

# Cardiac Infections

Endocarditis, Rheumatic Fever, Myocarditis, and Kawasaki Disease

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# Infective Endocarditis: Etiologic Agents

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## ■ Streptococci

- Viridans accounts for more than 50% of streptococci causing infective endocarditis, including nutritionally variant *S defectivus* and *S adjacens*
- Enterococci ~ 5%
- *S pneumoniae*, beta streptococci - rare

## ■ Staphylococci: especially post-op or in normal hearts

- *S aureus* ~ 10-15%
- Coagulase-negative ~ 10%

## ■ HACEK group: 5-10%

- *H aphrophilus*, *Actinobacillus*, *Cardiobacterium hominis*, *Eikenella Corrodens*, *Kingella kingae*
- Fastidious Gram-negative coccobacilli

## ■ Others -5%

- Fungi especially *Candida*
- Aerobic gram negatives: neonates; line-associated infective endocarditis
- *Coxiella burnetii*

Infective endocarditis. Streptococci and Staphylococci make up a very large fraction of cases of infective endocarditis, with Streptococci accounting for 50 to 60% of such infections and Staphylococci accounting for another 25%.

The viridans group of Streptococci includes the nutritionally variant organism which now has a new genus. They are now called abiotrophia. *Abiotrophia defectivus*. These are organisms that look like a viridans or any green hemolytic Streptococci that have unusual nutritional requirements.

Enterococci. Enterococcal infections are much less common in kids than they are in adults, and it is certainly true for endocarditis.

Occasionally, we have seen other Streptococcal organisms. *Strep pneumoniae* in beta hemolytic Streptococci, such as group C and T, Bs occasionally. So, this is the predominant group of origin. The two situations in which Staphylococci are particularly common, as far as this hemolytic carditis, are in the postoperative patient and in the patient who developed endocarditis in a normal heart.

The other common group of endocarditis agents that must be mentioned are the HACEK group. They account for 5 to 10% of cases of endocarditis.

About 5 % of cases of endocarditis are caused by other agents. Fungi, particularly *Candida*.

Aerobic gram negatives are not common in endocarditis, except occasionally in line-associated infections and in IV drug abusers; 3 to 5% of endocarditis is culture negative endocarditis and we will talk a little bit about that later on.

# Infective Endocarditis - Pathogenesis

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## ■ Factors Associated with Endocarditis

- Areas of turbulent flow (jet effect, eddies)
- Endothelial disruption
- Sterile fibrin-platelet thrombus development on the abnormal surface
- Entrapment of bacteria from "stray bacteremia" leads to focus of infection

Pathogenesis of this disease. There is turbulent blood flow. In pediatric lesions very often there is a jet effect, and in addition to the jet effect there is also non linear blood flow and eddies of blood. As a consequence of the jet effect, there is often endothelial disruption that occurs, which cumulates the development of the sterile fibrin-platelet thrombus in this area of endothelial damage or disruption. This is an outstanding place for "stray bacteremia" to settle out of the few organisms that become entrapped in this sterile fibrin-platelet fibrin. The slower the blood flow, the greater the opportunity for such organisms to be entrapped.

# Infective Endocarditis - Clinical Features

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## ■ Acute Presentation

- High fever, toxicity
- Occasionally congestive heart failure develops
- S. aureus is the most common cause
- Post-op; normal heart; indwelling lines

## ■ Subacute Presentation

- Insidious, non-toxic, malaise
- Viridans strep is the most common cause
- Fungal, HACEK agents

There are two presentations of infective endocarditis. The patient who presents acutely is very sick with high fever and very toxic. They may be in congestive failure, and this is the situation where most often one would expect to find Staph aureus as the etiologic agent of the endocarditis. Situations where this presentation is most common is in a patient in the early postoperative phase, who has recently had heart surgery and had lines in place, or the unusual patient who presents with endocarditis with a normal heart without any obvious antecedent event. Other patients who are not postoperative but who have indwelling lines may also become infected with Staph aureus.

The other rather distinctive presentation, and more common presentation of endocarditis, is a much more insidious one. Patients may have low-grade fever or no fever, they are non-toxic. They do not feel very well, they have malaise, decreased energy. These infections are most commonly due to the viridans Streptococci. The HACEK group and fungi also produce infections that are more insidious and subacute in their presentations. Of course, we have patients who do not quite fit exactly in this category.

# Infective Endocarditis - Evaluation

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- **Three** or more blood cultures (separate venipunctures) before therapy
- Trans-thoracic echocardiography (-60% sensitive)
- Role of trans-esophageal echocardiography is evolving

Evaluation of patients with suspected endocarditis. Blood cultures are obtained, and those blood cultures are to be obtained from separate needle punctures. The concern always is whether we are identifying a contaminated organism or one that is truly circulating in the blood stream. A single blood culture in a case of endocarditis will indeed be positive 80 to 85% of the time, but we really want to maximize our recovery. Before executing therapy you should have three cultures drawn at least an hour or two apart and from separate needle puncture sites. In fact, in the patients with the subacute presentation, it is recommended, and to withhold therapy in the non-sick patient, until we have a first report of blood cultures coming back positive.

Transthoracic echocardiography has been a big advantage in the diagnosis of endocarditis and will yield a positive, that is demonstrate a vegetation in about 60% of patients. In the adult the echo windows are not as good as they are in children, and visualization of vegetations in subtle findings is much enhanced by using transesophageal echo compared to transthoracic. The same thing is probably true for large children. Big teenagers should probably have a transesophageal echocardiogram.

# Infective Endocarditis - Diagnostic Criteria

## ■ Duke Criteria

- Incorporate clinical and echocardiographic features

### Major and Minor Criteria

- Definite Infective Endocarditis: Pathologic evidence of IE, or two majors, or one major and 3 minors, or 5 minors
- Possible Infective Endocarditis: Consistent with IE, not definite or rejected
- Rejected Infective Endocarditis: Firm alternate diagnosis, or resolution of illness or absence of evidence of IE at surgery or autopsy after <4 days of antibiotics
- **Major Criteria**
  - # Positive blood cultures
    - \* Typical IE organisms from  $\geq 2$  cultures or
    - \* Persistently positive cultures
  - # Evidence of endocardial involvement
    - \* Positive echocardiogram or
    - \* New valve regurgitation
- **Minor Criteria**
  - # Predisposing heart disease or IVDA
  - # Fever  $\geq 38$  degrees C
  - # Vascular phenomena
  - # Immunologic phenomena
  - # Positive blood cultures not meeting major criterion
  - # Echocardiogram consistent with IE but not meeting major criterion

The Duke Criteria categorized patients into three categories.

The Duke Criteria have incorporated clinical and echocardiographic features.

These allowed for the classification of patients into the three categories, and a definite case of endocarditis by the new criteria is made if there is pathologic evidence at surgery or autopsy. For example, the removal of an embolus, and one finds that a embolus looked like an endocarditic lesion that broke off. One can diagnose definitively by performing two of two major criteria or one major and three minors.

Cases will be rejected if a firm alternate diagnosis is established or if the illness resolves after four days or less of antibiotics or if the patient goes to surgery or autopsy and there is no evidence of endocarditis after four days or less of antibiotics.

Patients that do not fall into the definite category or the rejected category by Duke are then categorized as possible cases of suspected endocarditis. So, to summarize pathologic criteria, surgical or autopsy obtained, this refers to a culture of a surgical or autopsy material, and makes a definite diagnosis for two majors of clinical criteria, one plus three, or five minor.

The major criteria by Duke are two-fold. One is at least two positive blood cultures for a typical endocarditis organism. That would be a HACEK organism, a viridans Streptococcus organism for example. At least two positives or persistently positive cultures with an organism that is less commonly associated with endocarditis, but you have your findings persistently positive, that would be a major criterion. The second major criterion would be evidence of endocardial development by echo or by clinical finding. The clinical findings are the finding of a new onset of valvular regurgitation.

What are the minor criteria? Well, the minor criteria is the patient has predisposing heart disease or is an IV drug user. Secondly, the patient with fever. Third, the patient with vascular phenomena. Vascular phenomena by the Duke criteria are defined as things like an arterial embolus, septic pulmonary infarcts, mycotic aneurysm, an intracranial hemorrhage, and Janeway lesions.

Immunologic phenomena, on the other hand, are yet another minor and this refers to things like glomerular nephritis.

Patients who have positive blood cultures that do not meet these criteria. There are patients who have some echocardiographic features consistent with endocarditis, but not really good enough to make the major leagues. Here, we would also have a minor criteria.

I should point out that peripheral manifestations of endocarditis are less common in children than they are in adults. Cardiomegaly for example is much less common in children with endocarditis than it is in adults.

# Infective Endocarditis: Treatment

- Prolonged, parenteral, bactericidal antibiotics
- Highly sensitive streptococci (MIC  $\leq 0.1$  mcg/mL)
  - Penicillin G or Ceftriaxone 4 weeks
  - Penicillin G and Gentamicin 2 weeks
  - Vancomycin (for Pen-allergic) 4 weeks
- Relatively resistant streptococci (MIC  $>0.1, < 0.5$ )
  - Penicillin G 4 weeks and Gentamicin 2 weeks
  - Vancomycin (for Pen-allergic) 4 weeks
- Enterococci
  - Pen G or Ampicillin and Gentamicin 4-6 weeks
  - Vancomycin (for Pen-allergic) and Gentamicin 4-6 weeks
- Staphylococcus (without prosthetic material)
  - Nafcillin or Oxacillin 4-6 weeks and Gentamicin 3-5 days
  - Cefazolin (for Pen-allergic) 4-6 wks  $\pm$  Gentamicin 3-5 days
  - Vancomycin (for Pen-allergic or for MRSA) 4-6 weeks
- Staphylococcus (with prosthetic material)
  - For Methicillin Resistant Staph Vancomycin and Rifampin  $>6$  weeks
  - For Methicillin Sensitive Staph Nafcillin or Oxacillin and Rifampin  $>6$  weeks and Gentamicin 2 weeks
- HACEK Agents
  - Ceftriaxone 4 weeks or Ampicillin and Gentamicin 4 weeks

Treatment. The major principal of treatment for infective endocarditis is that it requires prolonged, parenteral, bactericidal antibiotics to be effective. If we do not treat it aggressively enough, it will ultimately kill the patient unless they receive prolonged, parenteral, bactericidal antibiotics.

Measuring serum bactericidal titers is not helpful in contrast to what many of us were taught some years ago in the management of patients with endocarditis.

The most uncomplicated and simplest forms of endocarditis to treat are those that are part of a highly sensitive Streptococci. These may be highly sensitive areas or may be hemolytic Streptococci or even pneumococci. These are organisms that have MIC of less than or equal to 0.1 mcg/ml.

The regimens sanctioned by the American Heart Association are four weeks of intravenous penicillin, four weeks of intravenous or intramuscular ceftriaxone, a short course therapy with two weeks of combined penicillin and gentamicin. For penicillin-allergic individuals, four weeks of vancomycin. This short course regimen, two weeks, should be limited to those patients that have uncomplicated endocarditis meaning that they are not in congestive failure, they do not have obstructive lesions, and they do not have mycotic aneurysms.

The second group of Streptococcal patients are those that have infections with a relatively resistant Streptococcus, where the MIC typically ranges from greater than 0.1 to about 0.5 mcg/ml penicillin. In these patients, combined ampicillin and gentamicin for the first two weeks followed by an additional two weeks of penicillin is the most commonly recommended regimen and that which is associated with the highest cure rate and the lowest relapse rate. For penicillin-allergic individuals, again four weeks of vancomycin.

For those Streptococci that have an MIC of 0.5 or greater in penicillin and for all Enterococci, penicillin or ampicillin together with gentamicin, and both drugs are administered for four to six weeks. Alternatively, the combination for the allergic individual is vancomycin and gentamicin also for four to six weeks.

Regimens recommended for treatment of Staphylococcal endocarditis. It is very important to differentiate between those patients that have Penicillin-sensitive or resistant Staphylococcal infections and those patients who have Staphylococcal endocarditis with or without prosthetic material. Streptococcal infections are less common in patients with prosthetic material, and if they do have prosthetic material, the general rule of thumb is to tack on a couple more weeks of therapy because we know those infections are more difficult to treat and more difficult to eradicate. This is a particularly common issue when we talk about Staphylococcal infections. In Staphylococcal infections without the presence of prosthetic material, the AHA recommended regimens of nafcillin or oxacillin for four to six weeks. The American Heart Association says that we have the option of adding gentamicin to the first three to five days. Now, that is a very short course of gentamicin, and that recommendation is driven by the fact that a fair amount of this kind of infection occurs in the elderly, where folks are concerned about giving prolonged courses of gentamicin. In many pediatric patients with Staphylococcal endocarditis, a week or even two weeks of gentamicin is well-tolerated and may be beneficial in this kind of situation.

In the penicillin-allergic individual who does not have anaphylactic-type of penicillin allergy, four to six weeks of cefazolin is recommended for endocarditis without prosthetic material. Again, with the option for addition of gentamicin for the first three to five days or a bit longer. In the patient who cannot tolerate these agents, vancomycin can be used for four to six weeks and of course the patient who has a methicillin resistant Staph aureus or staph infection that is methicillin resistant, vancomycin is the better choice for treatment.

In patients who have Staphylococcal endocarditis with presence of

# Fungal Endocarditis

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- Candida, Aspergillus, others
- Bulky vegetations, risk of emboli
- Intermittent positive blood cultures
- Surgical treatment is usually mandatory
- Neonates: NICU, lines

prosthetic material, again is most often in postoperative patients. If we have a methicillin resistant Staphylococcus, those patients need to be treated very aggressively. They really need triple therapy for at least six weeks of vancomycin and rifampin together with gentamicin for at least the first two weeks.

For methicillin sensitive Staphylococcal infections in patients who have prosthetic material, again in a serious infection, nafcillin or oxacillin together with rifampin for at least six weeks, with again the addition of gentamicin for the first couple of weeks. For patients needing triple therapy in these circumstances, for at least two weeks and then another 4 weeks or even six weeks of double therapy.

The most commonly recognized regimen for the HACEK group of agents is four weeks of ceftriaxone or four weeks of ampicillin and gentamicin. More and more we use antibiotics like ceftriaxone because it is so well tolerated.

Fungal endocarditis is a difficult problem. It is most commonly caused by Candida, occasionally it is caused by Aspergillus. There is a very, very long list of very, very rare causes of endocarditis. Virtually any fungus, any bacteria has been associated with endocarditis at some point in time. Fortunately, these cases are quite rare. These patients generally have very bulky vegetations, and they are at high risk for embolization. These bulky vegetations can cause obstruction, can actually completely obstruct a valvular orifice for example.

In bacterial endocarditis there is continuous shedding of low numbers of organisms, more or less on a continuous basis, and that is why in the typical patient with bacterial endocarditis, most or even all blood cultures will eventually turn positive.

In contrast, in fungal endocarditis there seems to be very little shedding of the fungus into the blood, so that blood cultures are very intermittently positive, and in Aspergillus it can be very, very difficult to catch the Aspergillus in blood cultures. Often this diagnosis is made when a patient has gotten into big-time cardiac difficulty. An echocardiogram is done, a big bulky lesion is seen, the patient is taken into the operating room, and the surgeon excises a big, huge bulky aspergilloma.

Surgical therapy in the endocarditis patient is almost always necessary to cure. There is an exception. There is at least one series of neonates with line association of Candida endocarditis, prematures who were treated medically and appeared to resolve without surgical therapy. That is one situation where one can at least think about, and often there is so much going on with these sick neonates that they are not candidates for surgery, and you have to hold off on surgical intervention unless they are developing serious and more dynamic problems.

# Infective Endocarditis - Complications

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## ■ Cardiac

- Obstruction, perforation, CHF
- Prosthetic Valve Endocarditis
- Perivalvar ('ring') abscess
- Myocardial abscess

## ■ Extra-Cardiac

- Thromboembolic events
- Stroke
- Immune-mediated phenomena: nephritis, Osier nodes, Janeway lesions, Roth spots

Complications of endocarditis. Patients may develop obstructive lesions. They may perforate a valve; so expect that even though the valve leaflets are open, there are holes in them, so they give you a lot of leak. Patients can have congestive failure from endocarditis because of a variety of hemodynamic problems, such as obstruction for example or severe incompetence of a valve.

Prosthetic valve endocarditis is a particularly difficult problem. Again, it is much less a problem in pediatrics than it is in adult medicine. The serious complication of prosthetic valve endocarditis is the development of a perivalvular ring abscess where the prosthetic valve is sewn into the surrounding structure. There is clearly a suture line that is a common site of infections in the early postoperative period, as well as later on. These infections can also extend into the myocardium and that is a very serious problem. In general, the management of prosthetic valve endocarditis and management of other forms of complicated endocarditis can become more aggressive surgically, and patients are going to the operating room more quickly than they use to.

A growing big emboli is not a good thing, and those emboli are most serious if they go to either the coronary or more commonly if they go to the cerebral circulation and cause the patient to stroke. There are these extra cardiac immune-mediated phenomena that I mentioned. The Janeway lesions is thought more commonly to represent emboli rather than immune-mediated phenomena.

# Culture-Negative Endocarditis

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- Partially treated endocarditis
- Nutritionally deficient streptococci
- Fungal endocarditis
- Q fever (rare in U.S.), Chlamydia
- Bartonella quintana

"Culture-negative" endocarditis, that 3 to 5% of every series, is probably the hardest on the patients. Some patients have had partial treatment, so that blood cultures are negative, but the disease really has not been cured. Some of these nutritionally deficient organisms, the abiotrophia, they fall into this group. Fungal endocarditis is sometimes in this category that is "culture-negative", and so the patient goes to the operating room with Q fever, which is rare as I said, and will be missed on routine culture. Chlamydia may cause a very small number of these cases. In adults, at least in the homeless, Bartonella quintana can cause fever, and trench fever has been associated with endocarditis. I am not aware of any pediatric patient contracting this.

The surgical indications for endocarditis are: 1. Patients with persistent bacteremia, despite appropriate therapy. 2. Refractory congestive failure that is on a hemodynamic basis, such as obstruction of a ruptured chordae or a leaflet that has been torn apart or torn off. 3. Classic literature talks about two systemic emboli as the indications to go to the operating room immediately. Many of us are concerned about the patient who has first systemic embolization, and unless the patient has clear cut indications for surgery, you have to be very serious about that because those patients are at considerable risk for subsequent embolization. 4. Fungal endocarditis, clearly an indications for surgery. 5. The development of valve abscesses or myocardial abscesses, those patients need to go to the operating room.

# Acute Rheumatic Fever: Treatment

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- **All patients:** Benzathine Pen 1.2 x 10<sup>6</sup> U IM, or oral penicillin or erythromycin for 10 days
- **No Carditis or Mild Carditis**
  - Aspirin 50-100 mg/kg/d x 2-3 weeks, then ½ dose x 2-3 weeks, then taper
- **Moderate or severe carditis (CHF or at least moderate cardiomegaly on chest x-ray)**
  - Prednisone 2 mg/kg/d x 2-3 weeks, then ½ dose x 2-3 weeks, then taper (with addition of aspirin)
  - Digoxin, diuretics as needed
  - Bed rest
- **Chorea**
  - Phenobarbital or haloperidol

Rheumatic fever. The contrast to rheumatic fever in the past is that more and more patients are being seen from the middle or the upper-mid social classes, as opposed to the inner-city poor.

More changes with respect to rheumatic fever in recent years has been updating of the Jones Criteria of the diagnosis of rheumatic fever. The significant changes are that the Jones Criteria now applies only to the first attack of rheumatic fever, so that the minor criteria of previous rheumatic heart disease or acute rheumatic fever was removed. Another change was that a Streptococcal positive antigen test from the throat is acceptable as evidence of recent GAS. The major criteria remains carditis, polyarthritis, chorea, subcutaneous nodules, and erythema marginatum.

The minor criteria are really as before, now. Number one is arthralgia in the patient who does not have polyarthritis. Fever, as nonspecific as we can get. Number two is laboratory minor criteria of acute phase reactants, such as ESR or CRP, and prolonged P-R interval on the electrocardiogram. It has been pointed out that prolonged P-R interval does not predict a patient who will go on to develop carditis or long-standing heart disease. In order to utilize the Jones Criteria, we use one major and two minors or we use two majors. In either case, we must have evidence of an antecedent group A Streptococcal infection, such as a positive throat culture of rapid antigen test or elevated or rising Streptococcal antibody titers.

Polyarthritis is typical in rheumatic fever and is typically very painful. Pain in excess of what you clinically see, but you should see some of it. You have to see some objective features to polyarthritis. It is migratory, meaning that in the absence of anti-inflammatory therapy, it will stay within a joint one or two days and then leave that joint and move on elsewhere- usually involving the large joints; knees, hips, ankles, shoulder. Polyarthritis dramatically responds to aspirin, so that if we see such a patient and hospitalize them, the most important order to write is "No aspirin". If we are not sure of the diagnosis, we need to see what is going to happen, and just a little bit of aspirin can make it very difficult to figure out what is going on.

Carditis, myocarditis, or pericarditis, alone or in combination, are not rheumatic fever. Rheumatic carditis is valvulitis; meaning a murmur that you can hear. In the Jones Criteria, what is not believed is that echocardiographic evidence of mild mitral regurgitation is sufficient to put a patient in this category. It must be evidence of valvular involvement. There may be pericarditis, myocarditis may be present as well. Often there is all three involved, but valvulitis is the critical feature here. Typically, this is mitral insufficiency, it may be mitral and aortic. Less common is aortic insufficiency alone.

Sydenham's chorea is a form of acute rheumatic fever that occurs after the group A Streptococcal infection. It is a form of acute rheumatic fever that may be diagnosed without clear antecedent evidence of group A Streptococcal infection. By the time the months elapse between that infection and the onset of chorea, you can not find any more evidence by titer or by microbiologic means.

Treatment of rheumatic fever. All patients should receive either a Benzathine injection or 10 days of appropriate antibiotic therapy for group A Streptococci- even if you do not isolate it. Patients who have acute rheumatic fever without carditis, or with only mild carditis, can be managed with salicylates, the usual dose that is 50 to 100 mg/kg/d, although larger children probably should not get 100 per kilo because they may become toxic. So, for larger children I never go above 70 to 75 mg/kg/d. Although salicylates are useful for about two to three weeks, I then drop it by half for another two to three weeks, and then taper that off over another three to four weeks or so. Rheumatic activity really lasts a couple of months, and if you remove all the anti-inflammatory therapy too quickly, patients may have a rebound.

For patients who have moderate or severe carditis associated with rheumatic fever, and that is defined as the presence of congestive failure or at least moderate cardiomegaly on a chest x-ray, those patients will

# Infectious Myocarditis

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## ■ Clinical Features

- Wide range of severity
- Fever, fatigue, malaise, dyspnea, tachypnea, chest pain
- CHF, pulmonary edema, shock may develop

## ■ Neonates

- Feeding difficulties, listlessness
- Cardiac signs, respiratory distress
- Hepatosplenomegaly

## ■ Lab Features

- Cardiomegaly, CHF on chest x-ray
- EKG: highly variable including arrhythmias
- CK-MB elevation (also ESR, WBC elevation)
- Echocardiogram: cardiac dilatation, poor contractility

benefit from prednisone. For steroids, prednisone is commonly used, usually at 2 mg/kg/d for two to three weeks, then cut that dose by half for another two or three weeks, and around that point as you continue to taper, you add aspirin. You want to keep them on some sort of anti-inflammatory therapy, again, for somewhere in the two to three month range in total.

Treatment for Sydenham's chorea. Phenobarbital is used because it is pretty well tolerated.

Pathogenesis of rheumatic fever. There is published evidence that certain populations are predisposed, there are certain HLA markers that are over-representative in rheumatic fever patients. Environmental conditions were listed because prior to the last decade, people lived in appalling conditions, were receiving poor medical care, and having poor nutrition. Those things all seem to predispose to rheumatic fever.

One third of rheumatic fever patients will be called symptomatic pharyngitis, they were seen by a doctor, and either were not appropriately treated or did not take the therapy. Another third of them we call symptomatic pharyngitis, never saw a doctor, and a third of them really can not recall a symptomatic pharyngitis that occurred two, three, four weeks earlier prior to the event. They probably still have a rheumatic fever.

Infectious myocarditis often follows other manifestations of infections with the same agents, with a very wide range of severity. Some patients simply have fever, fatigue, malaise, a little dyspnea, tachypnea, and chest pain. These are features that should cause us to think about myocarditis as a possible cause of the illness here. Patients, on the other hand, may have pulmonary edema or shock with acute myocarditis.

In the neonates, they may present a feeding difficulty, listlessness. Cardiac signs or respiratory distress and significant hepatosplenomegaly. The laboratory features of acute myocarditis are, of course, cardiomegaly and congestive failure on x-ray. EKG findings are highly variable, including arrhythmias. Cardiac muscle enzymes may be elevated, and sed rates and white counts are also elevated. Interestingly, cardiac enzymes are usually elevated. Echocardiogram will show poor contractility and dilated chambers.

# Myocarditis

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## ■ Microbial Etiologies

- Viral agents: enteroviruses (especially Coxsackie B1-5), adenovirus, HIV, influenza, measles, mumps, rubella, VZV, EBV
- Bacterial agents: *B. burgdorferi*, *N. meningitidis*, *H. influenzae*, *S. typhi*  
Toxin-mediated: *C. diphtheriae*, *S. pyogenes*, *S. aureus*
- Parasites: *Trypanosoma cruzi* (Chaga's), *Leishmania donovani*
- Others: *Blastomyces*, *Histoplasma*, *Coccidioides*, *Mycoplasma*, *Rickettsiae*, *Chlamydiae*

The agent of myocarditis is clearly a viral agent. Particularly the enterovirus, far and away the most common agent, particularly Coxsackie B negative, and a large variety of other viruses that can reportedly cause myocarditis. There are some bacterial agents. Lyme disease, which we will hear about later on, and some of the classical agents like meningitidis, H. flu and typhoid can cause a myocarditis. It is more common for us to see toxin-mediated myocarditis than these other bacterial agents.

For parasitic causes, the most important of which is Chagas's disease, which can cause very severe chronic myocarditis, and there are some rarer agents as well.

# Infectious Myocarditis: Diagnostic Methods

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- Recovery of agent on biopsy or autopsy
- Detection of agent by tissue PCR or antigen detection (visualization of Chaga's agent in blood or tissue)
- Recovery of agent from other site: Stool, throat, viral cultures
- Serologic evidence: Elevated IgM or rising IgG titers (difficult for Coxsackie)

We try to diagnosis these by endomyocardial biopsy or, unfortunately, autopsy. By recovering an agent or demonstrating an agent by PCR or antigen detection, you sometimes will be able to see the Chagas agent in blood or tissue. You may recover other agents from other sites, such as in stool, the throat, or viral cultures. You may find serologic evidence, although this is more difficult in Coxsackie infections.

# Viral Myocarditis: Epidemiology

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- Predominately Coxsackie virus-associated
- Fecal-oral spread, with fecal excretion for several weeks
- Summer - fall peaks of infection in temperate areas
- Humans are the only known hosts
- Incubation period: 3-6 days
- Coxsackie B3 and B4 are myocardial-tropic, but recognizable myocarditis is relatively rare
- Neonates are particularly susceptible (lack of maternal antibodies)

# Kawasaki Disease: Diagnostic Criteria

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Kawasaki disease. The classic criteria are there for you all to see. Classic Kawasaki disease is swollen red hands and feet. The rash is primarily on the trunk and with perineal accentuation. The rash takes a variety of forms.

- Fever for >5 days (usually >102 F)
- At Least Four of Five Features
  - Bilateral conjunctival injection (bulbar, non-purulent)
  - Cervical adenitis (unilateral >1.5 cm diameter, non-fluctuant)
  - Rash (truncal, perineal accentuation, polymorphous but non-vesicular)
  - Inflamed oral mucosae (fissured lips, strawberry tongue)
  - Hands and feet inflammation (periungual peeling around 14-21 days)
- No alternate diagnosis
- Fever plus 3/5 criteria are diagnostic when coronary abnormalities are present

# Kawasaki Disease: Epidemiology

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- Age: mean = 18-24 months, 80% <5 year old
- Gender: male-to-female ratio is 3:2
- Race: higher rates in Asians (even after emigration)
- Geography: world-wide, unrelated to climate, altitude

Boys clearly outnumber girls and are at higher risk for serious complications of coronary artery disease.

# Kawasaki Disease: Laboratory Features

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- Acute phase reactants: WBC, ESR, CRP, alpha, antitrypsin
- Others: anemia, thrombocytosis, pyuria
- Echocardiogram
  - Coronary aneurysms, especially proximal, beginning on day 8-10
  - Myocarditis                      acutely
  - Pericardial effusion              acutely
  - Mitral regurgitation              acutely

Acute phase reactants are useful, other features are seen of course. Echocardiographically, early on one sees myocarditis. In fact, it has been said that almost all cases have myocarditis. So, that is present acutely. Pericardial effusions and mitral regurgitation may be present acutely. Later problems such as coronary aneurysms begin to be seen around the tenth day of illness and peak out at around three to four weeks.

# Kawasaki Disease: Differential Diagnosis

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- Measles
- Scarlet fever
- Drug reactions
- Febrile viral exanthems
- Staphylococcal scalded skin
- Juvenile rheumatoid arthritis
- Toxic shock syndrome
- Leptospirosis
- Mercury poisoning

# Kawasaki Disease: Treatment

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- Treatment should be initiated within 10 days of illness onset
- **Acute Phase Treatment:** IVIG 2 gm/kg, plus aspirin 80-100 mg/kg/d until the 14th illness day
- **Convalescent Phase Treatment:** Aspirin 3-5 mg/kg/d x 6-8 weeks.
- **For patients with coronary abnormalities:** prolonged aspirin, 3-5 mg/kg/d (with Coumadin for severe coronary abnormalities)

The treatment for Kawasaki disease should be given ideally within 10 days of the onset of illness.

# Kawasaki Disease: Complications

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## ■ Early Complications

- Myocarditis (CHF possible)
- Peripheral ischemia (young infants)
- Pericardial effusion
- Hydropic gallbladder

## ■ Convalescent Stage (weeks-months)

- Coronary aneurysms
- Coronary thrombosis within aneurysm

## ■ Late Stage (months-years)

- Coronary stenosis and ischemia
- Coronary thrombosis and ischemia
- Valvular insufficiency (rare)

# Kawasaki Disease: Prognostic Factors for Coronary Complications

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- Boys
- <1 year old
- Prolonged fever and/or recurrent fever
- Other features of cardiac involvement (myocarditis, arrhythmias)
- Thrombocytopenia