THE NORTHERN HOSPITAL

PEPTIC ULCER DISEASE

Emperor Marcus Aurelius (Sir Richard Harris) and Maximus (Russell Crowe), do battle in Germania, "Gladiator", 2000.

MARCUS: *Tell me again, Maximus, why are we here?*

MAXIMUS: *For the glory of the Empire, sire.*

MARCUS: *(Quietly) Ah Yes. I remember.*

"Just when the lamps were lit, a messenger came and brought me to the Emperor, as he had bidden. Three doctors had watched over him since dawn, and two of them felt his pulse, and all three thought that a fever was coming. I stood alongside, but said nothing. The Emperor looked first at me and asked why I did not feel his pulse as the other two had. I answered: "These two colleagues of mine have already done so and, as they have followed you on the journey, they presumably know what your normal pulse is, so they can judge its present state better."

When I said this, he bade me, too, to feel his pulse. My impression was that - considering his age and body constitution - the pulse was far from indicating a fever attack, but that his stomach was stuffed with the food he had eaten, and that the food had become a slimy excrement. The Emperor praised my diagnosis and said, three times in a row: "That is it. It is just as you say. I have eaten too much cold food"

He then asked me what measures should be taken. I replied what I knew of a similar case, saying: "If you were any plain citizen of this country, I would as usual prescribe wine with a little pepper. But to a royal patient as in this case, doctors usually recommend milder treatment. It is enough for a woolen cover to be put on your stomach, impregnated with warm spiced salve".

Galen, "On the Diagnosis of Pulses", c. 169 AD.

Marcus Aurelius was one of Imperial Rome's greatest Emperors, arguably it's greatest. A philosopher in the "Stoic" tradition, he was one of the few Emperors whose writings remain extant. He would jot down seemingly random thoughts, ideas and philosophies, often whilst on campaign in the Northern provinces. These thoughts have come down to us in the form of his "Meditations", a fascinating window into the mind of one of Imperial Rome's greatest. Many of his writings are simple, yet profound, others, more difficult to interpret, their meaning lost in contexts long forgotten and unrecorded or obscured in attempts at translation from Second Century Latin, into 21st Century English.

After a long period of relative peace, by the mid Second Century AD increasing numbers of primitive Germanic tribes, of which we know very little as they were a pre-literate society, were putting immense on the Northern borders of the Empire, their attacks becoming more ferocious and more sustained with every passing year. Although Marcus abhorred war, one of the very few Roman Emperors who did, he was forced to spend the better part of the last ten years of his life in continual conflict with these Northern tribes. This he did admirably, though eventually the stress took a toll on his health and he was to die on campaign in the frozen Northern provinces of the Danube in the year 180 AD. He was greatly mourned by all within the Empire. Gibbon wrote of him…

"War he detested, as the disgrace and calamity of human nature; but when the necessity of a just defence called upon him to take up arms, he readily exposed his person to eight winter campaigns on the frozen banks of the Danube, the severity of which was at last fatal to the weakness of his constitution. His memory was revered by a grateful posterity, and above a century after his death, many persons preserved the image of Marcus Antoninus, among those of their household gods."

With his advancing age, and years of campaigning in the harsh Northern winters his health began to fail. In the motion picture "Gladiator" Marcus is depicted in a poignant moment, as age wearied and tired of interminable conflict. The stress of war is evident. He asks his leading general Maximus why they are doing what they are doing. Maximus gives the magnificently "stoic" response, "For the glory of the Empire, Sire", Marcus replies, "Ah Yes. I remember", yet the philosopher Emperor seems somehow unconvinced.

Apparently one complaint he suffered from, was possibly what we would call today "dyspepsia". His usual physicians were at a loss to explain his symptoms, and during one particularly severe attack, he called for the most revered physician of his day, Galen. Galen himself has left a description of this encounter. He was not impressed by his colleagues' deliberations, (nor must it be said did he show any of his colleagues much professional courtesy, modesty was never his strong point). Galen was an expert in the examination and interpretation of the pulse. By examining the pulse he diagnosed the Emperor's condition as a gastric disorder, brought about by too much "spicy" food, which Marcus enthusiastically agreed must be the case. The usual prescription for this ailment, at the time was pepper in wine, however Galen posited that this treatment was a little "second class" for such an important patient. He prescribed instead the very cutting edge management of the day, a "woolen cover to be put on your stomach, impregnated with warm spiced salve".

It is impossible not to over estimate the influence the great Roman physician Galen had on the Medical profession. This influence was dominant for a staggering one thousand three hundred years, until many of his ideas were directly challenged during the Renaissance, by the great anatomist Vesalius in particular. Even so, his influence in many areas still reached out even beyond the time of Vesalius. Perhaps one of his ideas even reached the late 20th Century! There was a common held belief, perhaps originating with Galen that dyspepsia was caused by stress and "dietary indiscretion". Marcus Aurelius certainly had stress in his life, however what we know of his "aesthetic" qualities he probably did not overindulge in the culinary sense, despite the pronouncements of his leading physician. The true discovery of the Emperor's complaint would not be known until late in the 20th Century, one thousand eight hundred years after his death, and this discovery would be made by two eminent physicians that would come from a land that in Marcus's time only the greatest Astronomer and Geographer of that age, Ptolemy would have dared to speculate that it even existed - Terra Australis Incognita, the legendary unknown "Great Southern Land".

Only the miracles of 21st Century medicine could have saved the great Marcus Aurelius. Endoscopy, instead of his pulse, could have diagnosed his condition. Antibiotics and proton-pump inhibitors, instead of "woollen covers impregnated with spiced salves" could have cured him. If Marcus eventually died of the well recognized complications of peptic ulceration, then this 21st Century medicine would not only have cured his symptoms , but saved his life as well.

PEPTIC ULCER DISEASE

Introduction

Patients with peptic ulcer disease may present to the ED with an already established diagnosis or without one.

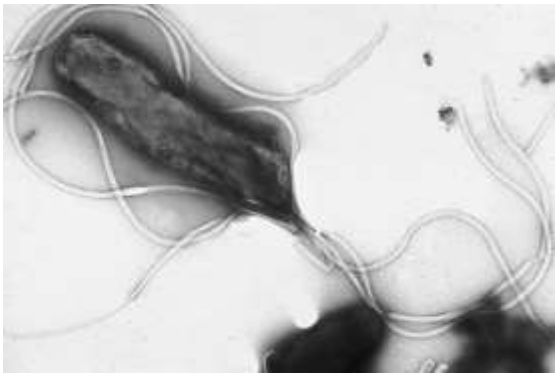
If the diagnosis has not already been established, management in the first instance will be presumptive.

In either case, the important issues from an acute ED presentation perspective will include:

- How unwell, is the patient?
- Does the clinical assessment indicate probable peptic ulcer disease?
- What empiric treatment should be given.
- Have important differential diagnoses, been (or need to be) ruled out?
- Does the patient require hospital admission?

Modern advances in the understanding of the pathophysiology of peptic ulceration, in the form of **early endoscopic diagnosis** and the administration of **anti-proton pump inhibiting drugs**, and of **antibiotics directed against Helicobacter pylori**, have revolutionized the management of this once chronic and intractable disease.

Pathophysiology



Electron micrograph of the multiple unipolar flagellated Helicobacter pylori, (see also Appendix 1 below)

In recent years the pathophysiology of peptic ulcer disease has been more clearly elucidated, by the brilliant work of two Australians, gastroenterologist **Barry Marshall** and pathologist **Robin Warren**, who discovered the helicobacter pylori organism and then elucidated its role in peptic ulcer disease. [2]

They were jointly awarded the 2005 Nobel Prize in Physiology and Medicine "for their discovery of the bacterium *Helicobacter pylori* and its role in gastritis and peptic ulcer disease".

It is now appreciated that by far the majority of cases of peptic ulcer disease are caused by stomach infection with the organism *Helicobacter pylori*, largely dispelling a multitude of historical theories on its causes such as stress or "spicy" foods.

Together with the technological advances in the endoscopic technique this discovery has lead to a "quantum leap" improvement in the prevention of both mortality and morbidity that was previously associated with this chronic condition. Early endoscopic detection and eradication of the organism *Helicobacter pylori*, together with modern anti-proton pump inhibiting drugs have revolutionized the management of this condition, which previously would often be treated surgically with various "vagotomy" techniques or even gastrectomy in advanced or complicated cases.

The term "peptic" ulcer disease encompasses a range of gastric and duodenal pathology caused primarily by the Helicobacter pylori organism. This range includes early inflammation (or gastritis) to erosions to frank ulceration. In histological terms, an erosion is a defect of the mucosa down to the level of the muscularis mucosae, whilst an ulcer penetrates through the muscularis mucosae and into the submucosa, however for practical purposes the distinction is largely academic.

Causes:

1. Helicobacter pylori:

    - It should be noted that the majority of patients infected with Helicobacter pylori are in fact asymptomatic.

    - Nonetheless, that vast majority of cases of peptic ulceration are the result of infection with this organism.

2. NSAIDS:

    - NSAIDS, including aspirin are the second most common cause of peptic ulcer disease.

    - These agents can result in ulceration even when given by non-oral routes, (parenterally or rectally).

3. Hyper-acidity:

    - This however requires large degrees of acid, as occurs in the Zollenger-Ellison syndrome, and is a rare cause.

Contributing factors that may aggravate peptic ulcer disease or delay healing, but do not of themselves cause it, include:

- Alcohol

- Smoking
- Lesser degrees of hyper-acidity.
- Corticosteroid use, (prolonged)

Complications:

Complications of peptic ulcer disease include:

1. **Hemorrhage**
2. **Perforation:**
3. Posterior penetration:
    - This can induce a secondary pancreatitis.
4. Obstruction:
    - In chronic disease, now becoming a rare complication.
5. Malignant change:
    - Chronic bacterial infection with *H pylori* is also a risk factor for gastric malignancy.

Hemorrhage and perforation in the past were common complications of chronic peptic ulcer disease and a major source of mortality and morbidity. With the advent of early diagnosis, however, through the use of endoscopy and the medical treatment of helicobacter pylori eradication and anti-proton pump inhibiting drugs, these two complications are becoming much less common.

Clinical Assessment

Untreated, peptic ulcer disease tends to run a chronic relapsing course characterized by periodic episodes of pain and the risk of complications including bleeding and perforation.

Important points of history:

1. Ask about any past GIT conditions, including any past endoscopic examinations.
2. GIT hemorrhage
3. The acuteness of onset of pain:
    - Very acute onset suggests the possibility of perforation.
4. Symptoms of reflux.

5. Past history in general, in particular is ischemic heart disease, (as a consideration in the differential diagnosis).

6. Nature of the pain:

    - Radiation of pain into the back, (this may indicate aortic aneurysm, myocardial ischemia, pancreatitis, biliary tract disease or a posterior penetrating ulcer)

    - Peptic ulcer disease pain is typically related to food. Often times this will bring on pain, however it may also relieve it. Antacids will typically relief it.

7. Medications:

    - In particular NSAID, warfarin use.

8. Alcohol abuse and smoking.

Important points of examination:

1. Check the patient's vital signs:

    - Uncomplicated peptic ulcer disease, does not in general present with abnormal vital signs. If these are found suspicion is raised for an alternative diagnosis or the presence of a serious secondary complication.

2. Abdominal signs:

    - There may be localized mild epigastric tenderness.

    - Frank signs of peritonism, (such as rebound tenderness or rigidity), may indicate GIT perforation or an alternative diagnosis.

3. The possibility of GIT hemorrhage (hematemesis and/ or melena) may need to be ruled out, according to clinical suspicion.

4. In the elderly, always check for the presence of an abdominal aortic aneurysm.

Differential diagnoses:

As there is no definitive investigation available in the ED to make the diagnosis of peptic ulcer disease, an important part of clinical assessment will be the ruling out of possible serious alternative diagnoses.

Alternative diagnoses, essentially include any cause of epigastric discomfort and hence the range of possibilities is extensive.

The most important considerations will include:

- Pancreatitis

- Esophageal reflux
- Other non-specific causes of gastritis.
- Abdominal aortic aneurysm, in the elderly
- Biliary tract disease.
- Myocardial ischemia
- Other GIT conditions, eg: obstruction or ischemic gut.

Investigations

In straight forward cases and where patients are not unwell, no investigation may be necessary in the ED.

The type and extent of investigation will be directed to ruling out alternative important diagnoses or secondary complications of peptic ulcer disease.

It will also depend on how unwell a patient is. **The more unwell the patient, the more likely will be the possibility of a serious alternative diagnosis or of a serious secondary complication.**

The following may need to be considered:

Blood tests:

1. FBE
    - A hypochromic microcytic anaemia suggests chronic blood loss.
2. CRP
    - This is not typically raised in uncomplicated peptic ulcer disease and if significantly elevated will suggest an alternative diagnosis or possible secondary complication, such as perforation.
3. U&Es/ glucose
4. Lipase:
    - This should always be considered in any patient who present with epigastric pain.
5. LFTs
    - Hepatitis or biliary tract disease.

6. Other blood tests may be required as clinically indicated n each case.

Plain radiography:

- CXR, to primarily look for free gas. This will not rule out the possibility of a perforation, however.
- AXR (erect and supine), looking for evidence of obstruction or perforation.

ECG:

- Myocardial ischemia should always be considered in any patient with epigastric discomfort and a significant risk profile for an ACS.

Ultrasound:

- This will primarily be used to rule out the possibility of biliary tract disease.

CT scan:

- This may be required to rule out possible alternative serious intra-abdominal pathology such as mesenteric ischemia or aortic aneurysm.

Endoscopy:

- *Emergency endoscopy* is usually reserved for cases of acute GIT hemorrhage.
- Electively, endoscopy is now the *investigation of choice* for the diagnosis of peptic ulcer disease. (This has replaced historical radiological contrast studies).

Helicobacter pylori testing:

The organism can be detected in a number of ways:

1. Mucosal biopsy:
    - Staining and microscopic examination of mucosal biopsy specimens can provide direct visualization of Helicobacter pylori.
    - The CLO (*Campylobacter*-like organism) test, allows for a diagnosis of *H pylori* infection of **biopsy specimens** within 24 hours. This test relies on the detection of urease activity (a highly specific marker of *H pylori*), which is responsible for the organism's ability to produce ammonia from urea.

Non-invasive tests include:

2. Urease breath testing:
    - In this test patients swallow urea labelled with an isotope of carbon (either radioactive carbon 14 or non-radioactive carbon 13). In the subsequent 10-

30 minutes, the detection of isotope-labelled carbon dioxide in the exhaled breath indicates that the urea was split by the enzyme urease and that *H. pylori* is therefore present in the stomach.

3. Serology:

- An IgG serology test is available. It has good specificity, but only moderate sensitivity.
- It is most useful when the result is negative and so helps exclude *H pylori* infection.
- IgG serology can remain positive for some time, even after successful eradication of the organism, and so is not generally useful in confirming its clearance.

Note that serology tests and urease tests, merely confirm infection with H. pylori, and do not necessarily indicate peptic ulcer disease. Confirmation of peptic ulcer disease is by direct visualization of mucosal surfaces via endoscopy.

However a negative urease breath test in a patient not taking NSAIDS makes the diagnosis of peptic ulcer disease unlikely.

Management

1. IV fluid resuscitation:

- This should be commenced as clinically indicated if the patient is dehydrated from associated vomiting and/ or poor oral intake.

2. Antacids:

- Such as “Mylanta” sometimes with added lignocaine and “Gaviscon” will often give good symptomatic relief.
- The advantage of these agents are their immediate effects, as opposed to the more specific anti-acid agents, such as the H_2 antagonists or the proton pump inhibitors which will take longer for full effect.

3. H_2 Receptor antagonists:

- These agents are effective for simple gastritis, but less so than for erosion or frank ulceration.

4. **Proton-pump inhibiting agents:**

- These are the agents of choice for the suppression of gastric acid production that aggravates peptic ulceration and delays healing.
- Inhibition of acid secretion by PPIs, although of slower onset, is greater and more sustained than with histamine H_2 -receptor antagonists.

- As a result, healing of erosive oesophagitis and peptic ulcers is **superior** with PPIs when compared with histamine H_2 -receptor antagonists or other antiulcerant agents (such as bismuth or sucralfate)

- **Patients with severe symptoms and known disease, may be prescribed an IV proton-pump inhibitor agent.**

See also Hematemesis and melena guidelines for proton pump inhibitor dosing in bleeding peptic ulcers.

5. Analgesia:

   - Acute pain may be sufficiently severe on occasions as to require opioid analgesia

   - This will necessarily mandate a prolonged period of observation and a lower threshold for considering possible alternative diagnoses.

6. **Antibiotics:**

   - Antacids and anti-gastric acid agents, may result in healing, however **in the presence of Helicobacter pylori infection, recurrence will be likely.**

   - Helicobacter pylori eradication with antibiotic therapy is therefore now a routine part of the treatment of endoscopically confirmed peptic ulcer disease, where the organism has been detected.

   Eradication therapy is usually undertaken as a triple combination therapy of a proton pump inhibitor together when two antibiotics:

   - **Omeprazole**

   Plus

   - **Amoxycillin** (or metronidazole if allergic to penicillins)

   Plus

   - **Clarithromycin**

   See latest Antibiotic Guidelines for full prescribing details.

7. Surgery:

   - With the great recent advances in medical management of peptic ulcer disease, surgery is now no longer required for treatment of the primary condition.

- In the past various vagotomy techniques were employed in an attempt to reduce gastric acid secretion, a presumed major factor in the aetiology of peptic ulceration. Partial or even total gastrectomies were not uncommon.

- Today surgery is usually reserved only for the life-threatening complications of peptic ulceration such as perforation or severe acute hemorrhage, (unable to be controlled by endoscopic techniques).

  These life threatening complications have become less common with the modern treatment of peptic ulcer disease.

Disposition:

Most uncomplicated cases of peptic ulcer disease can be managed symptomatically in the ED, then discharged when symptoms have settled

Antacids can be prescribed for "PRN" relief of symptoms.

There is some controversy as to whether the proton pump inhibitors should be prescribed before definitive diagnosis via endoscopy has occurred. The concern here is that treatment with these agents and with antibiotics will make diagnosis by biopsy less reliable. Resolution of symptoms may further induce patients not to have a follow-up endoscopy.

The advantages of endoscopy include:

- Definitive confirmation of the diagnosis.

- Identification of Helicobacter pylori, (a necessary prerequisite for prescribing full eradication antibiotic drug therapy).

- **Ruling out possible malignant disease.**

In practice if symptoms are mild, the patient is younger (< 50 years), and there are no associated "alarm symptoms" empiric treatment is often given. Proton pump inhibitors are prescribed to heal the ulcer and Helicobacter pylori eradication is undertaken if there is a positive urease breath test.

It is reasonable to prescribe antacids or H2 antagonists in the first instance for any suspected cases.

However endoscopy should be undertaken if there are associated "high-risk" features, such as:

- Symptoms are severe, (pain or associated vomiting).

- Symptoms are persistent.

- Evidence or suspicion of GIT bleeding.

- An inadequate response to empiric treatment.

- A suspicion of malignant disease, (eg: anemia, **older age groups**, weight loss, dysphagia/odynophagia (difficult/painful swallowing)

Admission:

This will be required when:

- Pain symptoms are severe and difficult to control.

- If there are significant secondary complications, such as dehydration, perforation or GIT haemorrhage.

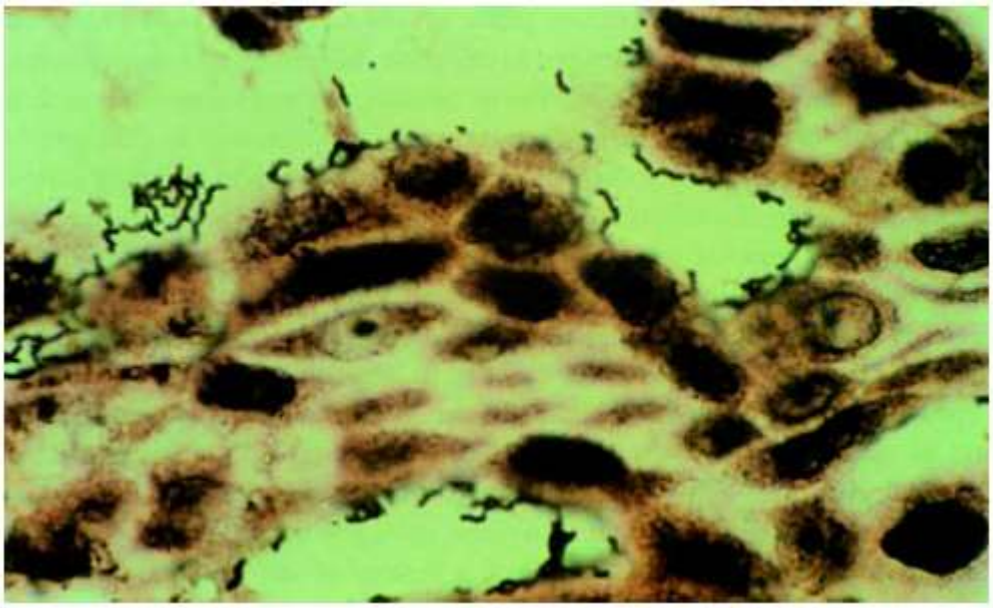
- Where diagnosis remains unclear, and important differential diagnoses need to be investigated and excluded.

In the early morning mists, Marcus Aurelius orders the legions into battle against a ferocious Germanic tribe, on the banks of the Danube River.

Maximus, his leading general, mobilizes the legions.

Appendix 1

Two Australians win the 2005 Nobel Prize for Physiology or Medicine:



Silver stain of Barry Marshall's gastric biopsy on Day 10 after ingesting 10^9 Helicobacter pylori organisms, (MJA December 2005).

The 2005 Nobel Prize for Physiology or Medicine was awarded to two Australians, Gastroenterologist Dr. ***Barry Marshall*** *and Pathologist Dr.* ***Robin Warren*** *for* ***"for their discovery of the bacterium Helicobacter pylori and its role in gastritis and peptic ulcer disease".***

Their discovery revolutionized the treatment of one of the most intractable scourges of the human race, peptic ulcer disease, a disease known since ancient times, yet not understood until the late 20th Century. Even within the time of my own experience as an Emergency Physician, I have (anecdotally) noticed a dramatic decline in the number of cases seen in the Emergency Department of the severe, often fatal consequences of this disease. Marshall and Warren's discovery must stand as one of modern medicine's major contributions to the betterment of the "human condition'.

In an MJA article in December of 2005, this discovery was celebrated by the authors Dr Martin Van Der Weyden, (a most respected tutor from my own medical student days, and who would delight us with stories and anecdotes from history, mostly from the "Golden Age of the Dutch", whilst teaching at the bedside) and colleagues. In the article the authors points out that the Helicobacter story demonstrated a host of the recurring hallmarks that history recounts on many major advances in medicine, including "being at the right place at the right time", the role of serendipity, the resistance of the establishment to the undermining of the perceived dogma, the flash of novel and inspired thinking about a seemingly trivial observation others had noted, but thought nothing of, but above all and in the truest and noblest spirit of scientific endeavour throughout the ages, the offering up of oneself as the proverbial "human guinea pig!"

In respect of this last point, Marshall, frustrated at the medical profession's seeming indifference to his theories ingested a pure culture of 10^9 Helicobacter pylori organisms

dished up courtesy of the Fremantle Pathology Department and waited to see what would happen. Nothing much for 5 days. But on the sixth, he suddenly developed halitosis, nausea, and intractable vomiting. He then persuaded his colleague Ian Hislop to endoscope him and take a gastric biopsy! This demonstrated a severe acute gastritis with swarms of infiltrating H. pylori. His wife Adrienne by this stage had had quite enough of his experiments and threatened that if he did not immediately take the prescribed antibiotics he would be evicted from the house. He did so, got better and avoided having to make alternative sleeping arrangements under a local bridge. The story also has a uniquely Australian, touch. Marshall would continuously pester the two most senior members of the Royal Perth Hospital Gastroenterology Service, Tom Waters and Chris Sanderson about his theories, until the latter bluntly advised him, "Barry, stop buggerising around and do a proper study!" That was the "Australian style" advice that lead to the 2005 Noble Prize for Medicine!

References

1. Dilley S. Peptic Ulcer Disease and Gastritis, in Cameron et al. "Textbook of Emergency Medicine" 2nd ed, 2004.

2. Marshall BJ, Warren JR (June 1984). "Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration". *Lancet* 1 (8390): 1311–5.

Further Reading:

M.B Van Der Weyden, The 2005 Nobel Prize in Physiology or Medicine, *The Helicobacter story illustrates some of the human hallmarks of revolutionary research.* MJA vol 183 no. 11/12, 5/19 December 2005

Dr J. Hayes

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