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The Crux

BIMONTHLY FORUM FOR THE LABORATORIANS

CONTENTS

Editorial

The **Middle East respiratory syndrome coronavirus (MERS-CoV)** is a novel coronavirus (nCoV) first reported on 24 September 2012 on ProMED-mail by Egyptian virologist Dr. Ali Mohamed Zaki in Jeddah, Saudi Arabia. He isolated and identified a previously unknown coronavirus from the lungs of a 60-year-old male patient with acute pneumonia and acute renal failure. Dr. Zaki then posted his findings on ProMed-mail. MERS-CoV is the sixth new type of coronavirus like SARS (but still distinct from it and from the common-cold coronavirus). The Middle East Respiratory Syndrome (MERS) that emerged in Saudi Arabia last year is unlikely to cause a SARS-like epidemic because it is not spreading as easily, scientists said earlier.

In the fullest clinical analysis yet of the new virus, British and Saudi researchers said that while there are many similarities between MERS and severe acute respiratory syndrome (SARS) — which emerged in China in 2002 and killed around 800 people worldwide — there are also important differences.

The MERS coronavirus, which can cause coughing, fever and pneumonia, emerged last year and has spread from the Gulf to France, Germany, Italy, Tunisia and Britain. The World Health Organization (WHO) puts the latest global toll at 45 deaths from 90 laboratory-confirmed cases. The WHO issued its travel guidance earlier for pilgrims going to the annual haj in Saudi Arabia and said the health risk posed by the MERS virus was "very low."

"It is very unlikely any epidemic will ensue. The public needs to be reassured," he told Reuters. "MERS is unlikely to spread as rapidly, and therefore also unlikely to kill as many people [as SARS]." It has been said that MERS was first identified 15 months ago and there have been 90 cases reported so far. SARS, spread far more rapidly, infecting more than 8,000 people between November 2002 and July 2003. An earlier study of how the MERS virus infects people found that the receptors it binds to are common in the lungs and lower respiratory tract but not in the nose, throat and upper respiratory tract. Some experts think this is why MERS is not currently spreading easily from one person to another. The study found that MERS killed around 60 per cent of the patients it infected who also had other underlying illness such as diabetes and heart disease.

The vast majority of MERS cases have been in Saudi Arabia or linked to people who contracted the virus there. As with SARS, MERS patients had a wide spectrum of symptoms. Most of those admitted to hospital had fever, chills, cough, shortness of breath and muscle pain. A quarter also had gastrointestinal symptoms, including diarrhoea and vomiting. But unlike with SARS, most MERS cases were in people with underlying chronic medical conditions including diabetes, high blood pressure, heart disease and chronic renal disease. A study by French researchers earlier said MERS had not reached pandemic potential and may just die out.

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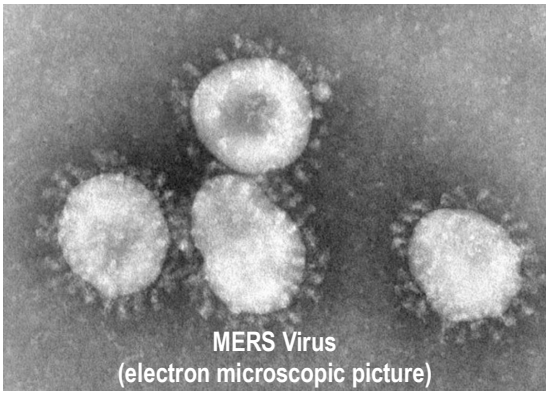
Editorial

The majority of infections have been in Saudi Arabia, although some infected people lived in or traveled to Jordan, Qatar and the United Arab Emirates. Among people admitted to the hospital with MERS, the most common symptoms were fever (98 %), chills (87 %t), cough (83 %) and shortness of breath (72 %). Some patients also reported gastrointestinal symptoms, including diarrhea and vomiting. Unlike SARS, which tends to affect younger and healthier people, MERS appears to mainly infect people with underlying chronic conditions. Ninety-six percent of people with MERS in the study had a chronic condition such as diabetes, high blood pressure, heart disease or kidney disease.


MERS Virus
(electron microscopic picture)

In those it does infect, MERS progresses rapidly, leading to death a week earlier, on average, compared with SARS, the researchers said. 60% of people with chronic illnesses who contracted MERS died, compared with just 1 % of people with chronic illnesses who contracted SARS.

The high death rate seen with MERS (50 %) may be because researchers are, so far, only picking up the very severe cases of illness. Many more people may have caught MERS, but do not show symptoms, the researchers said.

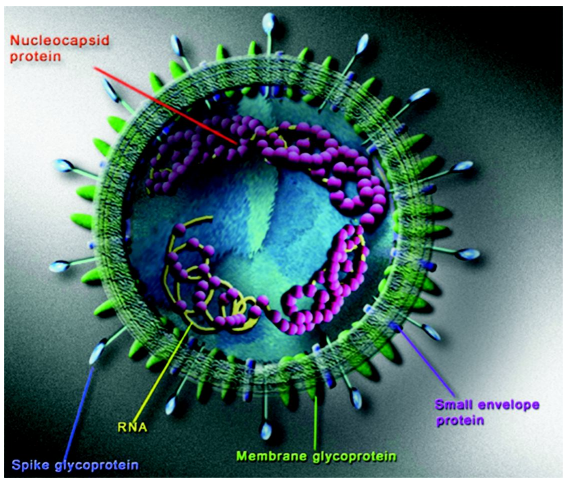
The researchers said rapid and accurate tests to diagnose the disease are urgently needed. And more studies are needed to determine the scope of the outbreak, as well as risk factors for infection, and factors that might predict which patients are most likely to die from the infection, the researchers said.

The **"DISEASE DIAGNOSIS"** segment discusses SARS/MERS in great length as treatment regimen and clinical features (excepting degree of respiratory tract involvement) are more or less the same. **"INTERPRETATION"** segment outlines value Maturation index in Pap's Smear; while **"TROUBLESHOOTING"** portion discusses FOBT in ample detail for you. **"BOUQUET"** is definitely lurking within!

DISEASE DIAGNOSIS

SARS (Corona Virus- CoV & Novel Corona Virus -NCoV)

Severe acute respiratory syndrome (SARS) is a serious, potentially life-threatening viral infection caused by a previously unrecognized virus from the Coronaviridae family, the SARS-associated coronavirus (SARS-CoV). Since the 2002-2003 outbreak of SARS, which apparently began in southern China but eventually involved more than 8000 persons worldwide, global efforts have virtually eradicated SARS as a threat.



Essential update:

Novel coronavirus potentially transmissible between humans after prolonged contact

According to the World Health Organization (WHO), it is possible for novel coronavirus, a new coronavirus that has killed at least 18 people in the Middle East and Europe, to be passed between humans, but only after prolonged contact. So far, however, there is no evidence that the virus is able to sustain generalized transmission in communities, a scenario that would raise the specter of a pandemic. The virus first emerged in Saudia Arabia in 2012, but cases have also been recorded in Britain and France among people who had recently been in the Middle East. To date, a total of 34 cases worldwide have been confirmed by blood tests. Although no specific vaccine or medication is currently available for novel coronavirus, patients have been responding to treatment.

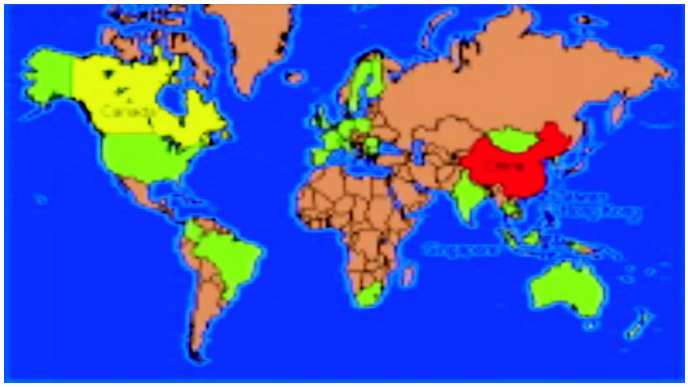
Background

Severe acute respiratory syndrome (SARS) is a serious, potentially life-threatening viral infection caused by a previously unrecognized virus from the Coronaviridae family. This virus has been named the SARS-associated coronavirus (SARS-CoV). Previously, Coronaviridae was best known as the second-most-frequent cause of the common cold. The SARS-CoV strain is believed to have originated in Guangdong province in southern China prior to its spread to Hong Kong, neighboring countries in Asia, and Canada and the United States during the 2002-2003 outbreak. In early 2004, several new cases of SARS were investigated in Beijing and in the Anhui province of China. The most recent outbreak was believed to have been successfully contained

without spread into the general population. There have subsequently been three instances of laboratory-acquired infection, and one reintroduction from animals in Guangdong Province, China. Despite concerns that new cases of SARS would emerge in the region, no new human-to-human transmission has been reported. The reasons for this maybe (1) a very high prevalence of serious illness, making identification of cases and transmission easier and (2) a low risk of transmission before the development of severe illness. The World Health Organization's (WHO's) timely updates on where SARS cases were occurring, the clinical and epidemiologic features of infection, laboratory methods, strategies to control the disease's spread, and the intensive collaborative global response to SARS were also responsible for the effective prevention of a global pandemic. Global efforts to acknowledge and research the CoV have virtually eradicated SARS as a threat. Although much has already been learned about the virus, ongoing efforts are being made to better understand it in hopes of developing medications and vaccinations to maintain its suppression. Global organizations, including WHO, the Centers for Disease Control and Prevention (CDC), and the National Institutes of Health (NIH) are still facilitating research on the virus and its family.

Epidemiology

In November 2002, an unusual epidemic of severe pneumonia of unknown origin in Guangdong Province in southern China was noted. There was a high rate of transmission to health care workers (HCWs). Some of these patients were positive for SARS-CoV in the nasopharyngeal aspirates (NPA), whereas 87% patients had positive antibodies to SARS-CoV in their convalescent sera. Genetic analysis showed that the SARS-CoV isolates from Guangzhou had the same origin as those in other countries, with a phylogenetic pathway that matched the spread of SARS to other parts of the world. The 2002-2003 SARS outbreak predominantly affected mainland China, Hong Kong, Singapore, and Taiwan. In Canada, a significant outbreak occurred in the area around Toronto, Ontario. In the United States, 8 individuals contracted laboratory-confirmed SARS. All patients had traveled to areas where active SARS-CoV transmission had been documented. SARS is thought to be transmitted primarily via close person-to-person contact, through droplet transmission. Most cases have involved persons who lived with or cared for a person with SARS or who had exposure to contaminated secretions from a patient with SARS. Some affected patients may have acquired SARS-CoV infection after their skin, respiratory system, or mucous membranes came into contact with infectious droplets propelled into the air by a coughing or sneezing patient with SARS. Leaky, backed-up sewage pipes; fans; and a faulty ventilation system were likely responsible for a severe outbreak of SARS in the Amoy Gardens residential complex in Hong Kong. Transmission may have occurred within the complex via airborne, virus-laden aerosols. The worldwide number of SARS cases from the original outbreak (November 2002 through July 31, 2003) reached more than 8000 persons, including 1706 healthcare workers. Of those cases, 774 resulted in death, with a case fatality ratio of 9.6% deaths, and 7295 recoveries. The majority of these cases occurred in mainland China (5327 cases, 349 deaths), Hong Kong (1755 cases, 299 deaths), with Taiwan (346 cases, 37 deaths), and Singapore (238 cases, 33 deaths). In North America, there were 251 cases, with 43 resulting in death (all in Canada). The map below shows the worldwide distribution of SARS cases during the 2002-03 outbreak. World map of severe acute respiratory syndrome (SARS) distribution from the 2002-2003 outbreak infection. The greatest number of past and new cases of SARS are in mainland China, Hong Kong, Taiwan, and Singapore (red). Canada, more specifically Toronto, Ontario (yellow), is the fifth-ranked area, although community transmission of SARS now appears to be contained, according to the US Centers for Disease Control and Prevention. Green represents the other countries reporting SARS cases.



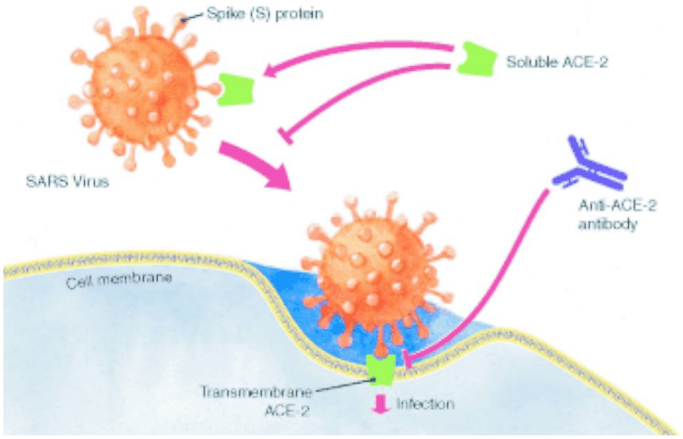
Etiology

Sources:

Coronaviruses (CoVs) are found in a wide range of animal species, including in cats, dogs, pigs, rabbits, cattle, mice, rats, chickens, pheasants, turkeys, and whales, as well as in humans. They cause numerous veterinary diseases (eg, feline infectious peritonitis, avian infectious bronchitis); they can also cause upper and, more commonly, lower respiratory tract illness in humans (group 1 [human CoV 229E] and group 2 [human CoV OC43]). The near absence of SARS-CoV antibodies in persons who did not have SARS demonstrated that SARS-CoV had not circulated to any significant extent in humans before 2003 and was introduced into humans from animals. Preliminary data after the outbreak started suggested that animals in the markets of Guangdong province in China may have been the source of human infection. However SARS-CoV-like viruses were not found in animals prior to arrival in the markets. A wide range of other coronaviruses in bats has been found, suggesting that bats are the most likely animal reservoir for the SARS outbreak. SARS infection in animals before arrival in the markets was uncommon, and these animals were probably not the original reservoir of the outbreak, although they may have acted as amplifying hosts. The proximity in which humans and livestock live in rural southern China may have led to the transmission of the virus to humans.

Cellular binding:

Single-stranded ribonucleic acid (RNA) viruses such as the SARS-CoV have no inherent proofreading mechanism during replication. Accordingly, mutations in the RNA sequence replication of coronaviruses are relatively common. Such mutations can cause the resulting new virus to be either less or more virulent. The surface envelop S protein of SARS-CoV is thought to be a major determinant in



establishing infection and cell and tissue tropism. This protein, after binding to its receptor—which is thought to be angiotensin-converting enzyme 2 (ACE-2) and is expressed in a variety of tissues, including pulmonary, intestinal, and renal—undergoes conformational change and cathepsin L–mediated proteolysis within the endosome. The binding of SARS-CoV to DC-SIGN (dendritic cell–specific intercellular adhesion molecule–grabbing nonintegrin), which recognizes a variety of microorganisms, does not lead to entry of the virus into dendritic cells. It instead facilitates the transfer and dissemination within the infected host.

Immune response:

The type I interferon (IFN-alfa/beta) system represents a powerful part of the innate immune system and has potent antiviral activity. However, SARS-CoV discourages attack by the IFN system. Replication of the virus occurs in cytoplasmic compartments surrounded by a double membrane layer. Such concealment within cells probably causes a spatial separation of the viral pathogen-associated molecular patterns (PAMPs) and the cellular cytoplasmic pattern recognition receptors (PRRs). In addition, the activation of IFN regulatory factor–3 (IRF-3) is actively inhibited by SARS-CoV, with IRF-3 being targeted by 5 known SARS-CoV proteins in order to prevent IFN-system activation. IFN induction can also be affected by unspecific degradation of host messenger RNA (mRNA). These defensive measures prevent tissue cells from mounting an antiviral IFN attack following SARS-CoV infection. Ultimately, however, an IFN immune response can occur. Plasmacytoid dendritic cells (pDCs) use Toll-like receptors (TLRs) to recognize pathogen structures and use IRF-7 to induce IFN transcription. Large amounts of IFN are thus produced by the pDCs following infection with SARS-CoV. In a study that examined 40 clinically well-defined human SARS cases, high levels of IFN were found in the infection's early stages, except in more severe cases, and early production of IFN correlated with a beneficial outcome for the infected individuals.

Nuclear factor:

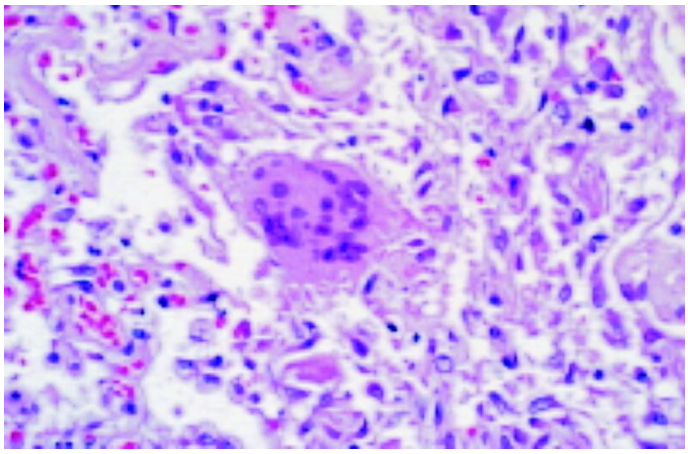
SARS-CoV membrane protein, most likely by interacting directly with IkappaB kinase (IKK), also suppresses nuclear factor-kappaB (NF-kappaB) activity and reduces cyclooxygenase-2 (COX-2) expression. These disturbances may aid SARS pathogenesis.

Novel coronavirus:

Novel coronavirus (NCoV), a new virus from the same family as the common cold virus and SARS-CoV, emerged in the Middle East in 2012. Although only distantly related to SARS-CoV, NCoV is also apparently of zoonotic origin and causes severe respiratory illness, fever, coughing, and breathing difficulties. Interferons have been shown to efficiently reduce NCoV replication in human airway epithelial cell cultures, suggesting a possible mode of treatment in the event of a large-scale outbreak.

Pathophysiology

The lungs and gastrointestinal tract have been demonstrated to be the only major organ systems that support SARS-CoV replication. After establishment of infection, SARS-CoV causes tissue damage by (1) direct lytic effects on host cells and (2) indirect consequences resulting from the host immune response. Autopsies demonstrated changes that were confined mostly to pulmonary tissue, where diffuse alveolar damage was the most prominent feature. (See the image below.)



Pathologic slide of pulmonary tissue infected with severe acute respiratory syndrome–associated coronavirus. Diffuse alveolar damage is seen along with a multinucleated giant cell with no conspicuous viral inclusions.

Multinucleated syncytial giant cells were thought to be characteristic of SARS but were rarely seen. Angiotensin-converting enzyme-2 (ACE-2), being a negative regulator of the local rennin-angiotensin system, was thought to be a major contributor to the development of this damage. The other mechanism was thought to be the induction of apoptosis. The SARS-CoV–3a and –7a proteins have been demonstrated to be inducers of apoptosis in various cell lines. Immunologically, SARS is characterized by a phase of cytokine storm, with various chemokines and cytokines being elevated.

History

SARS initially manifests as a flulike syndrome that may progress to pneumonia, respiratory failure, and, in some cases, death. The mortality rate associated with SARS is significantly higher than that of influenza or other common respiratory tract infections. Epidemiologic statistics and exposure history are critical to the diagnosis of SARS.

Exposure history:

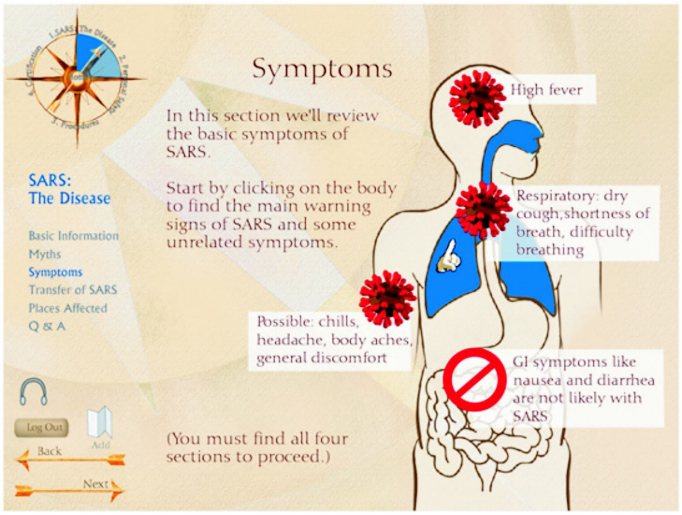
Research suggests that the major modes of SARS transmission are contact and droplet based. Fecal-oral transmission may also be possible via diarrhea. Evidence indicates that SARS may also be transmitted through airborne, virus-containing aerosols. Anyone who has had close personal contact with a person with known or suspected SARS within 10 days of symptom onset (eg, healthcare workers, family members, caregivers) is at high risk of SARS-CoV infection. Close contact is defined as caring for or living with a person known to have SARS or having a high likelihood of direct contact with respiratory secretions or body fluids from a patient known to have SARS. Examples of close

contact include kissing, embracing, sharing eating or drinking utensils, conversing closely (< 3 ft [1 m]), performing a physical examination, or sharing any other direct physical contact. Close contact does not include walking by a person or briefly sitting across from a patient with SARS in a waiting room or office. Traveling to an area where community transmission of SARS has been recently documented or suspected (including visiting an airport) within 10 days of symptom onset in that area is a risk factor.

Disease stages:

The clinical course of SARS generally follows a typical pattern. Stage 1 is a flulike prodrome that begins 2-7 days after incubation and is characterized by fever (>100.4°F [38°C]), fatigue, headaches, chills, myalgias, malaise, anorexia, and, in some cases, diarrhea. This stage lasts 3-7 days. This phase is characterized by increasing viral load. Stage 2 is the lower respiratory tract phase and begins 3 or more days after incubation. Patients experience a dry cough, dyspnea, and, in many cases, progressive hypoxemia. Chest radiography findings may initially be normal, and 7 days or longer may elapse before findings become abnormal. Radiographs may show focal interstitial infiltrates that may progress to a patchier, generalized distribution. Respiratory failure that requires mechanical ventilation may occur. This phase is thought to be secondary to immunopathologic injury and is characterized by a decreasing viral load.

Signs and symptoms



The clinical course of SARS generally follows a typical pattern. **Stage 1** is a flulike prodrome that begins 2-7 days after incubation, lasts 3-7 days, and is characterized by the following: Fever (>100.4°F [38°C]), Fatigue, Headaches, Chills, Myalgias, Malaise, Anorexia. **Less common features** include the following: Sputum production, Sore throat, Coryza, Nausea and vomiting, Dizziness, Diarrhea. **Stage 2** is the lower respiratory tract phase and is characterized by the following: Dry cough, Dyspnea, Progressive hypoxemia in many cases, Respiratory failure that requires mechanical ventilation in some cases.

Physical Examination

Physical examination findings in patients with SARS are consistent with those of a combined mild to severe respiratory tract infection and influenza like illness. However, from a respiratory standpoint, patients can deteriorate quickly and may require mechanical ventilation during hospitalization. Moderate respiratory illness is indicated by fever and 1 or more clinical findings of respiratory illness (eg, hypoxia, cough, dyspnea, breathing difficulties). Severe respiratory illness is indicated by fever, 1 or more clinical findings of respiratory illness (eg, hypoxia, cough, dyspnea, breathing difficulties), and radiographic evidence of pneumonia or respiratory distress syndrome or autopsy findings consistent with pneumonia or respiratory distress syndrome without an identifiable cause. Cough associated with SARS can be mild to severe and tends to be dry and nonproductive. Chest auscultation results can be unremarkable. If abnormal, findings are more commonly upper respiratory tract in nature as opposed to lower respiratory tract. Research on patients with SARS found the estimated mean incubation period to be 4.6 days (range of 2-14 d), with the mean time between the development of symptoms and hospitalization ranging from 2-8 days. The major clinical features on presentation included fever, chills/rigor, myalgia, dry cough, headache, malaise, and dyspnea. Sputum production, sore throat, coryza, nausea and vomiting, dizziness, and diarrhea have been found to be less common features. Hepatitis was a common complication of SARS-CoV infection, with 24% and 69% of patients respectively having increased alanine aminotransferase (ALT) levels on admission and during the subsequent course of the illness. Patients with severe hepatitis had worse clinical outcomes. A severe, acute neurologic syndrome may occasionally accompany SARS. An atypical presentation, such as malaise, decreased oral intake, fall/fracture, and, in some cases, delirium, without fever, was more likely in older patients. Children: There was no reported fatality in young children and teenage patients, but SARS in pregnancy carried a significant risk of mortality. Documentation of a temperature of more than 100.4°F (38°C) is preferred for diagnosis, but clinical judgment is important in the absence of this finding. Features consistent with respiratory illness, such as cough, wheezing, dyspnea, and other breathing difficulties, are noted. The incidence of asymptomatic infection remains unknown, although 0.1% for the general population and higher rates for healthcare workers have been estimated.

Diagnostic Considerations

Conditions to consider in the differential diagnosis of SARS include the following: Foreign body aspiration, Influenza, *Mycobacterium avium-intracellulare* and other atypical mycobacterial diseases, Mycoplasma infections, Parainfluenza virus, Pleural effusion, Pneumococcal infections, *Pneumocystis (carinii) jiroveci* pneumonia, Aspiration pneumonia, Bacterial pneumonia, Fungal pneumonia, Viral pneumonia, Psittacosis, Q fever, Rhinoviruses, Rickettsialpox, Bacterial sepsis, Upper respiratory infection.

Differential Diagnoses

Adenoviruses, Arenaviruses, Atelectasis, Bronchiectasis, Bronchiolitis, Bronchitis, Chronic Obstructive Pulmonary Disease, Coxsackieviruses, Cytomegalovirus, Echoviruses, Emphysema.

Diagnosis

Initial tests in patients suspected of having SARS include the following: Pulse oximetry, Blood cultures, Sputum Gram stain and culture, Viral respiratory pathogen tests, notably influenza A and B viruses and respiratory syncytial virus, *Legionella* and pneumococcal urinary antigen testing should also be considered. Data from the 2002-2003 outbreak indicate that SARS may be associated with the following laboratory findings: Modest lymphopenia, leukopenia, and thrombocytopenia: Series have shown white blood cell (WBC) counts of less than 3.5 x 10^9/L and lymphopenia of less than approximately 1 x

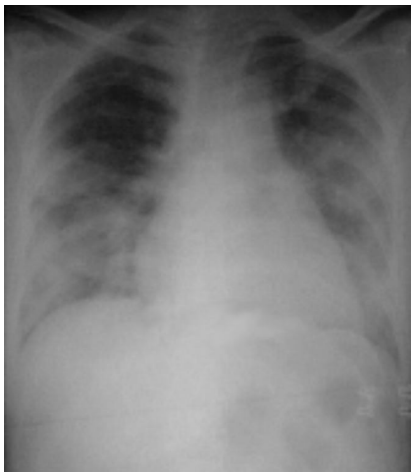
10^9/L, Mild hyponatremia and hypokalemia, Elevated levels of lactate dehydrogenase, alanine aminotransferase, and hepatic transaminase, Elevated creatine kinase level. According to guidelines from the Centers for Disease Control and Prevention (CDC), the laboratory diagnosis of SARS-CoV infection is established on the basis of detection of any of the following with a validated test, with confirmation in a reference laboratory: Serum antibodies to SARS-CoV in a single serum specimen, A 4-fold or greater increase in SARS-CoV antibody titer between acute- and convalescent-phase serum specimens tested in parallel, Negative SARS-CoV antibody test result on acute-phase serum and positive SARS-CoV antibody test result on convalescent-phase serum tested in parallel, Isolation in cell culture of SARS-CoV from a clinical specimen, with confirmation using a test validated by the CDC, Detection of SARS-CoV RNA via reverse transcriptase polymerase chain reaction (RT-PCR) assay validated by the CDC, with confirmation in a reference laboratory, from (1) two clinical specimens from different sources or (2) two clinical specimens collected from the same source on 2 different days. Chest radiography results in SARS are as follows: In one study, abnormalities were found on initial studies in approximately 60% of patients and were observed in serial examinations in nearly all patients by 10-14 days after symptom onset, Interstitial infiltrates can be observed early in the disease course, As the disease progresses, widespread opacification affects large areas, generally starting in the lower lung fields. High-resolution computed tomography (HRCT) scanning is controversial in the evaluation of SARS but may be considered when SARS is a strong clinical possibility despite normal chest radiographs. HRCT findings consistent with SARS include the following: In early-stage SARS, an infiltrate in the retrocardiac region, Ground-glass opacification, with or without thickening of the intralobular or interlobular interstitium, Frank consolidation.

Laboratory Findings and Techniques

Data from the 2002-2003 outbreak indicate that SARS may be associated with the following laboratory findings: Modest lymphopenia, leukopenia, and thrombocytopenia - Series have shown white blood cell (WBC) counts of less than 3.5 x 10^9/L and lymphopenia of less than approximately 1 x 10^9/L, Mild hyponatremia and hypokalemia, Elevated levels of lactate dehydrogenase, alanine aminotransferase, and hepatic transaminase, Elevated creatine kinase level. Coronavirus antibody testing methods include indirect fluorescent antibody or enzyme-linked immunosorbent assays, which are used to test for specific antibodies after infection. Although these antibodies are found in some patients during the acute phase (ie, within 14 d of onset), a negative test finding using a sample that has been obtained less than 28 days after symptom onset does not exclude the diagnosis of SARS. Reverse-transcriptase PCR (RT-PCR) assay results can be positive in some patients within the first 10 days of fever. RT-PCR assay can be used to detect SARS-CoV in serum, stool, and nasal secretions. SARS-CoV can also be isolated in viral cultures. A negative SARS-CoV antibody test finding less than 28 days after symptom onset, a negative PCR assay finding, and a negative viral culture finding do not exclude the diagnosis of SARS. Obtaining convalescent serum for a final antibody determination 28 days or more after symptom onset is critical to the disease's diagnosis. Below are the CDC's guidelines for the laboratory diagnosis of SARS-CoV infection. Diagnosis is established based on the detection of any of the following with a validated test, with confirmation in a reference laboratory: Serum antibodies to SARS-CoV in a single serum specimen, A 4-fold or greater increase in SARS-CoV antibody titer between acute- and convalescent-phase serum specimens tested in parallel, Negative SARS-CoV antibody test result on acute-phase serum and positive SARS-CoV antibody test result on convalescent-phase serum tested in parallel, Isolation in cell culture of SARS-CoV from a clinical specimen, with confirmation using a test validated by the CDC, Detection of SARS-CoV RNA via RT-PCR assay validated by the CDC, with confirmation in a reference laboratory, from (1) two clinical specimens from different sources or (2) two clinical specimens collected from the same source on 2 different days.

Imaging Studies

Initial chest radiography findings were found to be abnormal in approximately 60% of patients. Abnormalities on chest radiographs were observed in serial examinations in nearly all patients by 10-14 days after symptom onset. Interstitial infiltrates can be observed early in the disease course, although in the early stage, a peripheral, pleural-based opacity (ranging from ground-glass opacification to frank consolidation) may be the only abnormality. High-resolution computed tomography (HRCT) scanning of the chest during this time may reveal an infiltrate in the retrocardiac region.



Chest radiograph of a 52-year-old symptomatic woman with severe acute respiratory syndrome (March 20, 2003) taken 5 days after presentation.

Moderately severe-to-severe ground-glass and consolidative bilateral changes are noted in the lung fields and are somewhat worse on the left side. As the disease progresses, widespread opacification affects large areas. These changes tend to affect the lower lung fields first. Calcification, cavitation, pleural effusion, and lymphadenopathy are not observed in SARS.

HRCT scanning of the chest:

The role of HRCT scanning in the evaluation of SARS is still controversial. Patients with abnormal chest radiographic findings do not need HRCT scanning. However, when SARS is a strong clinical possibility despite a normal chest radiographic finding, the clinician should consider HRCT scanning. Findings consistent with SARS include ground-glass opacification, with or without thickening of the intralobular or interlobular interstitium, or frank consolidation. Indeed, a combination of ground-glass opacification (with or without thickening of the interstitium) and frank consolidation may be noted.

Prognosis:

WHO data indicate that mortality from SARS is highly variable. The mortality rate has been found to range from less than 1% in patients below age 24 years to more than 50% in patients aged 65 and older. Certain risk factors, including the following, have been associated with a poorer prognosis: Older age, Chronic hepatitis B infection, Laboratory

features - Including marked lymphopenia and leukocytosis, elevated lactate dehydrogenase level, hepatitis, high SARS-CoV viral load, and comorbidities such as diabetes mellitus. Elevated levels of interferon-inducible protein 10 (IP-10), monokine induced by IFN-gamma (MIG), and interleukin 8 (IL-8) during the first week, as well as an increase of MIG during the second week, have also been associated with a poor prognosis. A study of SARS survivors found that most of these had significant improvement clinically, radiographically, and in their pulmonary function studies. However, 27.8% of patients still exhibited abnormal radiographs at 12 months. Significant reductions in the diffusing capacity of carbon monoxide and in exercise ability (6-min walking distance) were also documented at 12 months. Polyneuropathy and myopathy associated with critical illness, avascular necrosis (possibly steroid induced), steroid toxicity, and psychosis were some of the other long-term sequel observed in the SARS survivors.

Morbidity and mortality:

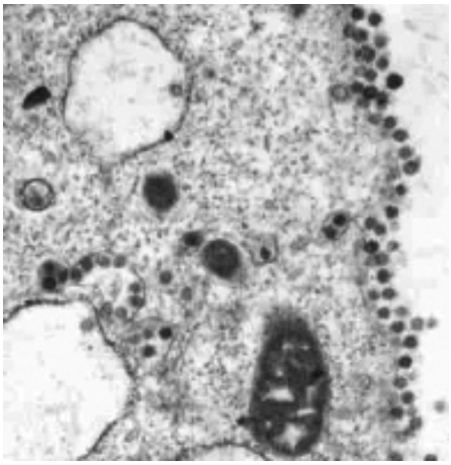
SARS can result in significant illness and medical complications that require hospitalization, intensive care treatment, and mechanical ventilation. Morbidity and mortality rates were observed to be greater in elderly patients. The overall mortality rate of SARS has been approximately 10%. According to the CDC and WHO, the death rate among individuals older than age 65 years exceeds 50%.

Approach Considerations:

Initial tests in patients suspected to have SARS include pulse oximetry, blood cultures, sputum Gram stain and culture, and viral respiratory pathogen tests, notably influenza A and B viruses and respiratory syncytial virus. *Legionella* and pneumococcal urinary antigen testing should also be considered. Specimens should also be made available for antibody testing, polymerase chain reaction (PCR) assay, and viral culture/isolation tests. Acute and convalescent (>28 d after symptom onset) serum samples should be collected. Paired sera and other clinical specimens can be forwarded through state and local health departments for testing at the CDC. Test results for human metapneumovirus, a virus genetically related to respiratory syncytial virus, have been positive in some patients with SARS.

Histologic findings

Autopsies demonstrated changes mostly confined to pulmonary tissue, with diffuse alveolar damage being the most prominent feature. Multinucleated syncytial giant cells were thought to be characteristic but were rarely seen. SARS-CoV infection causes significant damage to lung tissue, as shown below.



Thin-section electron micrograph of the severe acute respiratory syndrome–associated coronavirus isolated in FRhK-4 cells.

Airport identification:

Infrared scanners designed for use by the military for night operations were adapted for airport screening use in various locales (eg, Singapore). These scanners were used to identify potentially febrile passengers by measuring their body heat. False-positive results were common with these scanners. Individuals with positive scanner results were temporarily isolated and brought to a special cubicle, where temperatures were confirmed with an oral thermometer.

Management:

No definitive medication protocol specific to SARS has been developed, although various treatment regimens have been tried without proven success. The CDC recommends that patients suspected of or confirmed as having SARS receive the same treatment that would be administered if they had any serious, community-acquired pneumonia. The following measures may be used: Isolate confirmed or suspected patients and provide aggressive treatment in a hospital setting. Mechanical ventilation and critical care treatment may be necessary during the illness. An infectious disease specialist, a pulmonary specialist, and/or a critical care specialist should direct the medical care team. Communication with local and state health agencies, the CDC, and World Health Organization is critical.

Approach Considerations:

Currently, no definitive medication protocol specific to SARS has been developed, although various treatment regimens have been tried without proven success. The CDC recommends that patients suspected of or confirmed as having SARS receive the same treatment that would be administered if they had any serious, community-acquired pneumonia. Isolate confirmed or suspected patients and provide aggressive treatment in a hospital setting. Mechanical ventilation and critical care treatment may be necessary during the illness. No benefit has been shown with prone ventilation. An infectious disease specialist, a pulmonary specialist, and/or a critical care specialist should direct the medical care team. Communication with local and state health agencies, the CDC, and WHO is critical.

Pharmacotherapy

Corticosteroids:

Various steroid regimens have been used around the world as part of the initial SARS treatment cocktail. In the initial Hong Kong cohort of patients, corticosteroids were first given (with ribavirin) because of the similarity of the clinical and radiographic findings of SARS to those of bronchiolitis obliterans-organizing pneumonia. Despite anecdotal reports of success, the efficacy of steroids has not been confirmed in a clinical trial. During phase 2 of the clinical course, intravenous (IV) administration of steroids has been shown to suppress cytokine-induced lung injury. It was also associated with favorable clinical improvement, with resolution of fever and lung opacities within 2 weeks. However, a retrospective analysis showed an increased risk of 30-day mortality. Carefully designed studies will be needed to clarify the optimal role systemic steroids in the treatment SARS. Findings show that local pulmonary inflammation may be reduced with systemic glucocorticoid therapy.

Antiviral agents:

The most widely used of these to date is ribavirin (usually in conjunction with steroids). Despite early anecdotal reports of patients with SARS improving with a combination of ribavirin and steroids, ribavirin does not have proven activity against Coronaviridae. It does have significant adverse effects, including hemolysis. It is unlikely that ribavirin is of any clinical benefit in SARS.

Protease inhibitors:
Lopinavir/ritonavir was shown to have in vitro effects against the SARS-CoV. Some synergistic benefits with ribavirin were also demonstrated. However, the outcome of the subgroup that received lopinavir/ritonavir as rescue therapy after receiving pulsed methylprednisolone treatment for worsening respiratory symptoms was not better than that for the matched cohort.

Interferon:
Type 1 IFNs inhibit a wide range of RNA and DNA viruses, including SARS-CoV, and these effects have been demonstrated in vitro, as well as in some human and animal cell lines. In experimentally infected cynomolgus macaques, prophylactic treatment with pegylated IFN-alfa significantly reduced viral replication and excretion, viral antigen expression by type 1 pneumocytes, and pulmonary damage. However, the results of post exposure treatment with pegylated IFN-alfa were not as impressive. In patients, use of IFN-alfacon1 plus corticosteroids was associated with improved oxygenation, more rapid resolution of radiographic lung opacities, and lower levels of creatine phosphokinase (CPK). These findings, although encouraging, need to be supported by further studies.

Monoclonal antibodies:
A high-affinity human monoclonal antibody (huMab) to the SARS-CoV S protein, known as 80 R, has potent neutralizing activity in vitro and in vivo. This antibody was shown to neutralize SARS-CoV and inhibit syncytia formation between cells expressing the S protein and those expressing the SARS-CoV receptor ACE2. It reduced replication of SARS-CoV in the lungs of infected ferrets, decreased viral secretion, and prevented macroscopic lung pathology. This may be a useful viral entry inhibitor for the emergency prophylaxis and treatment of SARS.

Intravenous immunoglobulin:
Intravenous immunoglobulin (IVIG) was used in particular in Singapore during the SARS outbreak. However, its use was associated with a hypercoagulable state, and as many as one third of the patients who received IVIG were diagnosed with venous thromboembolism, including some cases of pulmonary embolism. Pentaglobulin (immunoglobulin-M [IgM]-enriched immunoglobulin) was also used in a small study, with encouraging results, but its use was also complicated by embolic events. The use of convalescent plasma was also attempted in some centers.

Nitric oxide (NO):
Nitric oxide use was associated with improved oxygenation and weaning from ventilator support in a small study.

Glycyrrhizin:
In vitro replication of the virus was shown to be inhibited by glycyrrhizin. A study showed that the use of traditional Chinese medicine was more effective than Western medicine in reducing hypoxemia in patients with phase 1 SARS, although it was unclear what components of the traditional medicine contributed to this effect.

Vaccine:
Chinese researchers began testing a SARS vaccine in humans in May 2004. The Chinese vaccine trial used an inactivated SARS virus vaccine developed through conventional vaccine technology. The first US SARS vaccine trial began at the NIH in December 2004. The NIH vaccine is composed of a small, circular piece of deoxyribonucleic acid (DNA) that encodes the viral spike protein. Five monoclonal antibodies (MAbs) against the recombinant nucleocapsid protein (NP) of SARS-CoV were developed by hybridoma technology. These anti-SARS-CoV NP MAbs, with their high specificity, are potentially ideal candidates for developing early and sensitive diagnostic assays for SARS-CoV and may be candidates for vaccines or drugs. The disappearance of SARS from humans has impaired the potential for development of a successful vaccine.

Activity and Isolation
The CDC has issued guidelines governing the activity and isolation of patients with SARS, their immediate contacts, and the healthcare professionals who treat SARS. Patients with SARS pose a risk of transmission to close household contacts and healthcare personnel. In household or residential settings, infection control measures, as described below, are recommended. Patients with SARS should limit interactions outside the home and should not go to work, school, out-of-home child-care facilities, or other public areas until 10 days after the fever resolves, provided that respiratory symptoms are absent or improving. During this time, infection control precautions should be used to minimize the potential for transmission. All members of a household of a patient with SARS should carefully follow recommendations for hand hygiene (eg, frequent hand washing, use of alcohol-based hand rubs), particularly after contact with body fluids (eg, respiratory secretions, urine, feces). Disposable gloves should be used for any direct contact with the body fluids of a patient with SARS. However, gloves are not intended to replace proper hand hygiene. Immediately after activities involving contact with body fluids, gloves should be removed and discarded, and hands should be cleaned. Gloves must never be washed or reused. Each patient with SARS should be advised to cover his or her mouth and nose with a facial tissue when coughing or sneezing. If possible, patients with SARS should wear surgical masks during close contact with uninfected persons in order to prevent the spread of infectious droplets. If a patient with SARS cannot wear a surgical mask, his or her household members should wear surgical masks when in close contact. Sharing of eating utensils, towels, and bedding between patients with SARS and others should be avoided, although such items can be used by others after routine cleaning (eg, washing with soap and hot water). Environmental surfaces soiled by body fluids should be cleaned with a household disinfectant according to the manufacturer's instructions; gloves should be worn during this activity. Household waste soiled with body fluids of patients with SARS, including facial tissues and surgical masks, may be discarded as normal waste.

Precautions by close patient contacts:
Household members and other close contacts of patients with SARS should be actively monitored by local health departments. Household members or other close contacts of patients with SARS should be vigilant for the development of fever or respiratory symptoms and, if these develop, should seek a healthcare evaluation. Prior to the evaluation, healthcare providers should be informed that the individual is a close contact of a patient with SARS so that necessary arrangements can be made to prevent transmission of the disease in the healthcare setting. Household members or other close contacts who have symptoms of SARS should follow the precautions recommended for patients with SARS.

Medication Summary:
Currently, no definitive medication protocol specific to SARS has been developed, although various treatment regimens have been tried without proven success. The CDC recommends that patients suspected of or confirmed as having SARS receive the same treatment they would be administered if they had any serious, community-acquired pneumonia. Because SARS is a viral infection, antibiotics are not indicated. In some of the early cases, antibiotics were administered as part of the treatment regimen, but no positive effect was noted.

TROUBLESHOOTING

FOBT

(continued from previous issue)

Clinical application

The stool guaiac test for hidden (occult) blood in the stool can be done at home or in the doctor's office, or can be performed on samples submitted to a clinical laboratory. Testing kits are available at pharmacies in some countries without a prescription, or a health professional may order a testing kit for use at home. If a home fecal occult blood test detects blood in the stool it is recommended to see a health professional to arrange further testing.

Sources of gastrointestinal bleeding

Gastrointestinal bleeding has many potential sources, and positive results usually result in further testing for the bleeding site, usually looking for lower gastrointestinal bleeding before upper gastrointestinal bleeding causes unless there are other clinical clues. Colonoscopy is usually preferred to computerized tomographic colonography. An estimated 1–5% of large tested populations have a positive fecal occult blood test. Of those, about 2–10% have cancer, while 20–30% have adenomas. A positive test can result from upper gastrointestinal bleeding or lower gastrointestinal bleeding. The common causes are: 2–10%: cancer (colorectal cancer, gastric cancer), 20–30% adenoma or polyps, Bleeding peptic ulcer, Angiodysplasia of the colon, Sickle cell anemia. In the event of a positive fecal occult blood test, the next step in the workup is a form of visualization of the gastrointestinal tract by one of several means: Sigmoidoscopy, an examination of the rectum and lower colon with a lighted instrument to look for abnormalities, such as polyps. Colonoscopy, a more thorough examination of the rectum and entire colon. Virtual colonoscopy. Endoscopy refers to upper gastrointestinal endoscopy. It is sometimes performed with chromoendoscopy, a method that assists the endoscopist by enhancing the visual difference between cancerous and normal tissue, either by marking the abnormally increased DNA content (toluidine blue) or failing to stain the tumor, possibly due to decreased surface glycogen on tumor cells(Lugol). Infrared fluorescent endoscopy and ultrasonic endoscopy can interrogate vascular abnormalities such as esophageal varices. Double contrast barium enema: a series of x-rays of the colon and rectum.

Stool color

Although red or black stools can be an indication of bleeding, a dark or black color can be due to black licorice, blueberries, iron supplements, lead, Pepto-bismol, and a red color can come from natural or artificial coloring such as red gelatin, popsicles, Kool-Aid, and large amounts of beets.

Colorectal cancer screening

Screening methods for colon cancer depend on detecting either precancerous changes such as certain kinds of polyps or on finding early and thus more treatable cancer. The extent to which screening procedures reduce the incidence of gastrointestinal cancer or mortality depends on the rate of precancerous and cancerous disease in that population. gFOBT and flexible sigmoidoscopy screening have each shown benefit in randomized clinical trials. Evidence for other colon cancer screening tools such as iFOBT or colonoscopy is substantial and guidelines have been issued by several advisory groups but does not include randomized studies. Guaiac FOB testing of average risk populations may reduce the mortality associated with colon cancer by about 25%. It is not always cost effective to screen a large population. If colon cancer is suspected in an individual (such as in someone with an unexplained anemia) fecal occult blood tests may not be clinically helpful. If a doctor suspects colon cancer, more rigorous investigation is necessary, whether or not the test is positive. The 2009 recommendations of the American College of Gastroenterology (ACG) suggest that colon cancer screening modalities that are also directly preventive by removing precursor lesions should be given precedence, and prefer a colonoscopy every 10 years in average-risk individuals, beginning at age 50. The ACG suggests that cancer detection tests such as any type of FOB are an alternative that is less preferred and which should be offered to patients who decline colonoscopy or another cancer prevention test. However, two other recent guidelines, from the US Multisociety Task Force (MSTF) and the US Preventive Services Task Force (USPSTF) while permitting immediate colonoscopy as an option, did not categorize it as preferred. The ACG and MSTF also included CT colonography every 5 years, and fecal DNA testing as considerations. All three recommendation panels recommended replacing any older low-sensitivity, guaiac-based fecal occult blood testing (gFOBT) with either newer high-sensitivity guaiac-based fecal occult blood testing (gFOBT) or fecal immunochemical testing (FIT). MSTF looked at 6 studies that compared high sensitivity gFOBT (Hemoccult SENSA) to FIT, and concluded that there were no clear difference in overall performance between these methods. In colon cancer screening, using only one sample of feces collected by a doctor performing a digital rectal examination is strongly discouraged.

Iron deficiency anemia

An extensive literature has examined the clinical value of FOBT in iron deficiency anemia.

Gastrointestinal disease and medications

Conditions such as ulcerative colitis or certain types of relapsing infectious diarrhea can vary in severity over time, and FOBT may assist in assessing the severity of the disease. Medications associated with gastrointestinal bleeding such as Bortezomib are sometimes monitored by FOBT.

Alcoholism

Several aspects of FOBT in alcoholism warrant further discussion.

Outpatient clinics

Several studies have reported clinical benefit from gFOBT testing including urology and gynecology clinics.

Inpatient guaiac testing

Several studies have questioned the traditional Admission Screening Guaiac (ASG). The utility of following stool guaiac in ICU settings is also questioned.

Testing of upper gastrointestinal or aerodigestive tract secretions for occult blood

The use of tests for occult blood in disorders of the mouth, nasal passages, esophagus, lungs and stomach, while analogous to fecal testing, is often discouraged, due to technical considerations including poorly characterized test performance characteristics such as sensitivity, specificity, and analytical interference. However, chemical confirmation that coloration is due to blood rather than coffee, beets, medications, or food additives can be of significant clinical assistance.

A related concept to colon cancer screening by FOBT, based on most neoplasms affecting the surface epithelium and losing small amounts of blood but no visible blood loss, is screening in populations at high risk for esophageal or gastric cancers by testing for blood by swallowing a small capsule that is recovered after 3 to 5 minutes by gentle retrieval by means of an attached nylon thread.

Fecal occult blood in marathon runners

Gastrointestinal (GI) complaints and low intensity GI bleeding frequently occur in marathon runners. Strenuous exercise, particularly in elite athlete runners and less frequently in other exercise activities, can cause

acute incapacitating gastrointestinal symptoms including heartburn, nausea, vomiting, abdominal pain, diarrhea and gastrointestinal bleeding. Approximately one third of endurance runners experience transient but exercise limiting symptoms, and repetitive gastrointestinal bleeding occasionally causes iron deficiency and anaemia. Runners can sometimes experience significant symptoms including hematemesis. Exercise is associated with extensive changes in gastrointestinal (GI) tract physiology, including diversion of blood flow from the GI tract to muscle and lungs, decreased GI absorption and small intestinal motility, increased colonic transit, neuroimmunoendocrine changes in hormones and peptides such as vasoactive intestinal peptide, secretin and peptide-histidine-methionine. Substantial changes occur in stress hormones including cortisol, in circulating concentrations and metabolic behavior of various leucocytes, and in immunoglobulin levels and major histocompatibility complex expression. Symptoms can be exacerbated by dehydration or by pre-exercise ingestion of certain foods and hypertonic liquids, and lessened by adequate training.

BOUQUET

In Lighter Vein

A wealthy merchant of 84 married a 25-year-old fashion model. They had a wonderful honeymoon in Switzerland but, unfortunately, the old boy suffered a coronary and was hospitalised.

When his young wife came to see him, the old man said, "Sweetheart, your future has been taken care of regardless of what happens to me. You will have an income of $250,000 a year, my home in Palm Springs, my ranch in Texas, my Mercedes. You'll never need to worry about money."

"Oh, sweetheart, please don't talk that way," his young wife exclaimed. "You've been so good to me already. If you go, I'll be devastated. Oh, there must be something I can do to help you. Please... tell me what I can do?"

"Well," the old man gasped, "you can quit pinching the inlet tube to my oxygen supply for starters."

A married couple is driving down the interstate doing 55 mph. The husband is behind the wheel. His wife looks over at him and says, "Honey, I know we've been married for 15 years, but, I want a divorce."

The husband says nothing but slowly increases speed to 60 mph.

She then says, "I don't want you to try to talk me out of it, because I've been having an affair with your best friend, and he's a better lover than you."

Again the husband stays quiet and just speeds up as he clenches his hands on the wheels.

She says, "I want the house." Again the husband speeds up, and now is doing 70 mph.

She says, "I want the kids too." The husband just keeps driving faster, and faster, until he's up to 80 mph.

She says, "I want the car, the checking account, and all the credit cards, too."

The husband slowly starts to veer toward a bridge overpass piling, as she says, "Is there anything you want?"

The husband says, "No, I've got everything I need right here."

She asks, "What's that?"

The husband replies just before they hit the wall at 90 mph, "I've got the airbag!

Wisdom Whispers

- Respect people who find time for you in their busy schedule. But love people who never look at their schedule when you need them
- We still love ourselves even after doing many mistakes. Then how can we hate others for their single mistake?
- When nails grow long, we cut nails not fingers. Similarly when misunderstanding grow up, cut your ego, not your relationship.
- One great lesson I learned from my life.. there is no market for your emotions, so never advertise your feelings, just show your attitude.
- Two things define you, Your patience when you have nothing, and your attitude when you have everything.
- As soon as you die, your identity become a "body". People use phrases like: "Bring the body", "Lower the body in the grave", "Take the body to the grave yard", etc. People Don't Even call you by your name whom you tried to impress whole life. LIVE A LIFE TO IMPRESS THE CREATOR NOT THE CREATION.
- Do what you love, Love what you do
- FEAR has two meanings:
  1) F=forget; E= everything; A= and; R= run
  2) F= face; E= everything; A= and; R= rise
- Happiness will never come to those who don't appreciate what they already have.
- It is a long Journey between Human Being and Being Human..!!!
- Life is very complicated. Don't try to find answers, Because when you find answers life changes the question.
- Relationship never dies a natural death…they are murdered by Ego, Attitude and ignorance..
- "When you're Happy you enjoy the Music, But when you're Sad, you understand The Lyrics.

Brain Teasers

MATCH THE FOLLOWING TERMS/ PATTERNS WITH THE ORGANS OR PATHOLOGIES THEY REPRESENT

1. Strawberry	A. Gall Bladder
2. Cobblestone	B. Stomach
3. Pipestem	C. Intestine
4. Cerebriform lymphocyte	D. Sezary syndrome/mycosis fungoides
5. Hypersegmented neutrophil	E. Megaloblastic anemia
6. Butt cell	F. Follicular lymphoma
7. Starry-sky pattern	G. Burkitt lymphoma

Answers: 1.A, 2.B, 3.C, 4.D, 5.E, 6.F, 7.G

INTERPRETATION

UTILIZATION OF THE MATURATION INDEX FROM A PAP SMEAR

The body manufactures three main kinds of estrogen: estradiol, estrone, and estriol. Estrogens are promoters of tissue growth, stimulating the proliferation of cells in the reproductive organs of women, particularly in the endometrium, the blood-rich lining of the uterus that is shed during menstruation. The collective effect of estrogen (the "estrogen effect") in a woman's body can be estimated through evaluation of the squamous cell layer that lines the vagina in a test known as a maturation index.

The relationship between hormone cycles and the maturation of vaginal squamous cells were initially noted by Rameriz and then later by Papanicolaou in the 1920's. Papanicolaou's research focused on the hormonal cycles of the female genitalia, and the efficacy of exfoliative cytology in the detection of cervical cancer was an incidental finding. A Maturation Index (MI) is based on the assumption that the sex hormones estrogen, progesterone and androgens (testosterone) bring about maturation in squamous cells that can be detected by cytological examination. The higher the number of mature cells (those designated 'superficial' and 'intermediate', the higher the maturation index or estrogen effect in the body. This provides doctors with information regarding levels of estrogen and hormonal influence in their female patients.

An MI is a ratio obtained through performing a random count of three major cell types (parabasal cells, intermediate cells and superficial cells) that are shed from the squamous epithelium. The cell count is expressed as a percentage that reads as follows: MI= % parabasal cells, % intermediate cells, % superficial cells. Parabasal cells are the least mature cells having not been affected by estrogen or progesterone. Intermediate cells display mild maturation, having been affected by progesterone, and superficial cells display the most maturity, having been affected by estrogen. A patient's MI can vary on a daily basis, and of course MIs vary from patient to patient. There are only two absolutes when it comes to cellular patterns in an MI: the first is that a predominance of parabasal cells indicates an absence of estrogen stimulation, and second is that a predominance of superficial cells indicates estrogen stimulation. Intermediate cells have little clinical usefulness. The maturation index is useful for the evaluation of therapies designed to treat vaginal hormonal symptoms.

The Maturation Index provides practitioners with a simply obtained (samples are taken during the course of obtaining a pap smear) sample that is easily analyzed to detect hormonal changes in the vagina that are age-appropriate or an early sign of possible hormonal related disease processes. The best samples for an MI should be taken with a gentle scrape along the lateral wall of the upper vagina at the level of the cervix. Cellular tissue from this area accurately reflects the hormonal status at the time of collection. Samples obtained must be free from signs of inflammation (white blood cells) and endocervical cells, both of which may falsely elevate the MI. MIs are useful for evaluating hormonal function, evaluating cellular composition of the surface layers of vaginal tissue which reflects the balance of estrogen and progesterones effects on this tissue, and diagnosing conditions that produce abnormal hormonal balance (pituitary gland dysfunction, ovarian dysfunction, and hormone secreting tumors). Additionally, MIs can detect the beginnings of endometrial cancer in menopausal women, and have been used to screen for other cancerous process such as vaginal adenosis and clear cell carcinoma in women who were exposed in utero to diethylstilbestrol (DES), a synthetic estrogen. The sensitivity of using a smear to determine a maturation index in the diagnosis of vaginal intraepithelial neoplasia was estimated to be at 83% percent in one recent study.

Taking the following table into account, practitioners can decide on a course of treatment for the patient that presents with clinical symptoms once this hormonal 'cross check' has been measured. The maturation index is most useful for detecting hormonal effects in menopausal and post-menopausal women, who may be experiencing symptoms with and without treatment. Additionally, practitioners may find the use of an MI in post-menopausal woman to be a good screening tool for as-of-yet undetected vaginal cancers. Cellular cytology is useful in this process, detecting cellular changes prior to organ dysfunction, when the disease is in an advanced state.

Various treatments for female hormonal health and normalization exist, from standard hormone replacement therapies (HRT) and dietary and botanical medicines. Botanical medicines such as phytoestrogens have been shown to increase the MI in women consuming soy-rich diets over a 6-month period. Because of these effects, soy and other phytoestrogens should be considered as part of a preventative intervention in treating menopausal symptoms related to estrogen deficiency. However, the use of the maturation index should be correlated with clinical/symptomatic findings in order to accurately treat the patient's symptoms and take steps to prevent worsening of symptoms or disease processes.

TYPICAL MATURATION INDEXES*

MI=% Parabasal Cells: % Intermediate Cells: % Superficial Cells

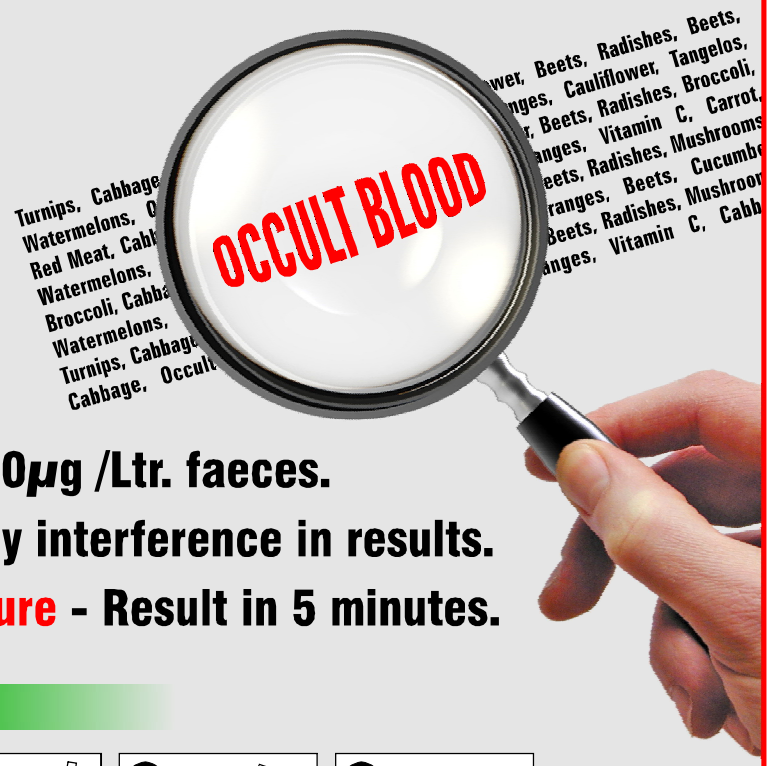
Day 14 – Ovulation	MI = 0:40:60	Indicates mostly estrogen stimulation.
Day 28 – Premenstrual	MI = 0:70:30	Indicates mostly progesterone stimulation.
Menopausal	MI = 0:100:0	Progesterone only, no estrogen.
Atrophic	MI = 100:0:0	No progesterone or estrogen.
Child	MI = 100:0:0	No progesterone or estrogen.
Puberty	MI = 0:90:10	Mostly progesterone stimulation, minimal estrogen.
Pregnancy	MI = 0:100:0	Progesterone only, no estrogen.
Post Partum	MI = 90:10:0	Minimal hormonal stimulation. Ovarian function returns in 6-8 weeks.

*This is an example only; actual patients will show marked variability depending on history.

TULIP NEWS

OCCULT BLOOD DETECTION....

CANCHECK® - FOBT



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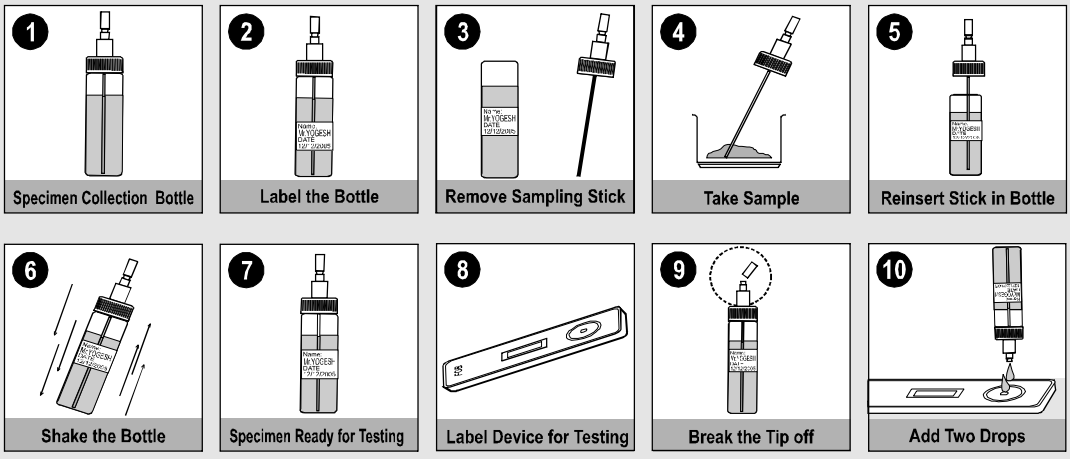

Now, so easy so specific...

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