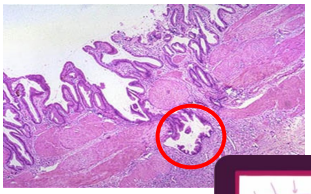
- The **morphologic** changes in chronic cholecystitis are extremely variable and sometimes minimal. Gall bladder may be contracted (fibrosis), normal in size or enlarged (from obstruction). The wall is variably thickened. Stones are frequent.

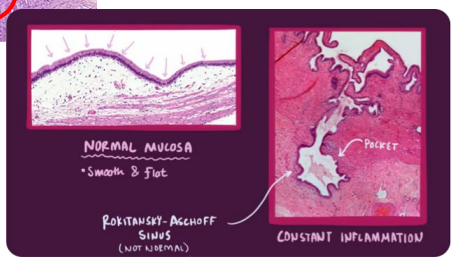


There will be chronic inflammatory cells, lymphocytes and histiocytes.

Histology:

- The degree of inflammation is variable. **Outpouchings of the mucosal epithelium through the wall** (**Rokitansky-Aschoff sinuses**) may be quite prominent. Epithelium going down into muscle layer.
- **Extensive dystrophic calcification** within the gallbladder wall may yield a **porcelain gallbladder** (entire it), occur rarely, notable for a markedly increased incidence of associated cancer.
- **Xanthogranulomatous** lipid granuloma **cholecystitis** is also a rare condition in which the gallbladder is shrunken, nodular, fibrosed and chronically inflamed with abundant lipid filled macrophages.
- **Hydrops of the gallbladder** an atrophic, chronically obstructed gallbladder may contain only clear secretions mucus





Complications

- Bacterial superinfection with cholangitis (bile duct and biliary tree) or sepsis septic shock ,septicemia
- GB perforation & local abscess formation
- GB rupture with diffuse peritonitis
- Biliary enteric (cholecystenteric) fistula with drainage of bile into adjacent organs, and potentially gallstone-induced intestinal obstruction (ileus) through fistula stones go to the small intestine leading to gallstones ileus with SI obstruction
- Aggravation of pre-existing medical illness, with cardiac, pulmonary, renal, or liver decompensation because of the inflammation more cytokines will be produced, more substances will be circulating in the blood to induce more damage to the organ which is affected like the heart, kidney, liver and lungs.

Pathoma

Pathology and pathogenesis of cholecystitis

GALLBLADDER AND BILIARY TRACT

II. CHOLELITHIASIS (GALLSTONES)

A. Solid, round stones in the gallbladder

B. Due to precipitation of cholesterol (cholesterol stones) or bilirubin (bilirubin stones) in bile 1. A rises with (1) supersaturation of cholesterol or bilirubin, (2) decreased phospholipids (e.g., lecithin) or bile acids (normally increase solubility), or (3) stasis

C. Cholesterol stones (yellow) are the most common type (90%), especially in the West

1. Usually radiolucent (10% are radiopaque due to associated calcium)

2. Risk factors include age (40s), estrogen (female gender, obesity, multiple pregnancies and oral contraceptives), clofibrate, Native American ethnicity, Crohn disease, and cirrhosis.

D. Bilirubin stones (pigmented) are composed of bilirubin

1. Usually radiopaque

2. Risk factors include extravascular hemolysis (increased bilirubin in bile) and biliary tract infection (e.g., E coli, Ascaris lumbricoides, and Clonorchis sinensis)

i. Ascaris lumbricoides is a common roundworm that infects 25% of the world's population, especially in areas with poor sanitation (fecal- oral transmission); infects the biliary tract , increasing the risk for gallstones

ii. Clonorchis sinensis is endemic in China, Korea, and Vietnam (Chinese liver fluke); infects the biliary tract, increasing the risk for gallstones, cholangitis, and cholangiocarcinoma

E. Gallstones are usually asymptomatic; complications include biliary colic, acute and chronic cholecystitis, ascending cholangitis, gallstone ileus, and gallbladder cancer.

IV. ACUTE CHOLECYSTITIS

A. Acute inflammation of the gallbladder wall

B. Impacted stone in the cystic duct results in dilatation with pressure ischemia, bacterial overgrowth (E coli), and inflammation.

C . Presents with right upper quadrant pain, often radiating to right scapula, fever with increase WBC count, nausea, vomiting, and t serum alkaline phosphatase (from duct damage)

V. CHRONIC CHOLECYSTITIS

A. Chronic inflammation of the gallbladder

B. Due to chemical irritation from long standing cholelithiasis, with or without superimposed bouts of acute cholecystitis

C. Characterized by herniation of gallbladder mucosa into the muscular wall (Rokitansky-Aschoff sinus)

D. Presents with vague right upper quadrant pain, especially after eating

E. Porcelain gallbladder is a late complication.

I. Shrunken, hard gallbladder due to chronic inflammation, fibrosis, and dystrophic calcification

2. Increased risk for carcinoma

F. Treatment is cholecystectomy, especially if porcelain gallbladder is present.

First aid

Gallstones (cholelithiasis)

↑ cholesterol and/or bilirubin, ↓ bile salts, and gallbladder stasis all cause stones.

2 types of stones:

- Cholesterol stones (radiolucent with 10–20% opaque due to calcifications)—80% of stones. Associated with obesity, Crohn disease, advanced age, estrogen therapy, multiparity, rapid weight loss, Native American origin.
- Pigment stones A (black = radiopaque, Ca^{2+} bilirubinate, hemolysis; brown = radiolucent, infection). Associated with Crohn disease, chronic hemolysis, alcoholic cirrhosis, advanced age, biliary infections, total parenteral nutrition (TPN).

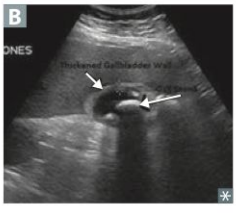
Risk factors (4 F's):

1. Female
2. Fat
3. Fertile (multiparity)
4. Forty

Most common complication is cholecystitis; can also cause acute pancreatitis, ascending cholangitis.

Diagnose with ultrasound. Treat with elective cholecystectomy if symptomatic.

Cholecystitis



Acute or chronic inflammation of gallbladder.

Calculous cholecystitis—most common type; due to gallstone impaction in the cystic duct resulting in inflammation and gallbladder wall thickening (arrows in B); can produce 2° infection.

Acalculous cholecystitis—due to gallbladder stasis, hypoperfusion, or infection (CMV); seen in critically ill patients.

Murphy sign: inspiratory arrest on RUQ palpation due to pain. Pain may radiate to right shoulder (due to irritation of phrenic nerve). ↑ ALP if bile duct becomes involved (eg, ascending cholangitis).

Diagnose with ultrasound or cholescintigraphy (HIDA scan). Failure to visualize gallbladder on HIDA scan suggests obstruction.

Gallstone ileus—fistula between gallbladder and GI tract → stone enters GI lumen → obstructs at ileocecal valve (narrowest point); can see air in biliary tree (pneumobilia).

Questions

Q1. A strawberry gallbladder appearance is a feature of?
A- Chronic Cholecystitis
B-Cholesterolosis
C-Acute calculous cholecystitis
D-Acute acalculous cholecystitis

Q2.Cholesterol gallstone formation involves which of the following?
A-Mucus hypersecretion in the gallbladder.
B-Unsaturation of bile with cholesterol.
C-Gallbladder hypermotility.
D. Mucus hyposecretion in the gallbladder.

Q3.Which of the following is NOT a complication of cholecystitis?
A-GB perforation & local abscess formation.
B-GB rupture with diffuse peritonitis
C-Alzheimer
D-Bacterial superinfection with cholangitis or sepsis.

Q4.Presence of unconjugated bilirubin in the biliary tract indicates which of the following?
A-Pigment stones
B-Cholesterol stones
C-Chronic Cholecystitis
D-Cholesterolosis

Q5. A patient presented to the ER with progressive upper right abdominal pain, tachycardia, sweating and nausea. His temperature was 37.8 ° C, upon abdominal examination his upper abdomen is tender. After several investigations, it was discovered that he has multiple gallstones. What is most likely the diagnosis?
A-Acute calculous cholecystitis
B-Acute acalculous cholecystitis
C-Chronic Cholecystitis
D-Cholesterolosis

Q6.A 47-year-old woman presents with a 3-month history of vague upper abdominal pain after fatty meals, some abdominal distension, and frequent indigestion. Physical examination shows an obese women (BMI = 30 kg/m2) with right upper quadrant tenderness. An ultrasound examination discloses multiple echogenic objects in the gallbladder. Which of the following metabolic changes is most likely associated with the formation of gallstones in this patient?
A-Decreased serum albumin
B-Increased hepatic calcium secretion
C-Increased hepatic cholesterol secretion
D-Increased bilirubin uptake by the liver

Answer: 1-B 2-A. 3-C. 4-A. 5-A. 6-C

يقول العرب هذا رابع المستحيلات إذا أرادوا أن يصفوا حدوث شيء بالاستحالة وهذه المستحيلات الثلاثة هي.

لَمَّا رَأَيْتُ بَنِي الزَّمَانِ وَمَا بِهِمْ خِلٌّ وَفِيٌّ، لِلشَّدَائِدِ أَصْطَفِي
أَيْقَنْتُ أَنَّ المُسْتَحِيلَ ثَلَاثَةٌ الغُولُ وَالعَنْقَاءُ وَالخِلُّ الوَفِي

الغول	العنقاء	الخل الوفي
		

اعزائي دارسيّ محاضرات فريق علم الأمراض نود ان نلفت انتباهكم ان علم أمراض الجهاز الهضمي ليس رابع المستحيلات لا تكن ايجابيًا الى حد الغفلة ولا تكن سلبيا الى حد تثبيط النفس،كن عقلانيا معتدلًا ،نحن نختلق المستحيلات لكننا نحن ايضًا من نصنع الفرص
(نستودعكم الله إلى (علم أمراض الغدد

لأعضاء الفريق لا يكفي شكركم على ما كل ما بذلتموه من وقت وجهد في العمل على كل صغيرة وكبيرة من اول لآخر محاضرة نِعم عمل الفريق ونِعم الأعضاء قد تظنون انه امر بسيط لكنكم ساعدتم الكثير ببذلكم ما تستطيعونه، عظيم عملكم وأجركم أعظم انتم الأفضل وتستحقون الأفضل.
في النهاية: لم نخلق عبثا، ووجودكم في هذا المجال دليل استطاعتكم، نتمنى التوفيق للجميع ابذلوا جهدكم فأنتم تستطيعون،

قادة فريق علم الأمراض

فايز غياث الدرسوني

شيرين العكيلي

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راكان محمد الغنيم
سلطان ناصر الناصر
عادل عبدالعزيز السحيباني
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تركي عيد الشمري
عبدالجبار اليماني
عبدالله المعيذر
منصور العبرة
خالد العقيلي
تركي آل بنهار
عبدالعزيز الضرغام
سعد الفوزان
عادل ابراهيم
عبدالاله الدوسري
عبدالله السرجاني
محمد المحيميد
عبدالرحمن آل الشيخ
عبدالرحمن الداوود

مها العَمري
مجد البراك
بتول الرحيمي
منيرة المسعد
مشاعل القحطاني
رناد الفرم
غادة الحيدري
دانة القاضي
مها بركه

رزان الزهراني
لين الحكيم
عهد القرين
غرام جليدان
ليلى الصباغ
ريناد الغريبي
نورة القاضي