

SSC MODULE

**Clinical Lab Science ( CLS Micro. )**

**university of Baghdad**

**college of medicine**

**Done by:**

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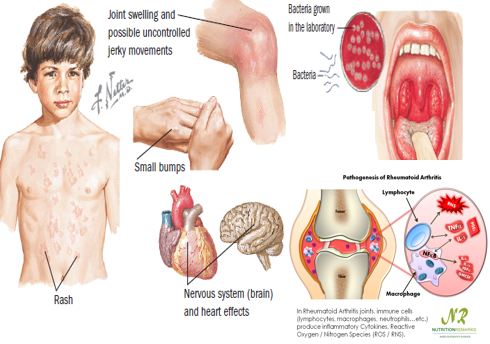
**Group: A2**

Contents :

1. [***introduction ……………………………………………………2***](#introduction)
2. [***Etiopathogenesis of Rheumatic Fever………………3***](#Etiopathogenesis)
3. [***Pathogenesis ………………………………………………...4***](#Pathogenesis)
4. [***Clinical features …………………………………………….7***](#Clinical)
5. [***The Laboratory Diagnosis …………………………….10***](#Laboratory)
6. [***The treatment………………………………….…………..11***](#treatment)
7. [***The prevention …………………………………………..12***](#Prevention)
8. [***References …………………………………………………15***](#refrence)

***Introduction:***

Acute rheumatic fever *(ARF)*, an **auto-immune response** **to group A streptococcus** *(GAS)* infection of the upper respiratory tract, may result in carditis or inflammation of the mitral and/or aortic valves. When the inflammation leads to permanent damage of the valves the individual has rheumatic heart disease *(RHD).* Recurrences of rheumatic fever are likely in the absence of preventative measures and may cause further cardiac valve and muscle damage, leading to heart failure, strokes and premature death . Bacterial endocarditis is also a complication.(1) Acute rheumatic fever usually affects children (most commonly between **5** and **15** years) or young adults, and has become very rare in **Western** **Europe** and **North America** However, it remains endemic in parts of Asia, Africa and South America, with an annual incidence in some countries of > 100 per 100 000, and is the most common cause of acquired heart disease in childhood and adolescence.(2) The burden of ARF in industrialised countries declined dramatically during the 20th century, due mainly to reduced transmission of GAS related to improved living conditions and increased hygiene standards along with better access to appropriate health services and increased access to **penicillin-based medications**. In most affluent populations, including much of Australia, ARF is now rare, and RHD occurs predominantly in the elderly.(3)



**Figure 1** : rheumatic fever feature .(3)

***Etiopathogenesis of Rheumatic Fever:***

Acute rheumatic fever (ARF) is a delayed non suppurative sequel of pharyngeal infection with group A beta hemolytic *Streptococcus* (GABHS). After a latent period of two to three weeks following initial pharyngitis various signs and symptoms of ARF appear. But there is no direct proof that GABHS is responsible for the manifestations of ARF. In other words ARF and Rheumatic heart disease (RHD) although commonly seen in clinical practice particularly in developing countries, the exact etiopathogenesis remains poorly understood.(4)

***Streptococcal Bacterial:***

Most streptococci that contain the group A antigen are *S pyogenes.* It is a prototypical human pathogen. It is used here to illustrate general characteristics of streptococci and specificcharacteristics of the species. *S pyogenes* is the main humanpathogen associated with local or systemic invasion and poststreptococcalimmunologic disorders. (5)

Group A beta hemolytic streptococci has an external capsule consisting of mainly hyaluronic acid, the next inner layer the ‘cell wall’ consist of protein (type M, T and R), carbohydrate and rhamnose. The innermost layer consists of mucopeptides like Nacetyl D-glucosamine, D-glutamic acid, L-lysine, Lalanine and then comes the cytoplasmic membrane

(having RNA and DNA protein) (Fig1). Not all streptococci are culprit to produce ARF. The type of *Streptococcus* that causes ARF is known as ‘rheumatogenic strain’ consisting of more than 130 M serotypes (Griffith classification) is responsible for ARF. It has the following specific features:

• The bacteria is very rich in M-protein (M serotypes

3,5,6,14,18,19, and 24)

• It is highly resistant to phagocytosis.

• It has a large hyaluronidase capsule which forms

distinct mucoid colonies in blood agar media.

• If properly stored, its virulent character is retained For a long time. (6)

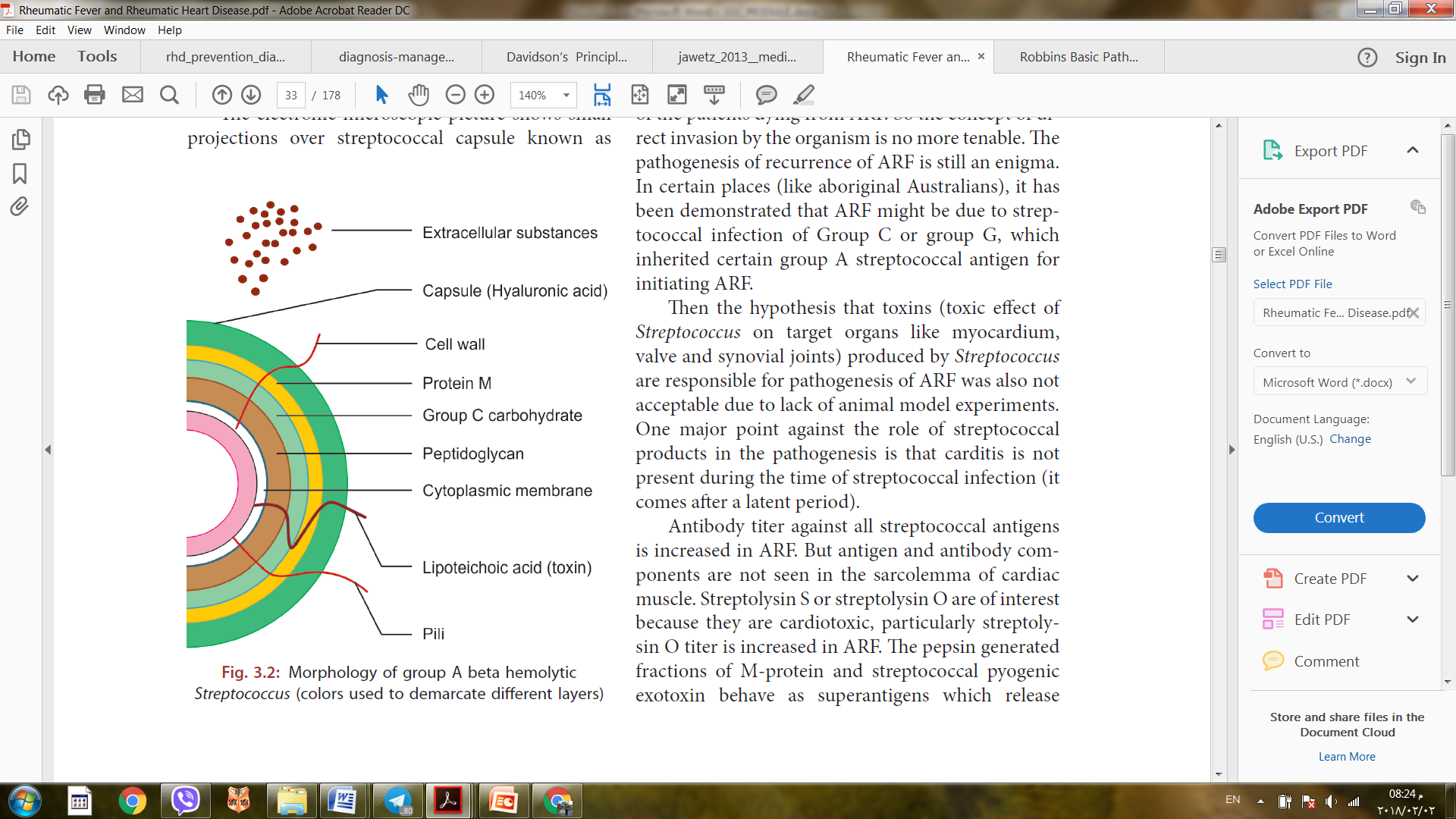
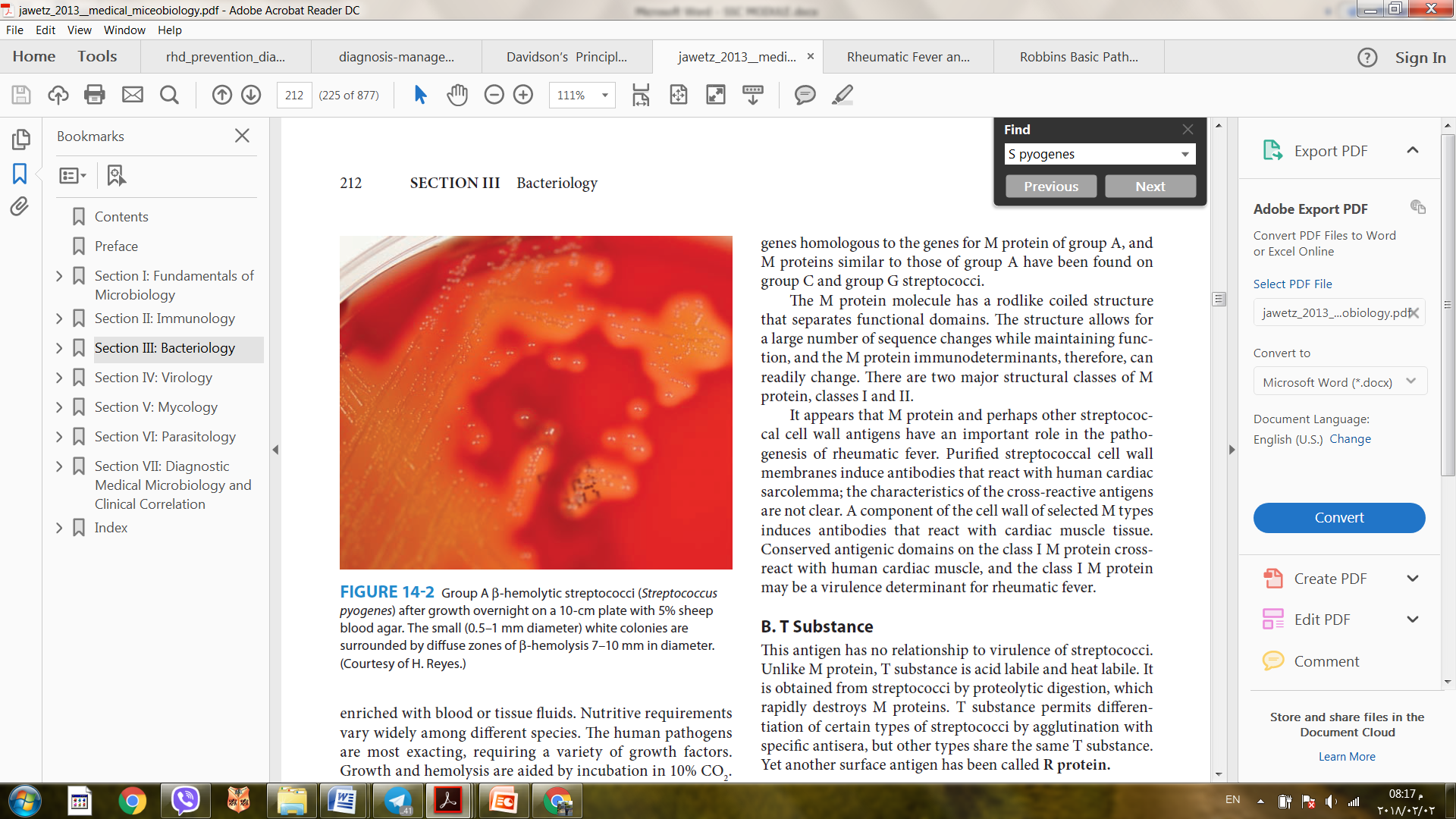
 

FIGURE 2: Group A β-hemolytic streptococci (*Streptococcus*

*pyogenes*) after growth overnight on a 10-cm plate with 5% sheep

Blood agar. The small (0.5–1 mm diameter) white colonies are

Surrounded by diffuse zones of β-hemolysis 7–10 mm in diameter.

(Courtesy of H. Reyes.) (5)

FIGURE 3: Morphology of group A beta hemolytic

*Streptococcus* (colors used to demarcate different layers) (6)

Note:

Epidemiological evidence shows that the host factor plays an important role pathogenesis of ARF. Out of all streptococcal throat infection only in three percent of cases Group A beta hemolytic rheumatogenic M-protein type) have been isolated Among these cases again (0.3–3%) are susceptible to develop ARF; and subsequently some of them develop RHD Children belonging to age 5 to 15 years are mainly affected by ARF and it is rare below four years of age.(7)

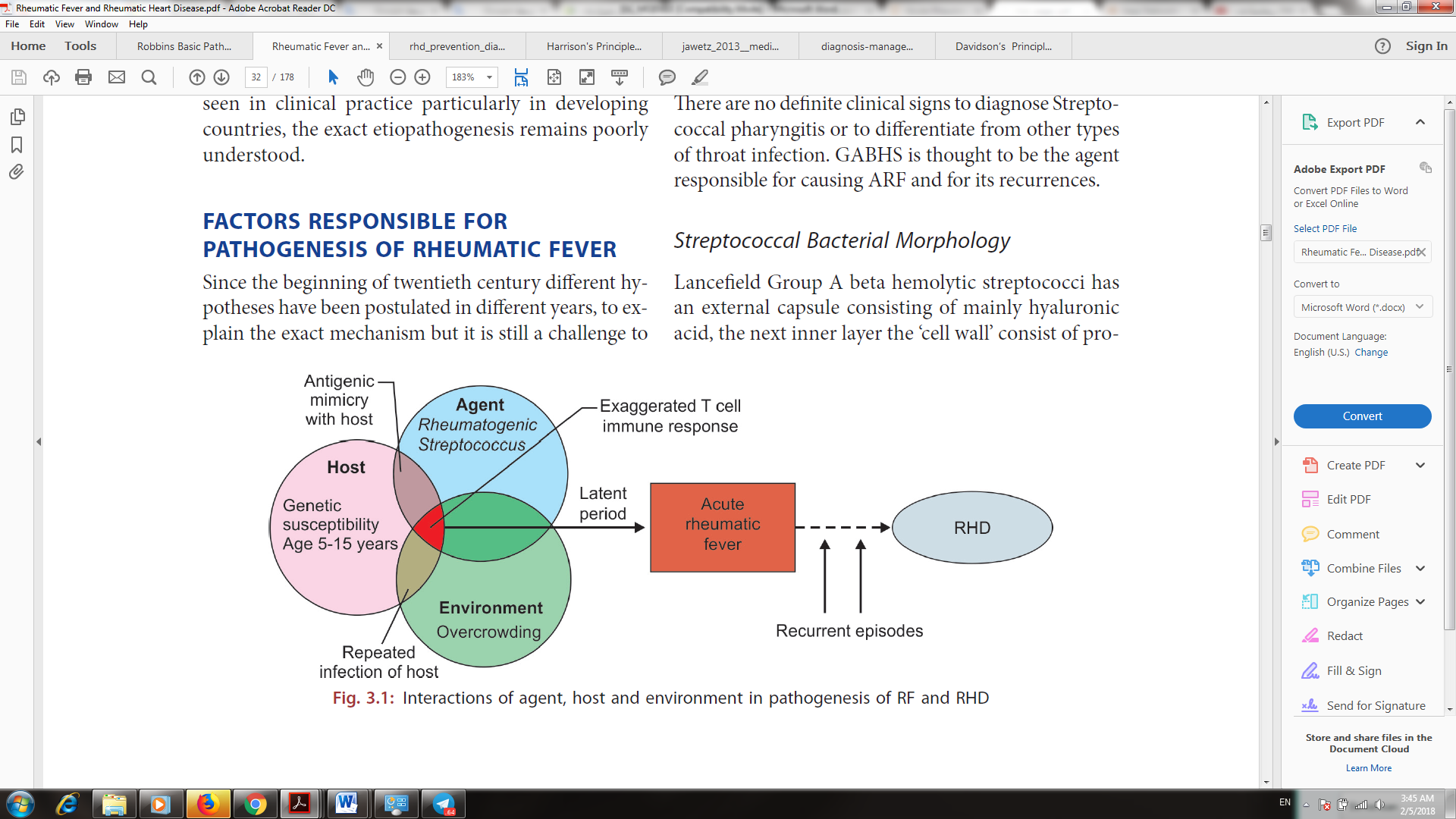
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***Pathogenesis***

Acute rheumatic fever (ARF) is primarily a post streptococcal connective tissue disorder (8). Antibodies produced against the streptococcal antigens cause inflammation in the **endocardium**, **myocardium** and **pericardium**, as well as the **joints** and **skin**.

*Histologically*:

1. **Fibroid degeneration** is seen in the collagen of connective tissues.
2. **Aschoff nodules** are pathognomonic and occur only in the heart. They are composed of multinucleated giant cells surrounded by macrophages and T lymphocytes, (and are not seen until the sub-acute or chronic phases of rheumatic carditis).(9)



**FIGURE 4:** Interactions of agent, host and environment in pathogenesis of RF and RHD (9)

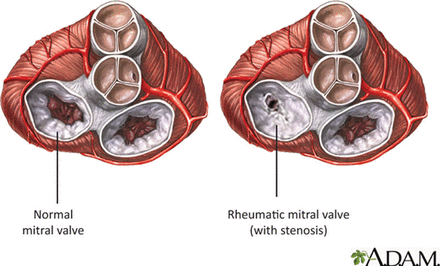
***Pathology of Cardiac Lesions:***

***Pericardium*** : In ARF both the layers of pericardium (parietal and visceral) show signs of inflammation. Rheumatic **fever** is one of the common causes of acute pericarditis. It is usually **mild** to moderate. It leads to **thickening** of the pericardium with fibrinous exudates over it and serosanguinous fluid inside the pericardial cavity. This characteristic **shaggy** appearance is known as (*bread and butter* appearance.(10)

***Myocardium:*** 1. Rheumatic myocarditis **does not** lead to heart failure,the histological damage is very meager (myocardialcontractility is preserved), the cause is not known.

2**. Aschoff nodule** although pathognomonic of ARF its formation and nature of function still remainsa mystery.

***Endocardium***: the valve apparatus mainly the **cusps** are affected producing mitral or aortic valvulitis leading to mitral or aortic **regurgitation**. The mitral regurgitation *(MR)* produced by mitral valvulitis disappears in majority of cases but *)AR(* persist in most of the cases of aortic valvulitis.( In the acute stage of inflammation there is **roughening** and in chronic stage there is **thickening** of thesurface linings.) .When signs of inflammation subside, the **sclerotic process** starts, resulting in fusion of cusps, chordae tendineae and also mitral Ring. That result in **valve damage** progresses over time because of blood flow across an abnormal valve cause further **fibrosis** and **calcium** deposition. Which leads to more narrowingof mitral valve **(mitral stenosis)** or to incomplete closure of leaflets (**mitral regurgitation**). Similarly fusion of aortic valve cusps leads to **aortic stenosis**.(11)



**FIGURE 5:** *Rheumatic mitral stenosis.(12)*

*Extracardiac Manifestations:*

***Joints:*** Swelling of articular and periarticular space occurs due to effusion. These effusions are **exudative** and **sterile** in nature (never **purulent**).

***Central Nervous System:*** **Arteritis** of small vessels inside cerebrum are usually noticed. Perivascular round cell infiltration and scattered petechial **hemorrhages** are seen throughout the **cortex**, **cerebellum** and **basal ganglia**.

***Lung :*** Pathological changes in the lung fields are usually secondary to cardiac involvement . Due to carditis, lungs parenchyma shows evidence of **congestion** with **hemorrhagic spots**.(13)

*Clinical features :*

**Major Manifestations :**

Acute rheumatic fever is a multisystem disorder that usually presents with **fever**, **anorexia**, **lethargy** and **joint pain***, 2–3* weeks after an episode of streptococcal pharyngitis. There may, however, be no history of sore throat. Arthritis occurs in approximately *75%* of patients. Other features include **rashes**, **carditis** and **neurological** changes . Only about *25%* of patients will have a positive culture for group A streptococcus at the time of diagnosis because there is a **latent period** between infection and presentation.(14)

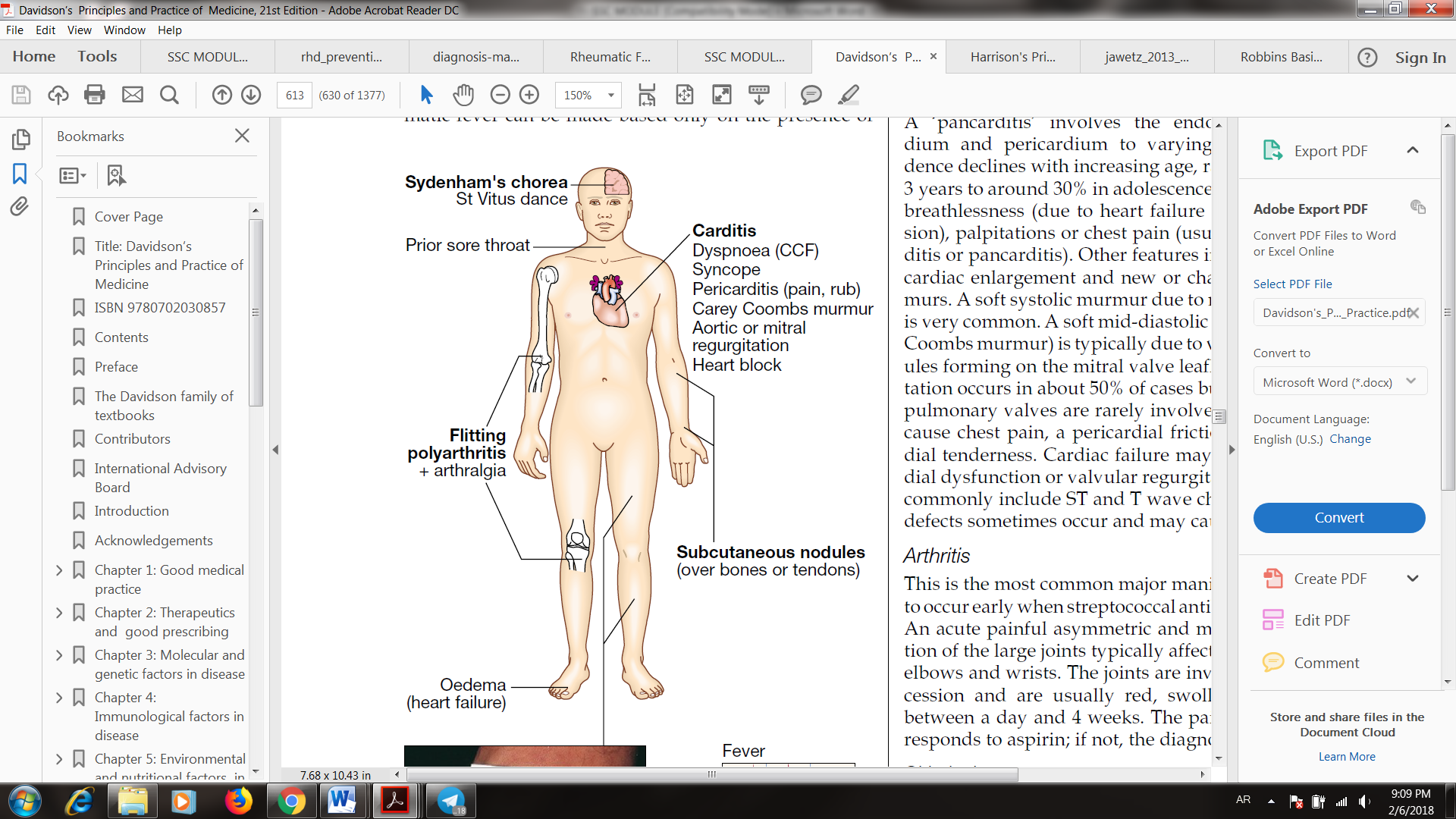


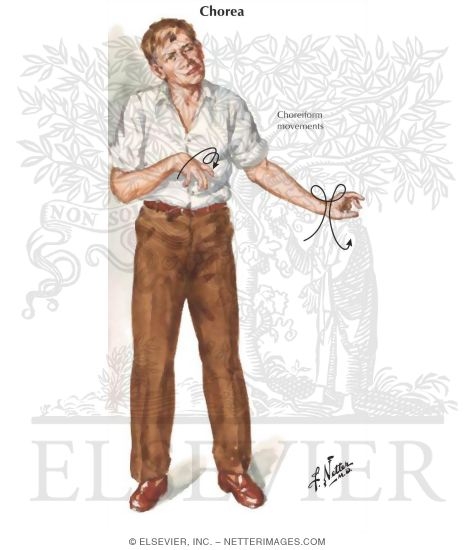
Figure 6 : Clinical features of rheumatic fever.(14)

Carditis :

General complaints are **puffiness** of face, **breathlessness** on exertion (dyspnea of various grades), **fatigue**, **cough**, loss of appetite (**anorexia**), irregular **fever**, **arthritis** or **arthralgia** and **palpitation**. On examination disproportionate **tachycardia**, sleeping pulse more than *100 beats/min* and rarely **bradycardia** (pulse rate less than 60/min) are the signs of acute carditis. The apex is out and down and usually left ventricular type (heaving). The apex may not be felt if there is associated pericardial effusion. **Cardiomegaly** indicates either myocardium or endocardium is involved. **A soft mid diastolic murmur** (the Carey Coombs murmur) is typically due to *valvulitis*, with **nodules** forming on the *mitral valve leaflets*(15)*.*

Arthritis :

This is the most common major manifestation and tends to occur early when streptococcal antibody titres are high. An **acute painful asymmetric** and **migratory** inflammation of the large joints typically affects the **knees**, **ankles**, **elbows** and **wrists**. The joints are involved in quick succession and are usually red, swollen and tender for between a *day* and *4* weeks. The pain characteristically responds to aspirin; if not, the diagnosis is in doubt. (16)



**Figure 7**: Sydenham’s chorea (18)

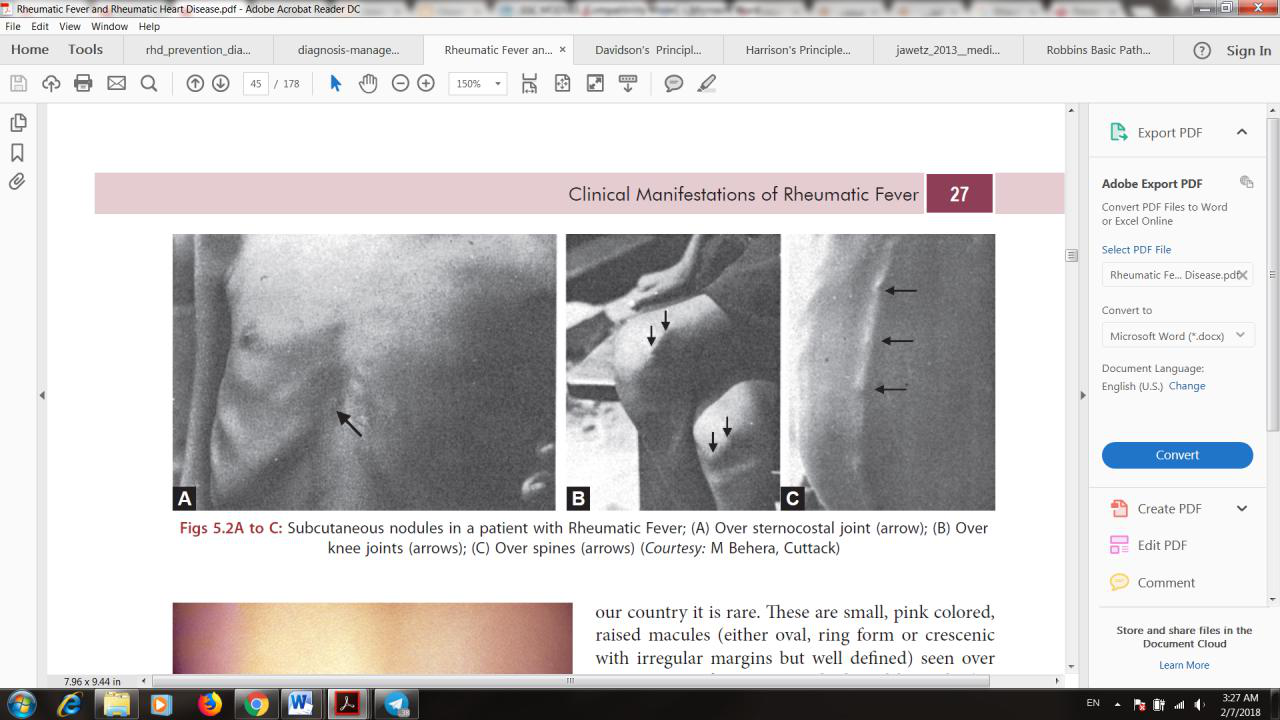
Sydenham’s chorea

(St Vitus dance) :

This is a late neurological manifestation that appears at least *3* *months* after the episode of acute rheumatic fever, when all the other signs may have disappeared. It occurs in up to *one-third* of cases and is more common in females. **Emotional lability** may be the first feature and is typically followed by **purposeless involuntary choreiform movements** of the hands, feet or face. Speech may be **explosive** and **halting**.(17)

*Subcutaneous nodules:*

These are very rare (less than *2%* of cases), but highly specific manifestations of ARF in Aboriginal people. They are *0.5–2* cm in diameter**, round**, **firm**, **freely mobile** and **painless** nodules that occur in crops of up to 12 over the elbows, wrists, knees, ankles, Achilles tendon, occiput and posterior spinal processes of the vertebrae. They tend to appear *1–2* weeks after the onset of other symptoms, last only 1–2 weeks (rarely more than 1 month) and are strongly associated with **carditis**.(19).



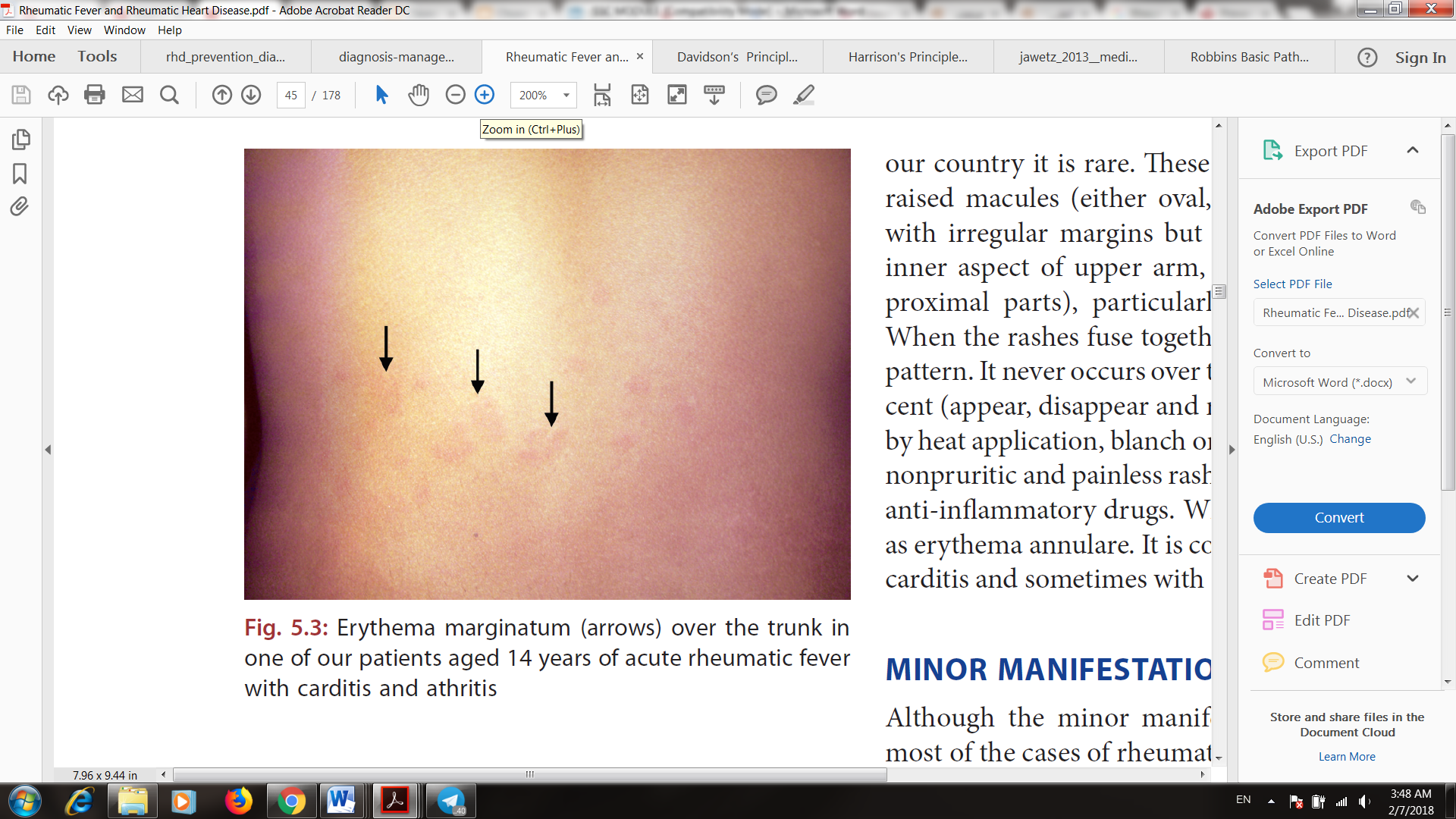
(!9)

Figure 8:

*Skin lesions:*

**Erythema marginatum** occurs in *< 5%* of patients. The lesions start as red macules (**blotches**) that fade in the centre but remain red at the edges and occur mainly on the **trunk** and **proximal extremities** (*but not the face.*)The resulting red rings or ‘margins’ may coalesce or overlap . Subcutaneous nodules occur in *5–7%* of patients. They are small *(0.5–2.0 cm*), **firm** and **painless**, and are best felt over extensor surfaces of bone or tendons. They typically appear more than *3 weeks* after the onset of other manifestations and therefore help to confirm rather than make the diagnosis.

.(20)



(20)

**Fihure 9:**

**Minor Manifestations :**

Fever :

it is present in almost **all** cases. Usually it is of high grade (more than *39° C*) and persists for *7 to 10* days. Sometimes it may be low grade, **irregular** or **intermittent** which may persist for *2 to 3* weeks. Presence of fever (high or low) indicates persistence of rheumatic activity. Fever subsides **without** treatment, but if treated with **analgesics** the patient becomes **afebrile** within a week.(21)

**Arthralgia :**

Arthralgia differs from arthritis in that there is pain on joint movement **without** evidence of **swelling** or **heat**. It is a non-specific symptom, and usually occurs in the same pattern as rheumatic polyarthritis (**migratory**, **asymmetrical**, **affecting large joints**)(22)

Note:

(A confident diagnosis of rheumatic fever can usually be made if at least **two** **'major'** symptoms are present, or there is **one major** symptom and **two 'minor'** symptoms.)(23)

**The Laboratory Diagnosis :**

**Blood teast :**

1. C reactive protein *(CRP)* – which tests the level of **C reactive protein** (CRP) in your blood. CRP is produced by the liver. If there's more CRP in the blood than usual, there's **inflammation in the body.**
2. **Antistreptolysin O titre** *(ASOT)* – this blood test looks for evidence of antibodies produced by the immune system in response to the [**streptococcal infection**](https://www.nhs.uk/Conditions/Streptococcal-infections/Pages/Introduction.aspx)**.**(24)

* **Erythrocyte sedimentation rate** *(ESR)* – in an ESR test, a sample of your red blood cells is placed into a **test tube**. ESR measures the **rate** at which red blood cells **fall** (sedimentation). If the blood is "**sticky**" due to various substances produced during the immune response, the red blood cells will fall more **rapidly**, increasing the ESR. (25)

1. **B**

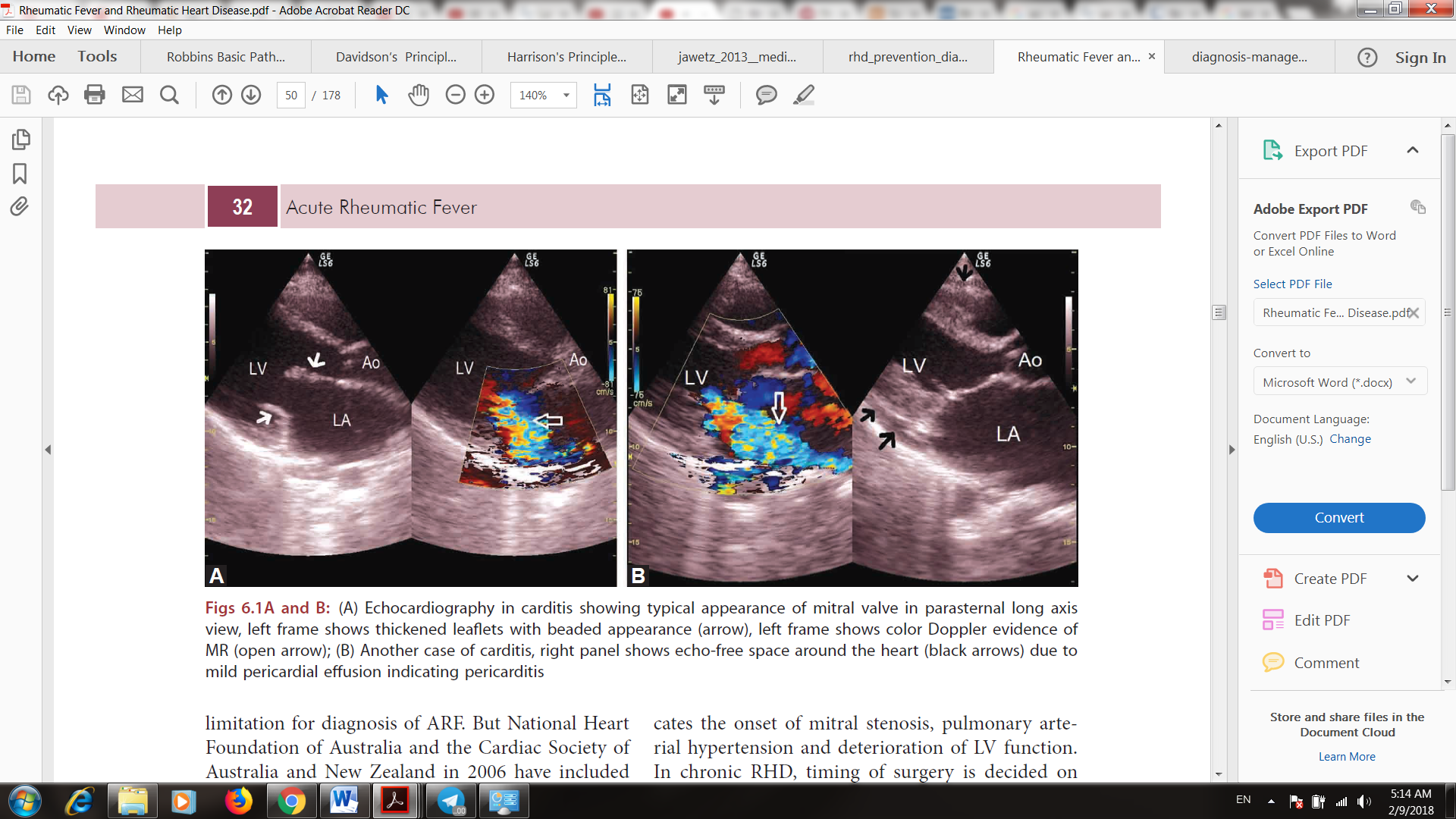
**Figure 10**: *sticky blood* (25)

**Electrocardiogram (ECG) :**

The ECG machine measures your heart's **electrical activity**, allowing your doctor to check for any abnormal heart rhythms. *PR* **prolongation** is seen in 25 percent of cases of ARF. It is a nonspecific finding which is present in healthy children but the difference is that in ARF the PR **interval returns back** to normal over next *few weeks* .(26)

**Echocardiography :**

Echocardiography typically shows **mitral regurgitation** with **dilatation** of the **mitral annulus** and **prolapse** of the anterior mitral leaflet, and may also show **aortic regurgitation** and **pericardial effusion.**(27)



**Figure 11**: Echocardiography (28)

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**The treatment:**

***Note:1***

***Eradication of the pharyngeal streptococcal infection is mandatory to avoid chronic* repetitive exposure *to streptococcal antigens.***

***Note 2:***

**two *throat cultures should be performed before starting antibiotics.***

***Note 3:***

***The eradication of pharyngeal streptococci should be followed by* long-term secondary prophylaxis *to guard against recurrent pharyngeal streptococcal infections .(29)***

***Treatment plan :***

* use [**anti-inflammatory** medications](https://www.nhs.uk/conditions/Anti-inflammatories-non-steroidal/Pages/Introduction.aspx) to relieve symptoms.
* use [**antibiotics**](https://www.nhs.uk/conditions/Antibiotics-penicillins/Pages/Introduction.aspx) to get rid of any remaining streptococcus bacteria in your child's body.
* ensure to have plenty of bed rest.(30)
* anti-inflammatory :

nti-inflammatory medications can be used to **relieve** symptoms of **joint pain**, **swelling** ([arthritis](https://www.nhs.uk/conditions/Arthritis/Pages/Introduction.aspx)) and, in severe cases, reduce inflammation of the heart.

**Salicylates (aspirin**) are recommended as **first-line** treatment, because of the extensive experience with their use in ARF and an established evidence. It should be commenced in patients with **arthritis** or severe **arthralgia** as soon as the diagnosis of ARF has been confirmed,but should be **withheld** if the diagnosis is not certain. The duration of treatment is dictated by the clinical response and improvement in inflammatory markers *(ESR, CRP)*. Many patients need anti-inflammatory therapy for only *1–2 weeks* (i.e. anti-inflammatory therapy can be **stopped** at *2 weeks* if the patient is **pain** **free** with improved inflammatory markers).(31) In some patients, joint symptoms may **recur** following the cessation of treatment **(so-called ‘rebound phenomenon’**); this does not indicate **recurrence** ,and can be treated with **another course of anti-inflammatory therapy**. Some patients who still **have** **symptoms** or **elevated** inflammatory markers at 2 weeks may require anti-inflammatory therapy for **up to** . In such cases, the anti-inflammatory dose can often be **reduced** after the initial *1–2 weeks*. Most ARF episodes subside within *6 weeks,* and *90%* resolve within *12 weeks*. Approximately *5%* of patients require *6 months* or **more** of anti-inflammatory therapy.(32)

Aspirin :

should be started at a dose of *50–60 mg/kg/ day*, up to a maximum of *80–100 mg/kg/day* (4–8 g/ day in adults) in four to five divided doses. If there is an **incomplete response** within *2 weeks*, the dose maybe increased to *125 mg/kg/day*, but at higher doses, the patient should be carefully observed for features of **salicylate toxicity**. In such cases, the dose can often be **reduced** to *60–70 mg/kg/day* once symptoms are controlled for the remainder of a *6-week* course.(33)



**Figure 12:** ibuprofen(34)

**Naproxen and ibuprofen**

**Naproxen** *(10–20 mg/kg/day)* can be used as **alternative** to aspirin. It has been used successfully in patients with ARF, including one small, randomized trial, and has been advocated as a **safer** **alternative** to aspirin. **Ibuprofen** has also been used successfully at a dose of *30 mg/kg/day* divided into **three doses .**(34)

**CHOREA :**

Medications to control the abnormal movements do not alter the **duration** or **outcome** of chorea. Milder cases can usually be managed by providing a *calm environment*. In patients with severe chorea, **carbamazepine** or **sodium valproate** is preferred to haloperidol. A response may not be seen for 1–2 weeks, and medication should be continued for *1–2 weeks* after *symptoms subside*. However, if the dose is too high, these medicines can cause side effects similar to being drunk, including **dizziness**, **double visionand** and **vomiting**.(35)

**BED REST:**

Traditional recommendations for long-term bed rest, once the cornerstone of management, are no longer widely practiced. Instead, bed rest should be prescribed as needed while arthritis and arthralgia are present and for patients with heart failure. Once symptoms are well controlled, gradual mobilization can commence as tolerated.(36)

***Prevention :***

**Primary prevention:**

The primary prevention of rheumatic fever (RF) is defined as the adequate antibiotic therapy of group A streptococcal upper respiratory tract (URT) infections to prevent an initial attack of acute RF. Primary prevention is administered only when there is group A streptococcal URT infection. The therapy is therefore intermittent, in contrast to the therapy used for the secondary prevention of RF, where antibiotics are administered continuously.(36)

***Secondary prevention :***

Patients are susceptible to further attacks of rheumatic fever if another streptococcal infection occurs, and **long-term prophylaxis** with **penicillin** should be given as **benzathine penicillin** *1.2 million U* i.m. **monthly** (if compliance is in doubt) or **oral phenoxymethylpenicillin** *250 mg 12-hourly*. Sulfadiazine or erythromycin may be used if the patient is allergic to penicillin; **sulphonamides** prevent infection but are not effective in the eradication of group A streptococci.(38) Further attacks of rheumatic fever are **unusual** after the age of *21*, when treatment may be stopped. However, it should be extended if an attack has occurred in the last 5 years, or if the patient lives in an area of high prevalence or has an occupation (e.g. teaching) with high exposure to streptococcal infection. In those with residual heart disease, **prophylaxis** should continue until *10 years* after the last episode or *40 years* of age, whichever is longer. Long-term antibiotic prophylaxis prevents another attack of acute rheumatic fever but does not protect against **infective endocarditis.**(39)

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