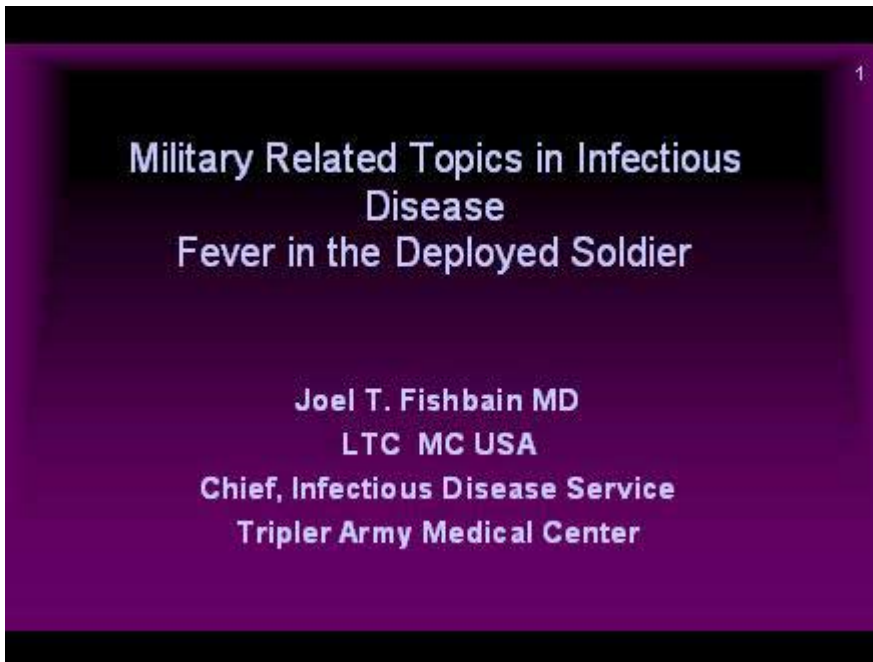


FEVER IN THE DEPLOYED SOLDIER

Joel T Fishbain, LTC, MC, USA, TAMC

Slide 1



Welcome to the Infectious Disease Service Presentation of Fever in the Deployed Soldier. This lecture could also be entitled Fever in the Returning Traveler.

Slide 2



Fever and deployment should be evaluated very carefully with information that is easily obtainable at the physician's or care provider's visit. Epidemiology is probably the single most important piece of information that you can obtain from an individual or patient.

- Where are you or the individual located in the world? What infectious diseases are endemic in your theater of operations? This information should be obtained prior to deployment.

- Is the individual from a city or rural area, or have they traveled to cities or rural areas? Exposures are very different in some countries.
- Was there any food or water exposure that might be unusual or uncontrolled?

- Were there any animal exposures? Even minimal animal exposure can put some individuals at risk for rabies.
- Does the individual have any new pets after returning from a deployment or travel?
- How long has the individual traveled, or how long have they been deployed?
- Did the individual recently arrive from the United States? In this case other endemic diseases in the U.S. would have to be included in the differential diagnosis of your patient's problem.
- Was there any illness while traveling or any illness upon return from traveling?
- Are there others who are also ill, suggestive of food borne illness?

Slide 3

Common Regardless of Travel

Don't forget the common problems despite travel.

- » URI's
- » Pneumonia
- » Sinusitis
- » Cellulitis

One must not forget that there are many common problems that will still occur during an individual's travel. Upper respiratory infections, pneumonia, sinusitis and even cellulitis will still occur, and the common pathogens should still be considered when evaluating an individual for fever and deployment.

Slide 4

Diagnosis & Incubation Period

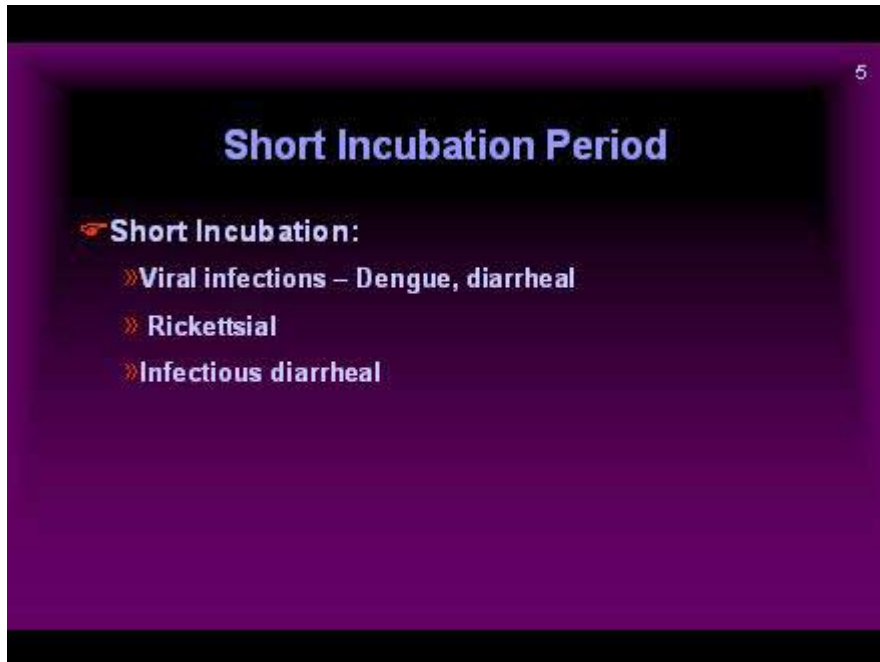
Specific etiologies resulting in illness are best approached by examining a differential diagnosis based on incubation periods

- » Especially in illness after returning from deployments

Examination and careful differential diagnosis are best approached by examining the specific etiologies of the individual's illness. This differential diagnosis can be shortened, depending on the incubation period suspected for the illness. This is especially true in illness after returning from deployment, since the short incubation period infections (usually less than 7 days) can be excluded when you evaluate a patient who's been back for

more than 30 days. This break down will assist in shortening the differential diagnoses of individuals returning from travel with fevers.

Slide 5



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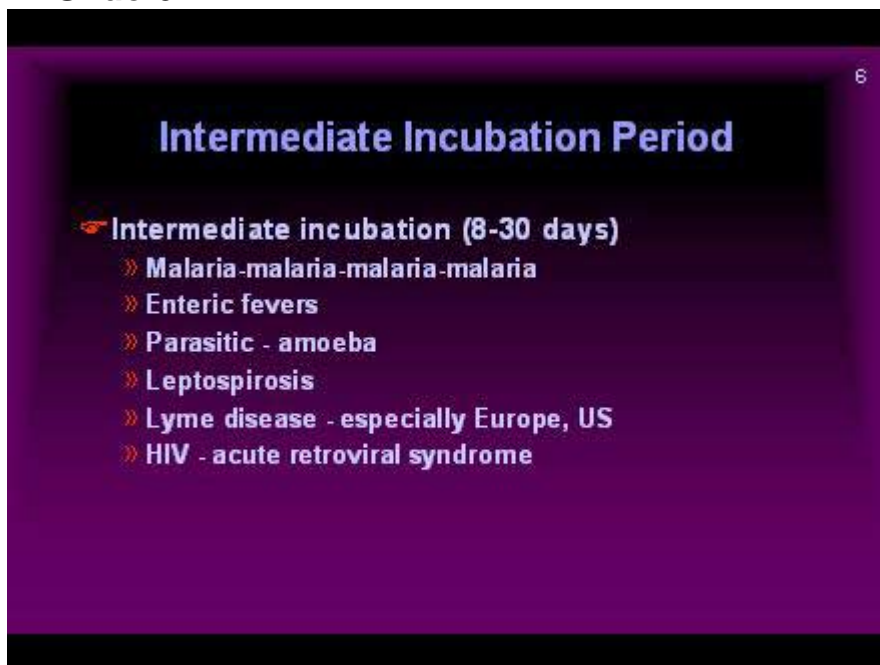
Short Incubation Period

Short Incubation:

- » Viral infections – Dengue, diarrheal
- » Rickettsial
- » Infectious diarrheal

Short incubation period infections include those with incubation periods of less than 7 days. These include viral infections such as dengue fever and viral gastroenteritides, the Rickettsial diseases (which are extremely important since they can be life threatening and very difficult to diagnosis without clinical suspicion) and the bacterial infectious diarrheal diseases. These are important because any of these short versus medium incubation period diseases must be included during a long deployment.

Slide 6



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Intermediate Incubation Period

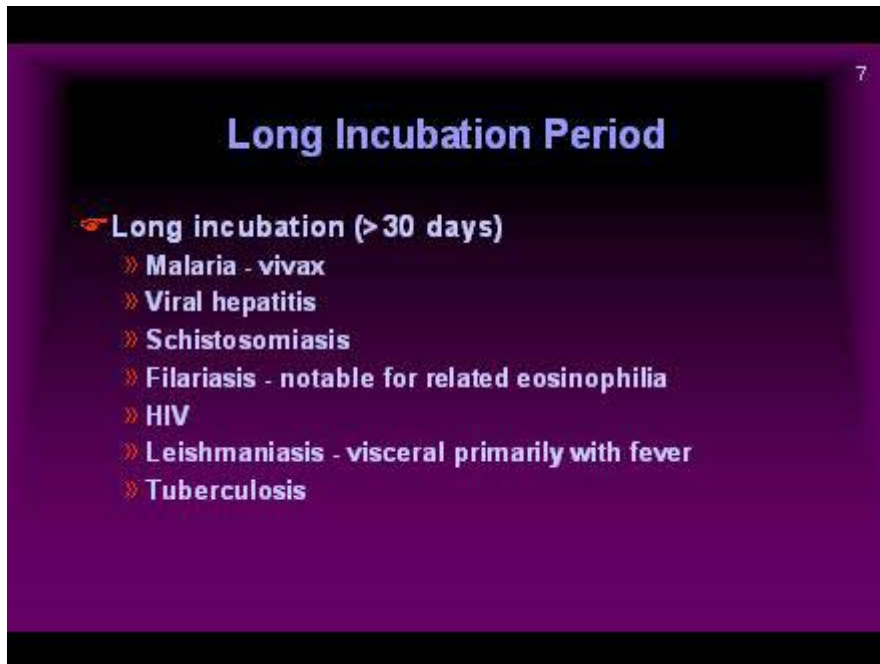
Intermediate incubation (8-30 days)

- » Malaria-malaria-malaria-malaria
- » Enteric fevers
- » Parasitic - amoeba
- » Leptospirosis
- » Lyme disease - especially Europe, US
- » HIV - acute retroviral syndrome

The intermediate incubation period diseases are important because of the first one listed here. Malaria must absolutely be excluded very carefully prior to moving on to some of the other diseases in this list. Enteric fever just refers to some of the bacterial diarrheal diseases that are associated with fever, abdominal pain and many times bacteremia. Parasitic diseases such as amebiasis, either colitis or extra-intestinal amebiasis, are included. Leptospirosis is important because it is a great mimicker of other diseases and can be difficult to diagnose

unless a clinical suspicion is encountered. Lyme disease, especially in Europe and from the United States, must be included in those individuals who have recently returned from the United States prior to deployment. One cannot forget the acute retroviral syndrome, which is typically called mono-like illness. Many health care providers will ignore this in the different diagnosis. A history of exposure or high-risk behavior should be explored when evaluating patients who may have the acute retroviral syndromes.

Slide 7



7

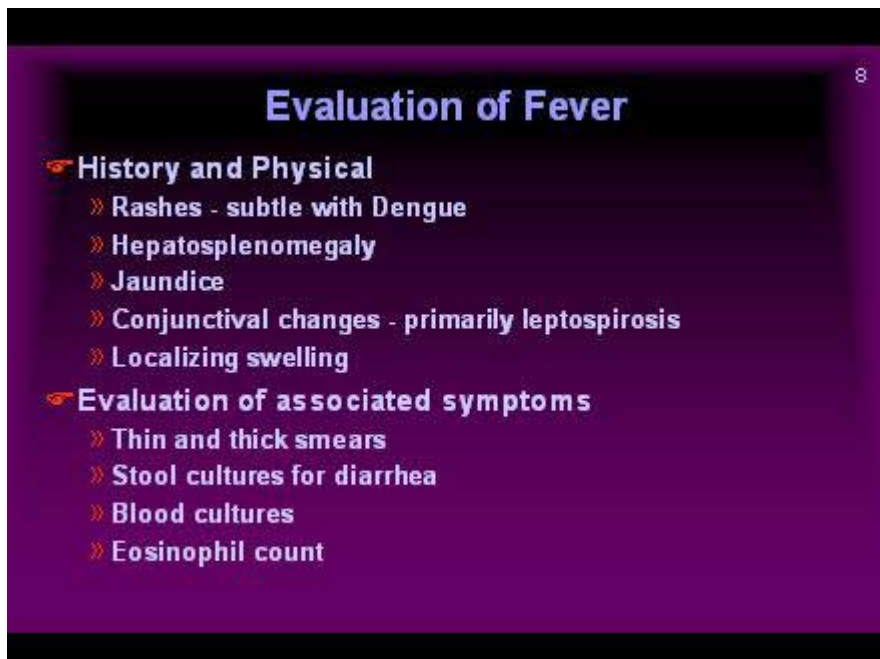
Long Incubation Period

- » Long incubation (>30 days)
 - » Malaria - vivax
 - » Viral hepatitis
 - » Schistosomiasis
 - » Filariasis - notable for related eosinophilia
 - » HIV
 - » Leishmaniasis - visceral primarily with fever
 - » Tuberculosis

Now, finishing with the long incubation period infections: Vivax malaria can recur any time within a year after leaving the endemic area, and this is especially true for those individuals who do not receive terminal prophylaxis with primaquine. Viral hepatitis can present with fever occasionally. Each of the viral hepatitises, of course, has a different incubation period. Schistosomiasis typically does not have fever associated with late complications and early infection is associated with Katayama fever. Filariasis is

most notable for its relationship with eosinophilia. Any returning traveler or soldier who develops fever and eosinophilia should undergo a thorough evaluation for filarial infections. HIV infection can present any time in the life span of the individual after infection, and typically will not present with fever later on. Only the acute retroviral syndrome is classically associated with fever. However, any of the opportunistic infections may be associated with fever. Visceral leishmaniasis is very uncommon in the American soldier or sailor, however it should be considered in the differential diagnosis of patients with fever, hepatosplenomegaly and bone marrow suppression. Tuberculosis can present any time after infection, but the highest risk for active disease is within the first two years following infection.

Slide 8



8

Evaluation of Fever

- » History and Physical
 - » Rashes - subtle with Dengue
 - » Hepatosplenomegaly
 - » Jaundice
 - » Conjunctival changes - primarily leptospirosis
 - » Localizing swelling
- » Evaluation of associated symptoms
 - » Thin and thick smears
 - » Stool cultures for diarrhea
 - » Blood cultures
 - » Eosinophil count

Evaluation of fever will require a detailed history and physical examination, and then a subsequent evaluation of any associated symptoms. A careful evaluation for rashes can be very useful in restricting your differential diagnosis. The erythroderma of dengue can be very subtle and should be looked for by pressing the palm of your hand on the individual's chest, looking for blanching that is more pronounced than you would expect for a normal individual.

Hepatosplenomegaly should be carefully sought after on your

physical exam. The appearance of jaundice would obviously direct your evaluation toward liver diseases. Look carefully at both conjunctiva for any changes suggestive of leptospirosis, and look over the arms and legs for localized swelling known as the Calabar swelling, which is associated with filarial infections. Appropriate studies would be indicated, especially for patients who returned from endemic areas for malaria. Thin and thick smears would be particularly useful. Remember that one negative smear does not exclude the diagnosis of malaria. Stool cultures for diarrhea can be appropriate in the acute diarrheal setting, but chronic diarrhea is rarely caused by bacterial infections. Blood cultures are always appropriate in a patient with a fever, and a careful search for eosinophilia can help you decide if the patient has a tissue based parasite infection.

Slide 9

Slide 9 is a presentation slide with a purple background and white text. The title is "Evaluation of Fever (2)". The content is organized into a list of points, each preceded by a right-pointing arrowhead. The points are: "Further work-up as indicated by history and physical", "Work-up may depend on prior immunizations, PPD history.", "RPR and HIV depending on sexual history, blood exposure.", and "Liver enzyme evaluation useful". The last point has two sub-points: "Rickettsial diseases" and "Hepatitis". A small number "9" is in the top right corner.

Evaluation of Fever (2)

- Further work-up as indicated by history and physical
 - » CT for hepatomegaly
 - » Amoeba titers
- Work-up may depend on prior immunizations, PPD history.
- RPR and HIV depending on sexual history, blood exposure.
- Liver enzyme evaluation useful
 - » Rickettsial diseases
 - » Hepatitis

Further work-up as indicated by your history and physical can be directed based on your results. CT scans for hepatomegaly may reveal liver abscess, in which case amoebae titers would be appropriate. Work-up may also depend on whether the prior immunizations were appropriate and up to date and what was the patient's prior PPD history compared to their PPD results now. An RPR and HIV may be indicated depending on the sexual history, and blood and body fluid exposure history. Liver enzyme elevation is extremely useful in determining if the patient has a systemic

illness such as rickettsial diseases or acute hepatitis.

Slide 10

Slide 10 is a presentation slide with a purple background and white text. The title is "Treatment". The content is organized into a list of points, each preceded by a right-pointing arrowhead. The points are: "Depends on risks of certain diseases", "Empiric therapy of dysentery", "Empiric therapy for enteric fevers", "If CT positive for liver abscess, therapy for amoeba", and "Empiric doxycycline for suspected rickettsial diseases". A small number "10" is in the top right corner.

Treatment

- Depends on risks of certain diseases
 - » Patient on prophylaxis for malaria may need empiric therapy despite negative smears.
- Empiric therapy of dysentery
- Empiric therapy for enteric fevers
- If CT positive for liver abscess, therapy for amoeba
- Empiric doxycycline for suspected rickettsial diseases

The treatment of the patient's febrile illness really depends on risk factors of certain diseases. An individual returning from an endemic area for malaria may need empiric therapy for malaria despite being on prophylaxis and despite negative smears. This is because the prophylactic medication may have failed, as it does in roughly 5% to 10% of cases (depending on the agent used). Also, prophylactic medication can suppress this parasite, thus making it difficult

to find them on your smears. Empiric therapy for dysentery is always appropriate. Your deploying medical officer should determine an appropriate antibiotic for this. [Note: See module entitled, "Travel Medicine for the Deploying Soldier"] Empiric therapy for enteric fevers is the same as that for dysentery. If a CT is positive for a liver abscess, therapy for amoeba empirically prior to the return of the amoeba titer result is definitely appropriate. Don't forget that empiric doxycycline for any of the suspected rickettsial diseases is critical since some of these rickettsial diseases are life threatening. It is highly unlikely that you will get a specific diagnosis prior to the individual returning from their deployment.

Slide 11

Malaria

- Two major forms
 - Falciparum - associated with very high levels of parasitemia
 - Fatal disease if untreated
 - No hypnozoite stage (persistent liver stage)
 - Vivax - milder form with lower parasitemia
 - Hypnozoite stage resulting in recurrences if terminal prophylaxis not given with primaquine

Now let's talk about some specific illnesses. There are two major forms of malaria. Falciparum malaria is associated with very high levels of parasitemia and is a very fatal disease in those with no underlying immune response to the infection. It must be treated immediately if suspected. There is no hypnozoite stage (or the persistent liver stage). Any malarial infection is unlikely to be falciparum after four weeks post-return from an endemic area. Vivax malaria is a much more mild form of malaria with much lower parasitemia. There is a hypnozoite stage to this

disease, and it does result in recurrences if terminal prophylaxis is not given with primaquine.

Slide 12

Malaria and Epidemiology

- Know the epidemiology before, during, and after travel
- Chloroquine sensitive malaria
 - Egypt
 - Saudi Arabia
 - Turkey
 - Iraq
 - UAE
 - Syrian Arab Republic
 - Central America west of Panama Canal
 - Haiti and Dominican Republic

Know the epidemiology before, during and after travel. This is especially true for malaria since we really have three different forms or sensitivities of malaria at this point in time. There is still chloroquine sensitive malaria in certain parts of the world, and I have listed them here for you. As a case in point, all of the soldiers deploying to Haiti during that operation were successfully receiving chloroquine prophylaxis.

Slide 13

Chloroquine & Mefloquine

- ☞ Chloroquine resistant malaria
 - » Everywhere else!!!
- ☞ Mefloquine resistance
 - » Thailand bordering Cambodia and Myanmar
 - » ??Laos, Vietnam, etc.

Chloroquine resistant malaria should be considered everywhere else, and therefore mefloquine should be used for chemoprophylaxis. However, mefloquine resistance has been reported in the areas of Thailand, Cambodia and Thailand-Myanmar border, in which case we've been using doxycycline for chemoprophylaxis. We don't have a lot of information on Laos and Vietnam. It is suspected that there may be mefloquine resistance in these areas, in which case doxycycline should be used for our soldiers as well.

Slide 14

Malaria - Common Problems

- ☞ Compliance with prophylaxis
 - ☞ Prophylaxis failure resulting in negative smears and malaria that may be difficult to diagnose
- ☞ Wrong medication used for prophylaxis
- ☞ Forgetting terminal prophylaxis
- ☞ Excluding malaria with single smear - never rules out malaria adequately
- ☞ Abdominal complaints misleading clinicians
- ☞ Inexperience with diagnosis and therapy

I would like to discuss some common problems associated with malaria. Compliance with chemoprophylaxis; it must be assumed that an occasional soldier or sailor will fail to take their appropriate medications. Prophylaxis failure results in negative smears in malaria that may be difficult to diagnose. This is particularly important in individuals who do take their malaria prophylaxis, but have a prophylaxis failure. Diagnosing the disease can be very difficult since the parasites will still be suppressed by the use of the medication. Picking the wrong medication for deployment can

happen because the exact epidemiology was not reviewed prior to deployment. Forgetting primaquine terminal prophylaxis can result in Vivax malaria occurrences. Malaria cannot be excluded with a single smear; this never rules out malaria adequately. Ignoring other symptoms such as abdominal complaints, which can be the first signs of malaria, are quite common in acute malarial infection.

Slide 15

15

Dengue Fever

- ◆ Very short period of 2-7 days
- ◆ Clinical presentation is marked by fever, headache (retro-orbital), severe myalgias/arthralgia (breakbone fever) and a blanching erythroderma
- ◆ Some patients have a biphasic nature to their fever pattern which recurs when the rash appears
- ◆ Self-limited benign illness first time

Dengue fever is a very common mosquito-borne viral illness in endemic areas. It has a very short incubation period of 2-7 days and clinically presents with high fever, headache which is retro-orbital in character, severe myalgias and arthralgias (thus the name break bone-fever), and a blanching erythroderma. Some patients have a biphasic nature to their fever pattern, which recurs when the rash appears. It is a self-limited benign illness the first time you get this infection.

Slide 16

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Dengue Fever (2)

- ☞ Common laboratory findings include:
 - » neutropenia
 - » thrombocytopenia
 - » transaminase elevation
- ☞ Don't be confused by Dengue Hemorrhagic Fever, Dengue Shock Syndrome
 - » These patients have prior Dengue fever infections
 - » Hemoconcentration and severe illness are the features
- ☞ Diagnosis made clinically and with IgM testing after fever resolution

There are some common tip-offs to the diagnosis of dengue fever. Common laboratory findings include neutropenia, thrombocytopenia and transaminase elevation. Don't confuse dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) with dengue fever. Patients with DHF and DSS have had prior dengue fever infections. The hallmark of these illnesses is hemoconcentration and severe illness. Diagnosis of dengue fever is made clinically with IGM testing after the fever resolves.

Slide 17

Rickettsial Disease - Epi

- World wide distribution of various types
 - Spotted fever group - RMSF, Queensland tick typhus, Rickettsialpox
 - Thyphus group - epidemic typhus, scrub typhus
- Vectors vary from ticks to lice to fleas to mites
- Almost all rickettsia infect endothelial cells (except Ehrlichiosis and Q fever) and every organ has endothelial cells
 - Helps to think of these as systemic infections with multiple organ system involvement

The rickettsial diseases are very important to discuss when discussing deployment. There is a worldwide distribution of various types of rickettsial diseases, which can be divided into the spotted fever group and the typhus group. Rocky Mountain spotted fever is probably the most famous of the spotted fever groups, but this is really one of many forms. Each country can have its own form of spotted fever group rickettsial infections. The two important diseases of the typhus group are epidemic and scrub typhus. The vectors vary from ticks, lice, fleas, and mites. Almost all

rickettsial diseases infect endothelial cells, and every organ has endothelial cells. That's the real tip-off to helping you think of these as systemic infections with multiple organ system involvement. That is the key to understanding rickettsial diseases.

Slide 18

Rickettsial Disease - Presentation

- Fever and rash in some
- Eschar at site of infection/inoculation in some
- Common themes in laboratory findings
 - Neutropenia
 - Thrombocytopenia
 - Transaminase elevation
 - Aseptic meningitis
 - Renal and pulmonary involvement in severe cases

Fever and rash do occur in some of the rickettsial diseases, but not all. An eschar at the site of infection or inoculation also occurs in some, but not all. There are some common themes and laboratory findings that may help you decide whether or not a patient does have a rickettsial illness. Neutropenia and thrombocytopenia are very common. Transaminase elevation just confirms the systemic nature of the infection. Aseptic meningitis has been reported, and in severe cases, renal and pulmonary involvement may also be a tip-

off to the nature of the infection.

Slide 19



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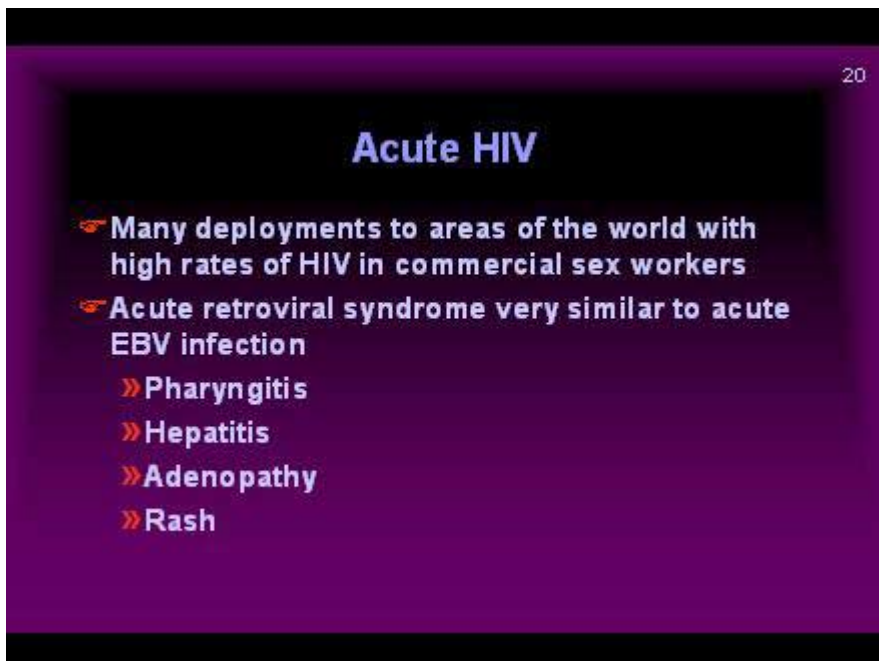
Rickettsial Disease Rule of Thumb

- » You will never make a definitive diagnosis before the patient recovers with treatment or dies
- » High index of suspicion with good understanding of epidemiology of deployment important for diagnosis
- » Empiric therapy with doxycycline with a VERY rapid improvement after only a few doses
- » Save acute and convalescent sera for testing if possible and send to the CDC

So when discussing rickettsial diseases, what rules of thumb can be advised? Remember that you will NEVER make a definitive diagnosis before the patient recovers with treatment or possibly dies. You must have a high index of suspicion and a very good understanding of the epidemiology of deployment, because that's very important for diagnosis. Empiric therapy with doxycycline with a VERY RAPID improvement after only a few doses can be diagnostic for any of the rickettsial diseases. Saving acute and convalescent sera for testing if possible when sending to the CDC will only

confirm your suspicions, but again, you won't have a definitive diagnosis prior to institution of therapy.

Slide 20



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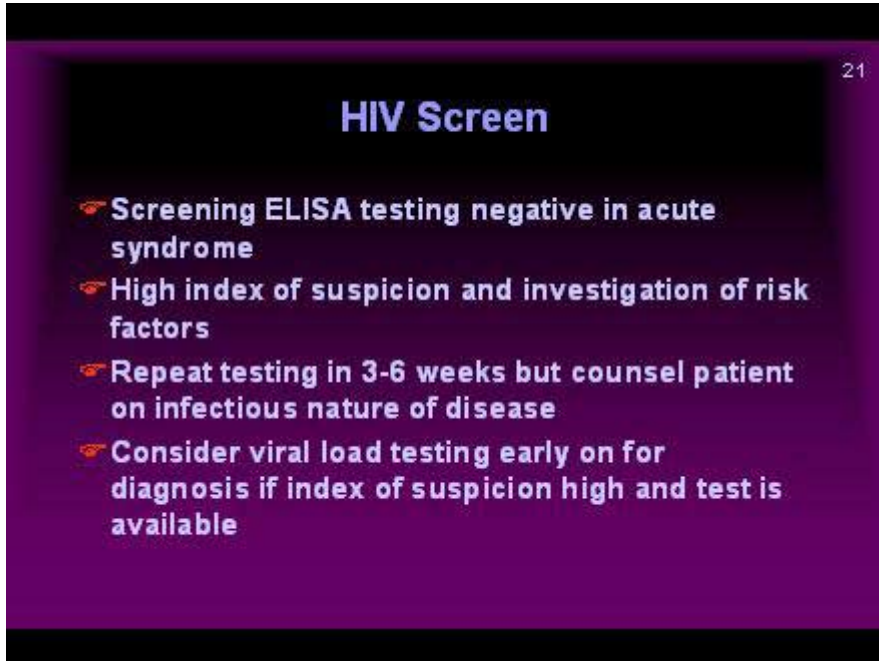
Acute HIV

- » Many deployments to areas of the world with high rates of HIV in commercial sex workers
- » Acute retroviral syndrome very similar to acute EBV infection
 - » Pharyngitis
 - » Hepatitis
 - » Adenopathy
 - » Rash

Acute HIV infection is very important to understand as it can mimic many other infections. There are many deployments to areas of the world with high rates of HIV infection in commercial sex workers; so understanding your soldiers and their possible exposures will help you. The acute retroviral syndrome is very similar to acute Epstein-Barr virus infection or mononucleosis. Patients have pharyngitis, hepatitis, adenopathy, rash and fever. It can be very difficult to distinguish. So any individual who has a possibility of exposure and presents with

mono-spot negative "acute mono" should undergo a thorough evaluation for acute retroviral syndrome.

Slide 21



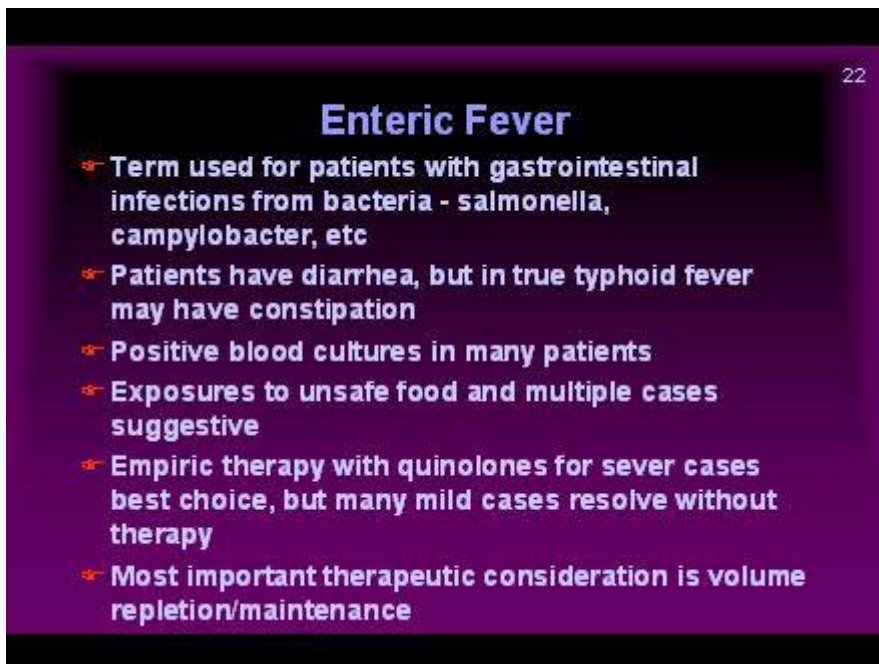
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HIV Screen

- Screening ELISA testing negative in acute syndrome
- High index of suspicion and investigation of risk factors
- Repeat testing in 3-6 weeks but counsel patient on infectious nature of disease
- Consider viral load testing early on for diagnosis if index of suspicion high and test is available

Screening ELISA testing is frequently negative in the acute syndrome, so a negative ELISA does not exclude HIV. A high index of suspicion and investigation of risk factors may help lead you toward this diagnosis. Repeat testing in 3-6 weeks is critical, but you must counsel the patient on the infectious nature of his or her disease. Consider viral load testing early on for diagnosis if the index of suspicion is very high and the test is available to you.

Slide 22



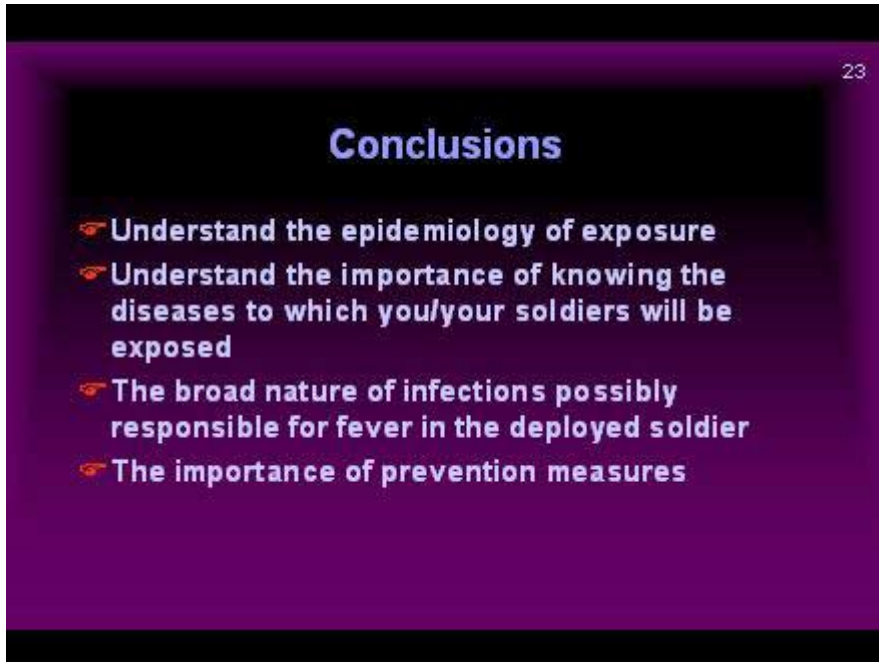
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Enteric Fever

- Term used for patients with gastrointestinal infections from bacteria - salmonella, campylobacter, etc
- Patients have diarrhea, but in true typhoid fever may have constipation
- Positive blood cultures in many patients
- Exposures to unsafe food and multiple cases suggestive
- Empiric therapy with quinolones for severe cases best choice, but many mild cases resolve without therapy
- Most important therapeutic consideration is volume repletion/maintenance

Enteric fever is a generic term used for patients with gastrointestinal infections from bacteria such as salmonella and campylobacter. Patients have diarrhea, but in true typhoid fever, they may actually have constipation as their presenting sign or symptom. Positive blood cultures are common in many patients. Exposures to unsafe food and multiple cases are highly suggestive of enteric fevers. Empiric therapy with quinolones for severe cases may be the best choice, but many mild cases resolve without therapy.

Slide 23



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Conclusions

- Understand the epidemiology of exposure
- Understand the importance of knowing the diseases to which you/your soldiers will be exposed
- The broad nature of infections possibly responsible for fever in the deployed soldier
- The importance of prevention measures

In conclusion, I hope that this lecture has given you some understanding of how important it is to be aware of the epidemiology of exposure, the importance of knowing the diseases which you and your soldiers will be exposed, the immense broad nature of infections possible for fever, and the importance of preventive measures.

Slide 24



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The End

This concludes the Infectious Disease Services presentation of Fever in the Deployed Soldier.