Digestive System

University of Jordan

Faculty of Medicine

Batch of 2013-2019

Medical Committee
The University of Jordan

◯ Slide ✦ Sheet ◯ Handout ◯ Other

☐ Anatomy ☐ Embryology

☐ Physiology ☐ Histology

✦ Pathology ☐ Pharmacology

☐ Microbiology ☐ PBL

Sheet #: **2**

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Date:

Price:

DESIGNED BY: TAMER ALTAMIMI "SMILE"

Pathology of the Stomach

There will be two lectures covering diseases of the stomach. This lecture will deal with acute and chronic gastritis; the next lecture will discuss peptic ulcer disease and stomach tumors and polyps.

Introduction:

The stomach is divided into four major regions:

(1) Cardia. (2) Fundus. (3) Body. (4) Antrum.

What we care about in pathology, when we're talking about the different diseases of the stomach, are the most prominent cells in each of these regions:

- Cardia: contains *foveolar cells* which produce mucin.
- Antrum: contains *foveolar cells* that produce mucin AND **characteristic** neuroendocrine cells "*G cells*" that produce gastrin. Gastrin stimulates acid production from parietal cells mostly in the body and the fundus.
- Body + Fundus: both contain *parietal cells* (acid-producing cells) AND *chief cells* that produce digestive enzymes such as pepsin.

The internal acidity of your stomach is at pH=1, which is million times more acidic than your blood, and that means the mucosa will not be able to withstand that kind of pH, which means you must have a protective layer from the interior contents of the stomach: the acid and the digestive enzymes.

These defensive (protective) forces include:

- The surface mucus secretion that creates an unstirred layer that prevents food and acid from actually touching your gastric epithelial cells.
- Bicarbonate secretion from the surface epithelial cells which neutralizes acid, so that the surface mucus layer will be neutral.
- Adequate blood flow that brings oxygen and nutrients required for cells to survive, as well as washing away any excess acidity that may get beyond the barrier.

- Like any other part of your GI, the epithelium of your stomach is a labile tissue. It is exposed to wear and tear and it will regenerate whenever it is damaged.

Acute Gastritis:

Pathogenesis:

The damaging forces are just normally the acid and enzymes. Acute or chronic gastritis occurs if there's an imbalance between the damaging forces and defensive forces, *either* there's more damaging forces *or* there's a problem with the host (you yourself or the stomach itself, such as: epithelial cells, blood flow, etc…). So for example if we are talking about host factors:

- Ischemia and shock: Reduced blood flow.
- Delayed gastric emptying: there's only certain much the stomach can withstand when it's full.
- Age: elderly people produce less mucin, which means their unstirred layer is going to be compromised, which is why gastritis is more common in the elderly, (which is why NSAIDs that can affect: blood flow, regeneration of the epithelium and bicarbonate synthesis are **more damaging in elderly** than they are in younger people).

Injurious exposures:

- Non-steroidals (NSAIDs): are **also directly damaging** if there is direct contact to the stomach lining, for example aspirin.
- *Helicobacter pylori* bacterial infection, the most common cause of gastritis (chronic).
- Cigarettes.
- Alcohol.
- Gastric hyperacidity: if you tip the balance towards more acid you're not going to be able to counteract that. So if you have, for example, a cranial injury that causes excessive vagal stimulation, it will result in excessive acid production, and it doesn't matter if your prostaglandins, blood supply, mucus and bicarbonate are there, it's just too much acid for those protective barriers to handle.

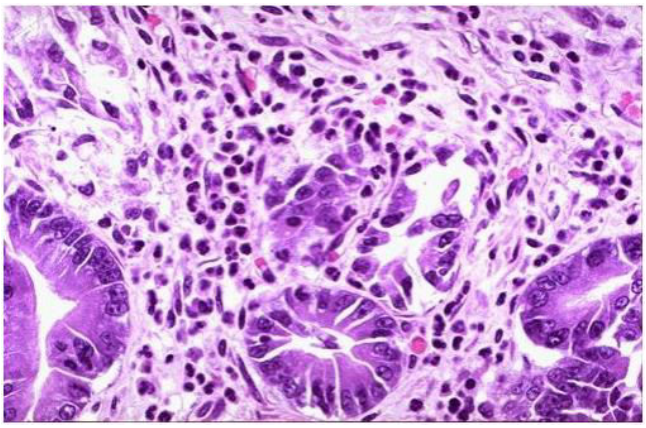
Eventually, if that balance keeps tipping towards damage, you're going to end up with erosion and maybe ulceration.

This disruption of the protective barrier can *either be asymptomatic* (you probably have had acute gastritis at some point and never even realized it; from taking NSAIDs, from being sick, etc…) *or symptomatic* you could have some gastric pain, nausea, and vomiting. If severe enough to go to erosion, bleeding and ulceration, you'll definitely present with ulcer symptoms.

Morphology:

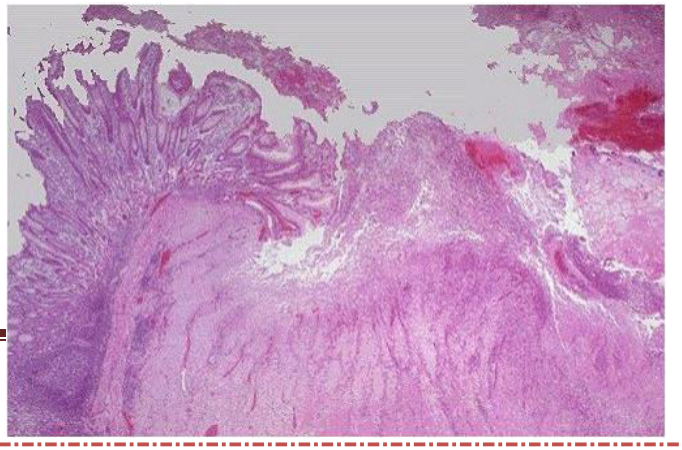
Unfortunately, the morphology is not very distinctive, so it's not going to help you. You're going to find some edema, congestion, maybe you'll find erosion of the superficial layer and maybe you'll find some bleeding.

In mild acute gastritis, you'll see some edema and the surface epithelium remains intact and that's not very indicative of what's going on (it's just that there's edema, so something wrong is going on but not clear). The important thing is, if you find neutrophils above the basement membrane; that means that there's an active inflammatory process going on. **It is not normal at all to find neutrophils above the basement membrane, especially between the epithelial cells.**



Neutrophils in the submucosa indicate a somewhat mild inflammation, BUT if we're talking about epithelial cells interspersed with neutrophils, the inflammation is more severe. In case you're wondering, those are the interspersed neutrophils in the submucosal layer.

If you do progress to not just erosion, but ulceration, you're going to lose that epithelial barrier, and you're going to find some necrotic debris and obviously the acute inflammatory cells. There's the mucosal layer and now the mucosa is gone.



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Now as we've already mentioned, NSAIDs can directly injure your epithelial layer and *indirectly through inhibition of COX enzymes* that produce your **prostaglandins** that are responsible for: (1) blood flow, (2) bicarbonate production, and (3) epithelial regeneration. Intact epithelium requires these prostaglandins to be available, which means that if somebody is on NSAIDs they are impairing their defensive abilities, and chronic NSAID use is associated with gastritis, erosion, ulceration.

Acute Peptic Ulceration:

Pathogenesis:

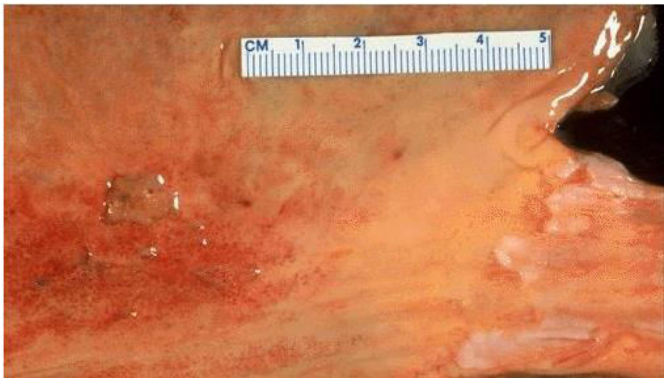
Now other than NSAIDs, severe physiologic stress can also induce ulcers. Remember we said it depends on the host factors so there are three major types of ulcers (although the first two are essentially the same thing; they are both stress ulcers):

1. **Stress ulcers:** although we don't fully understand why acute physiological stress or severe physiological stress can induce ulcers, the general consensus is that **shock, sepsis, and severe trauma** impairing blood supply and inducing acidosis & intracellular acidosis, will tip the balance towards more damage.
2. **Curling ulcers:** are stress ulcers – they're called curling according to the scientist that described them at the end of the 1800s. They frequently occur with **severe burns and trauma** and they typically occur in the **proximal duodenum**. They have a higher risk of bleeding and perforation because the underlying trauma is more severe.
3. **Cushing ulcers:** again named for one of the two scientists that described them, are associated with **intracranial damage**. What's happening here is that you are stimulating the vagal nuclei, and the vagus will stimulate hyperacidity in the gastric epithelium and you end up with acute ulceration.

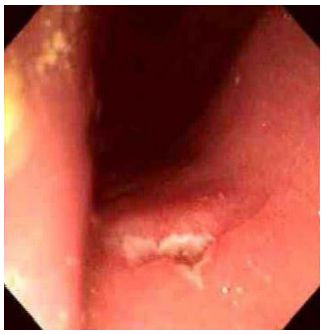
These can range anywhere between shallow erosion and complete mucosal perforation, depending on the underlying condition of the patient. The worse the patient is, the worse the ulcer is going to be.

Additionally, if you remove the physiologic stress: (if the patient recovers from his or her burns, or from the intracranial injury,or if the patient is no longer traumatized, you've treated their sepsis, you've treated their shock,) that means these patients will recover without any further intervention *as long as there hasn't been a catastrophic event* like perforation or massive bleeding. In that case, you need to intervene for those beside the underlying trauma of the physiological stress that occurred.

Morphology:

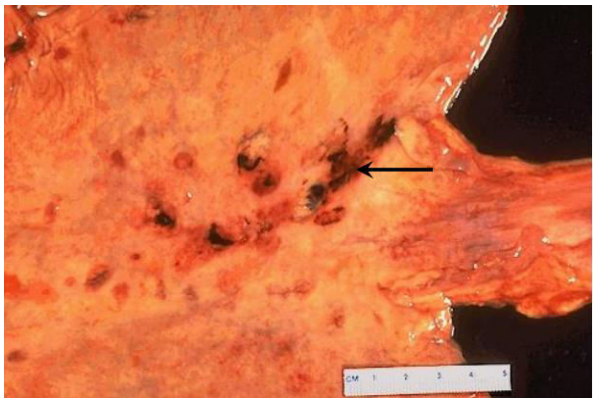


Now, the acute peptic erosions or ulcerations are typically **small** (usually less than 1 cm in diameter), could be **single or multiple**, and **very sharply demarcated** by the surrounding epithelium, which is normal as you can see here. (See picture in slides). The surrounding epithelium may be a bit edematous but you can see that it is limited to that location.



You can also see it endoscopically: like we said singly, or more commonly, multiple ulcers.

If some **bleeding has occurred**, you are going to find that the **base** of these ulcers is **stained brown to black** because of the acid digested red blood cells.



Clinical features:

Symptoms of acute peptic ulceration: *nausea, vomiting, and hematemesis.* If the hematemesis is due to acute peptic ulceration, it will look like "coffee ground", because the blood that

has been acid digested in the stomach is what is being expelled. But in the esophagus you're not going to see coffee ground appearance of hematemesis, because there is no acid digestion of blood. So if you see coffee ground hematemesis you know that it is stomach in origin.

Complications: (1) Excessive bleeding: means the patient could go into shock, (2) if that patient has underlying liver condition: worsening of their liver condition will occur, because of the massive amount of protein load that has been added to the liver to work on, (3) as well as perforation.

Treatment:

- More commonly nowadays, we use *proton pump inhibitors* (PPIs) to reduce the acidity and to tip the balance towards the defensive forces again.
- Less frequently, we would use *H2 receptor blockers*.

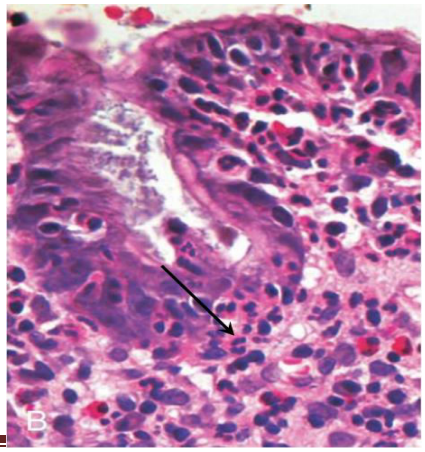
Proton pump inhibitors are more effective and have a safer long term profile.

Chronic Gastritis:

Signs and symptoms: essentially the same as acute gastritis, just that they are going to be less severe, but more persistent. Hematemesis is rare.

Causes:

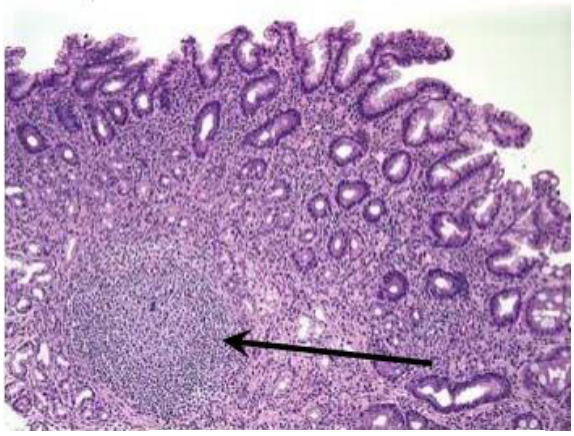
- *H. pylori*: the most common cause by a wide margin (about 90% of cases).
- Auto-immune gastritis: comes in second place at about 10%. Again these percentages vary from one location to another.
- Radiation injury: rare; either you're a cancer patient who had received radio therapy or you were recently exposed to a nuclear reactor. Both are not exactly common conditions.
- Chronic bile reflux: even rarer, bile reflux occurs from the duodenum up into the stomach.



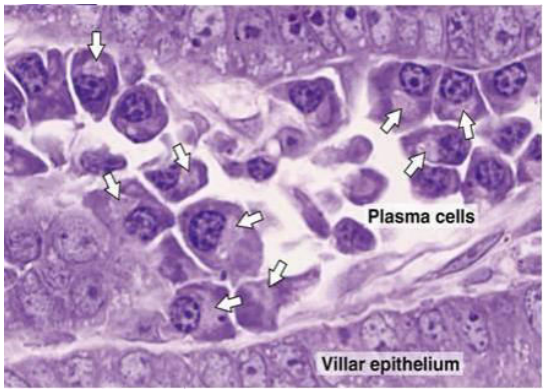
Morphology: When we're talking about chronic gastritis, we are more likely to see the neutrophils not just in the submucosa, but even in the epithelial layer, and you can see the **polymorphonuclear cells between the**

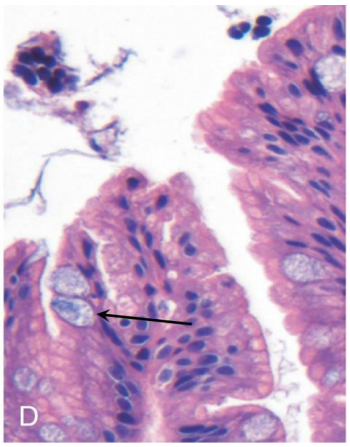
epithelial cells. They are prominent, and that means the inflammation has gone on long enough that more and more neutrophils had been recruited to the site.

You can also see **lymphoid aggregates** and **germinal centers**. (Germinal centers: sites where lymphocytes are developing, so we're talking about lymph nodes, etc…). So, it looks like you've got a germinal centre where it's not supposed to be. And you'll also see **sub-epithelial plasma cells**. You're wondering what plasma cells look like up close; here is a higher magnification.



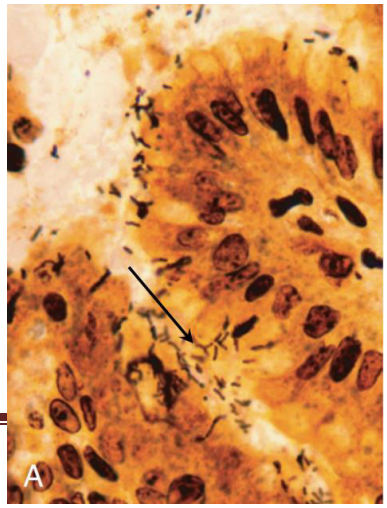
Germinal center





In chronic gastritis, you can also induce **intestinal metaplasia** and you already know what intestinal metaplasia looks like. You will see characteristic goblet cells (mucin producing cells). If chronic gastritis has induced intestinal metaplasia, this means that these patients are at a **higher risk of gastric adenocarcinoma**.

Should you do a specific stain called the "Warthin-Starry Silver stain", you will see in most patients these spiral-shaped or curved bacilli that are usually **abundant in the surface mucus**-where they live. Although invasion of mucosa by these bacilli has been reported, we don't know if that invasion has anything to do with the pathogenesis of the bacteria. These bacilli have a **tropism to** (i.e. they have an affinity; they like, they love, they want to be next to or invade) **foveolar epithelia**.



If you got some superficial acute gastritis from *H. pylori* invasion typically this acute infection doesn't produce sufficient symptoms to seek medical attention. But if the symptoms persist, then acute gastritis turns to chronic gastritis, and that is typically when the patient seeks medical attention.

Pathogenesis: What happens is that there's going to be a reaction that increases secretion of acid even though there is hypogastrinemia, which means that these patients are at risk of ulceration. The majority of patients with duodenal ulcers and even lots of patients with gastric ulcers, if you assay them, they will have *H. pylori* infections.

Along the way you can induce atrophy, metaplasia, dysplasia, and gastric adenocarcinoma. And you know this takes decades to develop and a really very small percentage of patients go through this road.

We've already mentioned lymphoid aggregates, and if the neoplastic damage is occurring to these lymphoid aggregates, we get or we produce mucosa-associated lymphoid tissue lymphoma (**MALT lymphoma**).

Also, last semester, when we talked about chronic inflammation, we talked about inflammatory by-products, (for example: reactive oxygen species, which can, among other things, damage DNA and activate certain proteins) which essentially help the neoplastic process.

The pathogenicity of *H. pylori* is enhanced, in addition to the chronic inflammatory by-products, by the following four things:

1. They have **flagellae**: which means they can move in the mucus layer. *H. pylori* cannot withstand stomach acidity, so it's very strange for these bacteria to choose stomach to colonize. So it stays within the mucus layer to protect itself from stomach acidity.
2. They have **urease**: that produces ammonia, which neutralizes acid around the bacteria itself.
3. Additionally, **adhesins**: Those enhance the bacterial specific adherence to stomach epithelial cells.
4. Finally, in addition to the chronic inflammation and the reactive oxygen species and the DNA damage, there are certain **toxins**: such as that encoded by CagA gene that can activate proliferation pathways of the epithelial cells.

So not only are you inducing, for example, DNA damage because of inflammatory by-products, you can also **induce proliferation** by damaging the cells; these cells are labile cells which means they will respond to damage by proliferation and you're further egging them on as these toxins activate certain proliferation pathways. (We don't fully understand exactly which pathways, but it's been reported in scientific literature that when you isolate this toxin and give it to epithelial cells, their proliferation increases.)

H. pylori, as we already know, **does not like acid**, so we are not going to find it in acid-producing mucosa of the gastric body, duodenum, or in areas of intestinal metaplasia. That doesn't leave many areas to look in, which is why typically when we do take a biopsy, although recently we don't take biopsies frequently, but if you do need to take a biopsy, you typically take it from the antrum to maximize your chances of finding that bacteria. There are now less invasive tests than biopsy where you can detect antibodies against *H. pylori* in the serum or you can detect *H. pylori* in the feces and there's even a "urea breath test", because the bacteria has a urease and you can detect the generated ammonia as some of it is going to be gaseous in the breath.

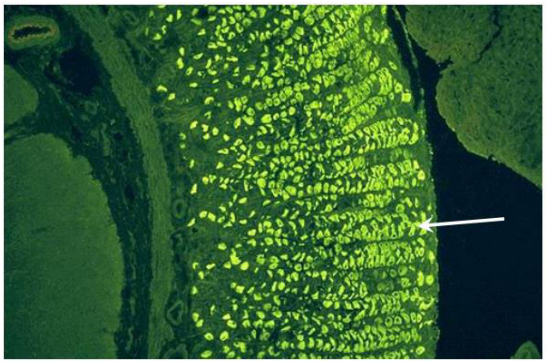
Treatment: Combinations of antibiotics and proton-pump inhibitors

- Antibiotics: to eradicate the bacteria.
- PPIs: to relieve the patient's symptoms.

After a period of antibiotics and proton pump inhibitors, typically these patients are OK. However, if they live in an endemic area, they could get re-infected, and a small minority of patients can also relapse. Whether the relapse is (1) re-colonization and re-infection, or (3) because the antibiotic treatment was not effective the first time (incomplete eradication); it's going to be very hard for you to know why.

Differential diagnosis for *H. pylori* gastritis: If you are talking about a gastritis that does not fit in the previous picture, it is autoimmune gastritis – the second most common cause of chronic gastritis after *H. pylori*. So if you don't find the bacteria, if you don't have a positive urease breath test, if the clinical sequelae are not fitting, but something is not quite right about this patient, you want to keep this in the back of your mind and think about autoimmune gastritis.

Autoimmune gastritis: Unlike *H. pylori gastritis*, the antrum here is spared and you will find G cell hyperplasia, (which is the opposite to that of *H. pylori* gastritis, where we said there is hypogastrinemia,) here we're going to have **hypergastrinemia**. You will also find **antibodies against parietal cells and intrinsic factor**. So you're going to end up with **achlorhydria** and, in a small number of patients, **pernicious anemia** because of impaired vitamin B12 absorption due to antibodies against intrinsic factor. This develops in the long run, that is why we say small percentage of these patients may present with pernicious anemia, also known as megaloblastic anemia.



You will also find **reduced serum pepsinogen levels** because you're losing chief cells as well. And there will also be overall atrophy (you will see a **reduction in the rugal folds** if you go through endoscopy because you have widespread atrophy).

If you compare chronic *H. pylori* gastritis to autoimmune gastritis you will find some very distinctive features between the two:

	H. pylori	**Autoimmune**
Location	Antrum	Body (spares antrum)
Inflammatory Infiltrate	Neutrophils & subepithelial plasma cells	Lymphocytes and macrophages
Acid Production	Increased to slightly decreased (very rarely)	Decreased – Achlorhydria (no acid secretion at all)
Gastrin	Normal or decreased (hypogastrinemia)	Increased*
Other lesions	Hyperplastic/inflammatory polyps	Neuroendocrine hyperplasia* (in antrum)
Serology	Antibodies to *H. pylori*	Antibodies to parietal cells and intrinsic factor
Sequelae (if patients left untreated)	Peptic ulcer, adenocarcinoma, lymphoma	Atrophy**,pernicious anemia, adenocarcinoma, carcinoid tumor
Associations	Low socioeconomic status, poverty, residence in rural areas (basically low hygiene)	Autoimmune diseases: thyroiditis, diabetes mellitus, Graves disease

* Here there's going to be hypergastrinemia: as you know the neuroendocrine cells in the antrum are producing gastrin to stimulate acid secretion, and when acid is detected, this shuts down the production of gastrin. If there are no parietal cells, (because they are being destroyed by the anti-parietal cell antibodies,) that means gastrin doesn't have a shut-off, no feedback to turn off gastrin secretion, so more and more gastrin will be produced, which is why these cells undergo hyperplasia (or increase their secretion without multiplying) and patients end up with hypergastrinemia.

** These patients have atrophy because you are damaging the acid producing cells in the mucosa of body and fundus.

Note: Acute gastritis→ full recovery. Chronic gastritis that developed to peptic ulcer → Scarring will occur instead of reepithelialization. (Scarring: fibrosis and angiogenesis)

Note: The H.pylori tips the balance towards more damage by affecting the mucosal barrier, inducing the production of acids and bringing inflammatory cells so that along with gastric acidity are the main inducers of ulceration.

END

Dedications to: Layan, Tara, Sarah, Omar, Sultan, Yanis, *Yasmine*, Haya, Leen, Dina, Xein, RAND, Maryanna, Amir, Omar, Sanad, Majd, Yazan, Farah, Yara, Bana, Omar, Lara, Dina, Ahmad, Musab, Yazan, Yousef, Tareq, Maryann, Aseil, Amer, and Rajai… sorry if I forgot anyone (except Justin).

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و تحية خاصة الى الأخت نجمه السعدي