BRAIN ABSCESS

I want to focus on brain masses.
And they usually go on differential diagnosis because a lot of things might present in the brain.
And some of the concerns and some support that you get are how they might be differentiated between infections and cancers.
Well, the definition (*fig.1*) is usually the collection of pus in the middle of the brain.
It usually starts with an area of cerebritis, so there's an area of inflammation, focal inflammation of the brain for example, that organizes usually in two to five days and get a capsule. So in the end, we get brain masses.
In recent years, we have seen much more early abscesses than before, because the imaging part is more used than before.
If you compare the case series we have now to those like 30 years ago, they're kind of very different in terms of mortality, for example.

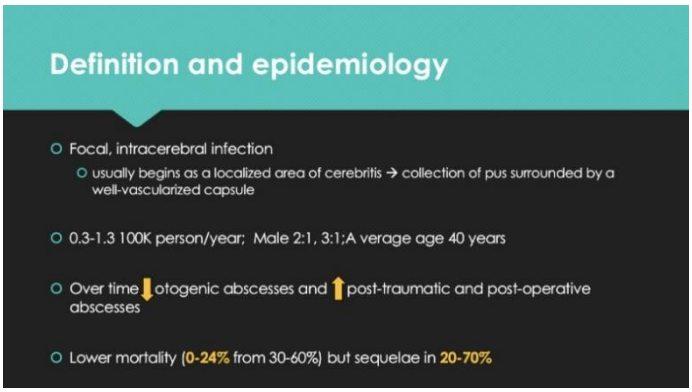


Fig.1

Over time, apart from being better at diagnosing, we had a decrease in otogenic abscesses, so people with holes in their teeth who have abscesses that evolved into brain abscesses, and more post-traumatic or post-operative, so people are being operated by the surgeons and again, it's a complication.
This is the reason that now we have a lower mortality rate than before: 0-24% (*fig.1*).

So that's a very complex slide (*fig.2*).
But I just want to tell you that we see, is very different according to the probable origin.
Most of the abscesses that we see now are actually a sequence of otitis media and otomastoiditis. So, the majority of them are streptococci, both anaerobic and aerobic.
Streptococci live in the mouth, so they actually can colonize all the sinuses and also the ears.
There are several causes; in certain cases, like, for example, in the cyclic neutropenia, cancer patients in chemotherapy, usually undergo nutropenia after chemotherapy and it's very common to have a gram-bacteremia.

Predisposing conditions and Microbiology	
Otitis media & Otomastoiditis	**Streptococci (anaerobic or aerobic)**, *Bacteroides* and *Prevotella* spp., Enterobacteriaceae
Sinusitis	**Streptococci**, *Bacteroides* spp., Enterobacteriaceae, *Staphylococcus aureus, Haemophilus* spp.
Dental Infection	**Mixed *Fusobacterium***, *Prevotella, Actinomyces,* and *Bacteroides* spp., streptococci
Penetrating trauma or postneurosurgical	***S. aureus***, streptococci, Enterobacteriaceae, *Clostridium* spp.
Lung abscess, empyema, bronchiectasis	***Fusobacterium***, *Actinomyces, Bacteroides,* and *Prevotella* spp., streptococci, *Nocardia* spp.
Bacterial endocarditis	***S. aureus*, streptococci**
Congenital Heart Disease	Streptococci, *Haemophilus* spp.
Neutropenia	**Aerobic gram-negative bacilli**, *Aspergillus* spp., Mucorales, *Candida* spp., *Scedosporium* spp.
Transplant	***Aspergillus* spp., *Candida* spp., Mucorales, *Scedosporium* spp.**, Enterobacteriaceae, *Nocardia* spp., *Toxoplasma gondii, Mycobacterium tuberculosis*
HIV	*T. gondii, Nocardia* spp., *Mycobacterium* spp., *Listeria monocytogenes, Cryptococcus neoformans*

Fig.2

I highlighted that in green (*fig.2*), because in that setting patients are immunocompromised, so transplant patients that have increased risk of brain abscess.
As you can see, there are very uncommon functions, there are very strange fungi, that you usually see only in very limited transplant patients. In that case, it's really impossible to get the diagnosis unless you're really aggressive in just trying to get the material from the brain.
We already talked about T. gondii, and it's the most common cause of brain abscess in HIV.
We talked about listeria when we talk about aseptic meningitis. We just touched nocardia, that can cause lung infections, but they can be sent into the brain, so you might see cavities in the lungs abscesses, and also at the same time you can see brain abscesses.
In low-income countries, TB is the leading cause of brain abscesses.

LOCALIZATION

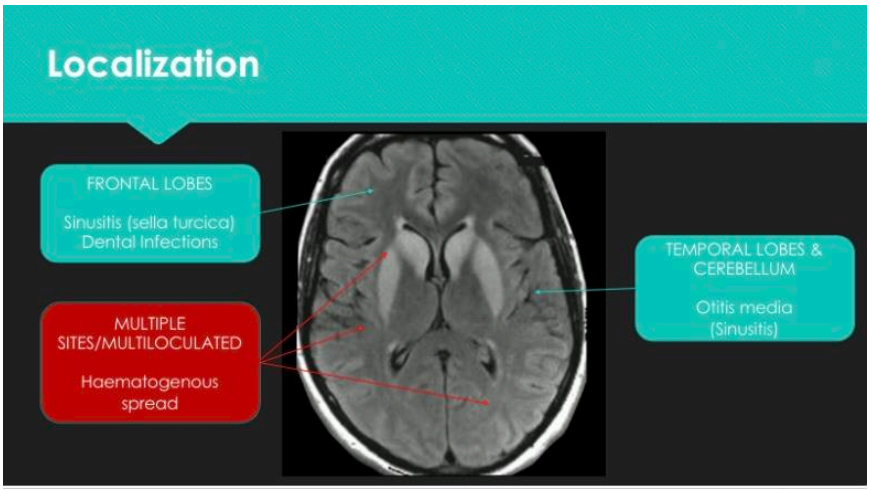


Fig.3

One thing that's important is actually the place where you see the abscesses, that can give you a hint of where they come from.
So, if they're in the front lobes, you must think they come from the sinuses. As you can see, they're sinusitis, or sometimes they have some infections.
If you see them in the temporal lobes, from the cerebellum down there, you must think they come from otitis media.
If you see multiple sites, they come from the blood. In that case, you want to think, where did they come from? So, source control is very important.

SYMPTOMS

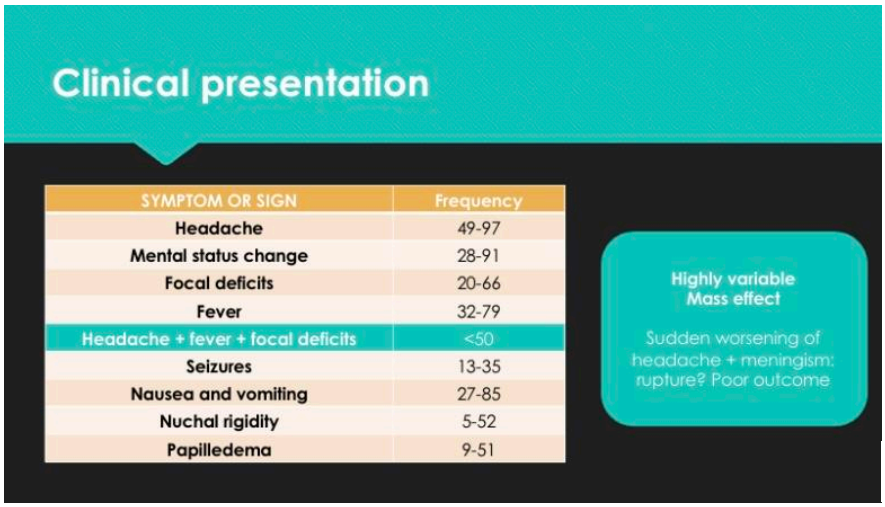


Fig.4

They're really variable, in different cases, in different patients. Usually, they should be headache, mental status change, and fever. If you want to have all three at the same time, you get them only in less than 50%. Just have headache, fever, or altered mental status. Don't always think that you need to have all the main symptoms at the same time.
And, of course, neurological symptoms depends on the mass effect. So, if it's cortical, it depends on frontal lobes, temporal lobes, occipital lobes, how big is it, how much edema is around the lesions…
So, highly variable effect, in terms of neurological symptoms.

DIAGNOSIS

Just to give you an idea, that's how we see the CT scan (*fig.5*).
It's a round lesion, with a hypodense center, and there's also some hypodense area that's around, that's edema.
We usually use corticosteroids, to reduce edema and antibiotics, to just kill what's inside.

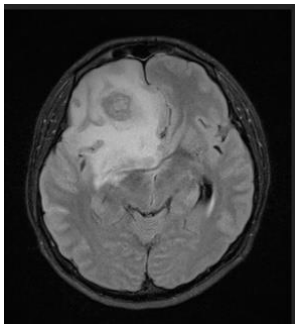


Fig.5

That's an MRI (*fig.6*).

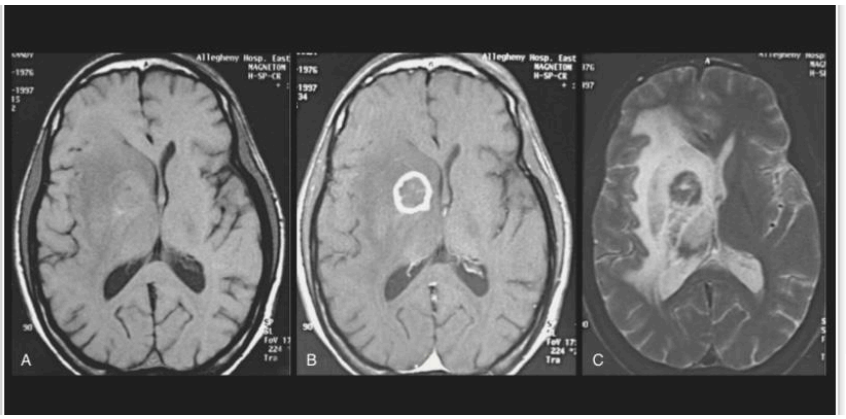


Fig.6A-B-C

You are estimating not just the abscess itself, but also the amount of edema that's around.
This can be totally asymptomatic (*fig.6A*). In that area, it's a very particular area, you don't have the cortex there.
It should compress the white matter, but the white matter is just fibrous, it can just go around the edema, go around the mass. So, this version can be totally asymptomatic.

MANAGEMENT

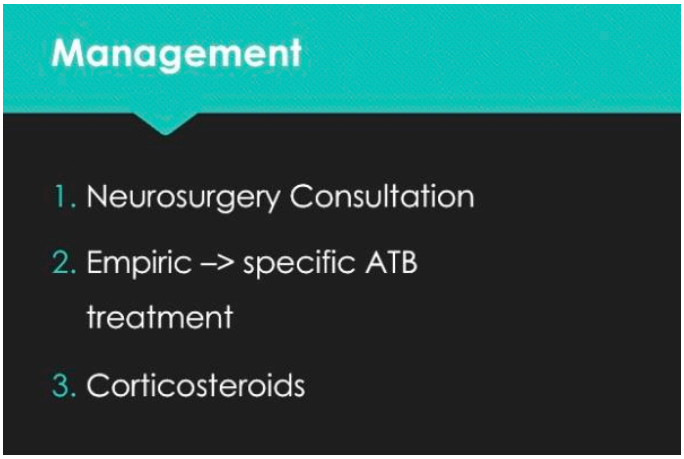


Fig.7

This year we've got new guidelines for brain abscesses, and they say to ask a neurosurgeon every time you see a brain abscess. So, you need to consult, and see if these can be either aspirated or excised.

NEUROCYSTICERCOSIS

What's the agent causing neurocysticercosis?
Tenia. Tenia is a flatworm, with two main types: tenia solium, and tenia saginata.
Tenia solium comes from pigs, tenia saginata from cows.
Tenia Africa is a version of tenia solium for the east of the world.
That's the way we get infected by tenia (*fig.9*).
So, we usually eat uncooked or undercooked meat, and the muscle of these animals have a kind of a dormant form of tenia.
So, when we use these undercooked or raw meat, these oncosphere grow up to be an adult tenia.
Usually, nothing happens.

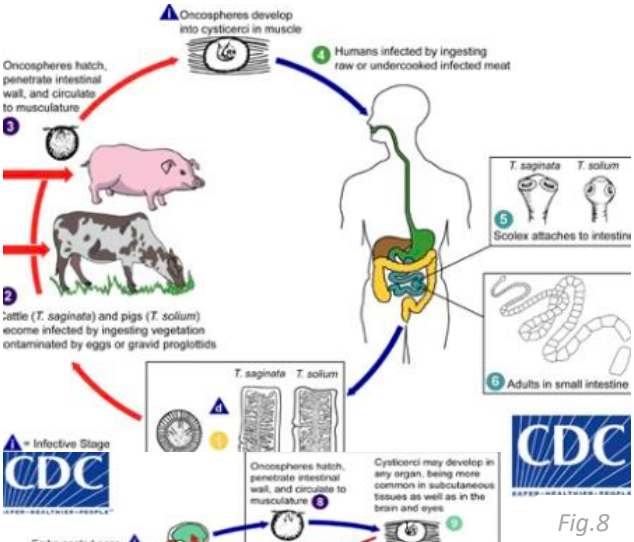


Fig.8

Fig.9

People come with abdominal discomfort, some have a little pain, they are not useful for losing weight.
People come to say that they have white things moving in the tools. I think I've already mentioned to you that some people get psychosis. I don't know why some people get a psychosis due to these things, they have white stuff in these tools moving.
Most of them are not real, so if you ask them to bring the tools, you don't see the white thing moving.
Last year, an old man came to the outpatient clinic, and he smelled like garlic so terribly I couldn't just stay in the same room without opening the windows. He came with his son, and he was telling me that he had tenia for a long time. Like two years, he showed me pictures, videos, of his tools. He had this white thing moving in these tools, so it was real.
But, the GP prescribed the wrong drug.
Tenia doesn't respond to venazole. He receive three courses of venazole without response, so he was taking one full garlic a day, for one year, because garlic has some helping elements probably.
I, with diagnoses, prescribed the treatment, I told him to stop with garlic, and his son actually told me thank you very much.
Usually, nothing happens. It doesn't produce any kind of complication.
But, tenia is ermaphrodite, so, it's able to self-impregnate itself.
Once some human, that's infected with tenia, defecates somewhere, in the garden, or in the soil,etc.
My fruit and vegetable was contaminated by someone's stools, in that case, it don't ingest the oncospheres, I ingest directly, the embroynated eggs, and they hatch into the stomach, in the first part of the intestine, they go through the circulation, and go to the muscle, and brain.

IS IT COMMON?

Well, it's very common, because it's everywhere in the world, it seems to be higher in limited resource countries countries, because of controls on animals.
Of course, only in countries where you have pigs, so in Muslim countries they don't consume pig, so you don't have neurocysticercosis.
It's considered to be the most frequent cause of seizures, in low resource countries.

HOW DOES IT WORK?

What happens usually? Nothing.
The cyst stays in the muscles, can be in the eyes, can be in the spine, can be in the brain, can be everywhere. Most of the people, don't have symptoms.
However, they can cause seizures, into an extra cortex, and the cyst reactivates, it's more active, it just moves. So, it causes inflammation in the cortex, seizures, chronic headaches, in certain cases it produces something that's similar to, to encephalitis, and can cause abnormalities in the vessels of the brain.

There are four stages (*fig.10*):
Phase one, in which you see the worm inside. So it's an active condition, with the worm there, there's some degree of inflammation.
Phase two is called colloidal vescicular, there you see there's some edema around.

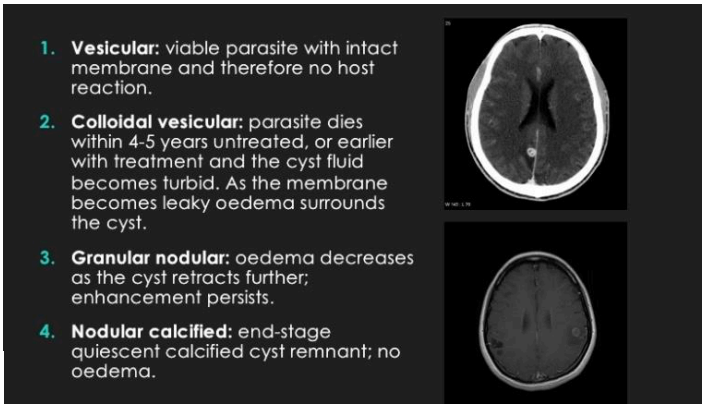


Fig.10

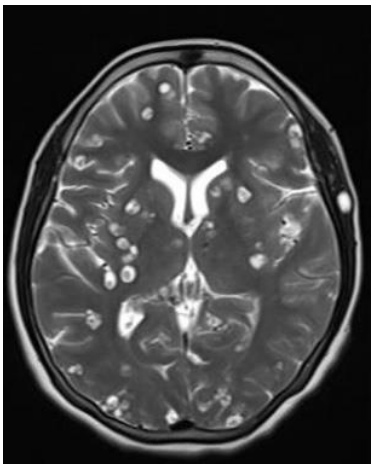


Fig.11

This (*fig.11*) is a 50 years old woman, coming from the east of Europe, with chronic headache, and you can see the cysts.
You see there are around 20 lesions in the brain.
We diagnose it, usually with MRI, but we do have a specific serology.

They can be everywhere, it can also be in the meningi, and that causes seizures. In this case actually, all the lesions are calcified, because they don't heal, they just calcify.

TREATMENT

How do we treat? We combine one or two antiepileptic drugs, albedazole, with steroids. They usually work. Depending on numbers, localization, we actually extend the treatment rules.

AN INTRODUCTION TO INFECTIOUS DISEASES OR HOST-ENVIROMENT-MICROORGANISMS INTERACTIONS

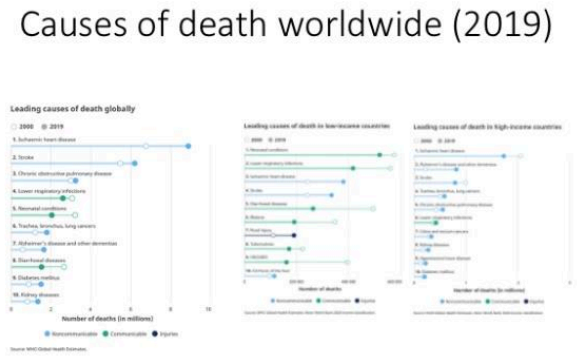


Fig.12

Infections are really important. If you take a look at causes of death (*fig.12*), the green ones are actually infections. They are 3 out of 10 causes of death in the world.
If you go to low income countries, you see that actually 6 out of 10, and the 2 most important causes of death are infections. So, basically, they're really important in terms of **mortality** when you move to a certain area of the world. They're also important in terms of **morbidity**. there was a study done in Canada about daily loss because of infections. Just to give you an idea that there's an impact about days loss, morbidity, and other conditions, consequences, like pneumonia, sepsis, UTIs, etcetera, are common causes of infection that we see in high income countries.

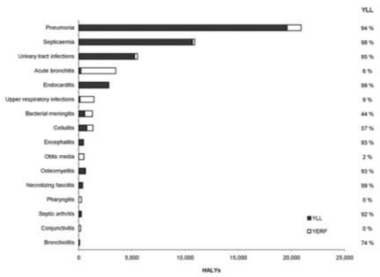


Fig.13

INFECTION AND COLONIZATION

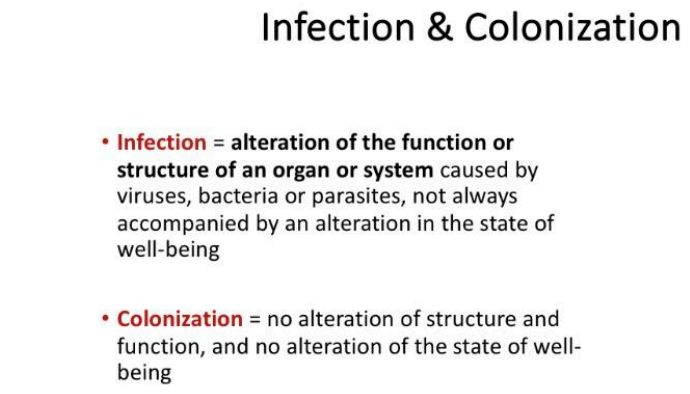
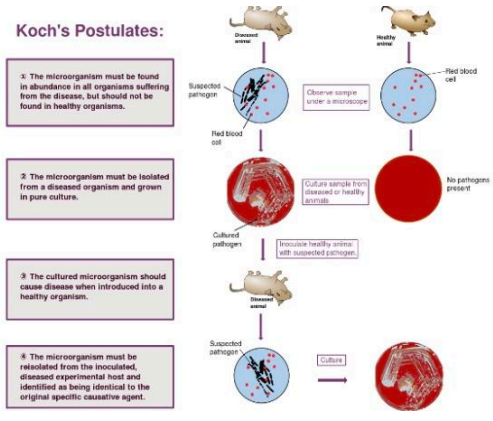


Fig.14

Well, this is concept number 1 I want to touch, I know it's very basic, but, you know, the consequences of these 2 ideas are really important, in terms of practice. So, that's (*fig.14*) the difference between infection and colonization. So, **colonization** is the presence of the microorganism without alteration of structure or function of an organ and tissue. So, you get bacteria somewhere, fungi, protozoa, but the organ or tissue is actually fine, there's no alteration in its function. So, which is the organ that takes more microorganism? The gut, the skin, the mucosa, the mouth it's really full of bacteria.
Infection is actually the presence of a microorganism with the alteration of the function, something doesn't work, think of the gut. Usually, the structure of the gut is not altered, certain infections actually are invasive, so they cause mucosa, and gut alterations, et cetera, but usually it just changes the function, so diarrhea is usually because of accelerated transit in the gut, and then people feel sick. Infections, apart from these I mentioned, can cause changes in the microscopic, or the macroscopic structure of the tissue.

Fig.15

I just put here (*fig.15*), the Koch's Postulate, I think you studied it in microbiology, but I wanted to remind you, because we'll talk about emerging infections afterwards, I think it's important that we think that infections can cause something; when you'll study IBD, intestinal inflammatory bowel disease, you will study that a certain type of bacteria was linked to Crohn's disease, when you study mitral sclerosis, you will study that there are certain infections associated with mitral sclerosis, but I think, most of them don't actually follow the Koch's postulate, so just put them there, I think it's important to consider them, when we try to see the difference between association and causation.



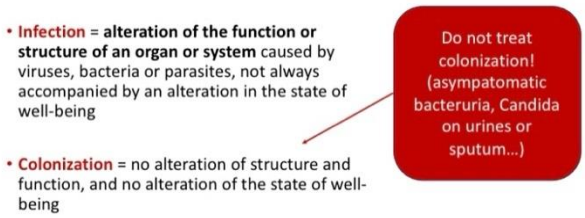


Fig.16

Which are the consequences of this? Well, first one is very important. **Do not treat colonization**. Another professor will teach about antimicrobial stewardship, one of the principles of antimicrobial stewardship is don't treat asymptomatic bacteruria. You have bacteruria, you don't treat it every time you find it, because it depends on symptoms, depends on the presence of nitrates, it depends on risk.

Secondly, with Candida. You have Candida in urines, candida lives in the mucosa. So, if you don't have perfectly sterile withdrawal of the urine, you find candida in urins. It's not an infection, it's just the presence of the fungus in the urine, so don't treat it. Same thing as sputum. If it is sputum culture, you find candida, it comes from the mouth. Candida lives the mouth.

We'll talk about stewardship, we'll talk about highly resistant bacteria. We don't treat them. Why? Well, first reason, we are (*unintelligible*) for treating these bacteria, but we reserve them for severe cases. Second thing these highly resistant bacteria are actually a consequence of the inflammation in the gut microbioma, so if we treat them, two weeks afterwards, there would be again bacteria in the gut, so it's useless. Colonization is not reason for treating, but it's important because we isolate the patients. So, you will see the wards, we do swabs, if it comes positive, we isolate the patient. They should be in a single room, or in a room with other patients with the same resistant bacteria.

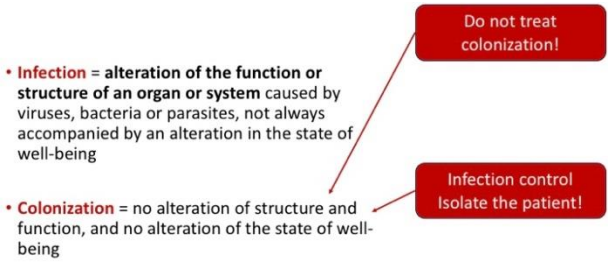


Fig.16

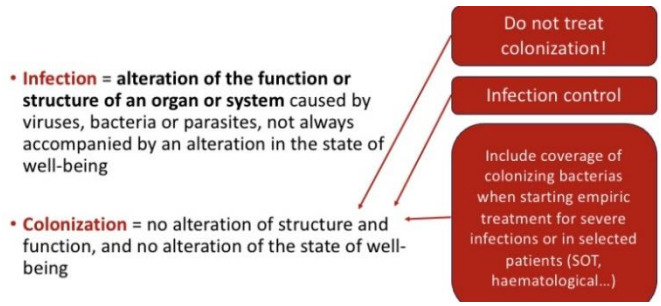


Fig.17

There's a second reason why it's important to know that the patient is colonized by resistant bacteria. If they develop a severe infection, we want to cover for this. Imagine we have a patient that's undergoing liver transplant, we know he's colonized, they're a very high risk of patient. Because of the procedure, the immunosuppression, if they develop fever, we won't treat them, but we have to start prepare for severe infection. Then, when we receive culture, so we go to a very specific narrow situation.

There are really hundreds of studies connecting microbiomas to a lot of diseases, some of them are actually inflammatory conditions, some others are even.

Association doesn't mean causation, it's very important to say this.

The microbiota could change due to bacteria, viruses, fungi it can change with age, it changes with nutrition, with sexual activity…

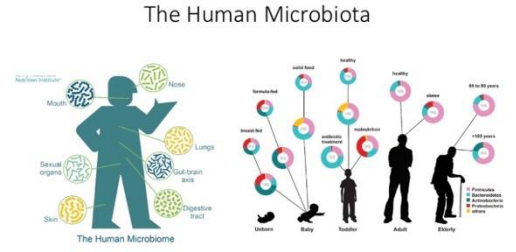


Fig.18

EXAMPLES OF MICROBIOTA/PATHOGENS INTERACTIONS

I wanted to make two examples. The first one is lactobacilli versus candida (*fig.19*), we said that candidosis is usually a dysbiosis where lactobacilli are reduced.

The second (*fig.20*) is the changes in the microbiome in clostridioides difficile. It's a very important colon infection. In hospitalized patients, as a consequence of anti-microbial treatment we have a reduction in certain bacteria in the gut and we have the predominance of clostridium difficile. Clostidium difficile is

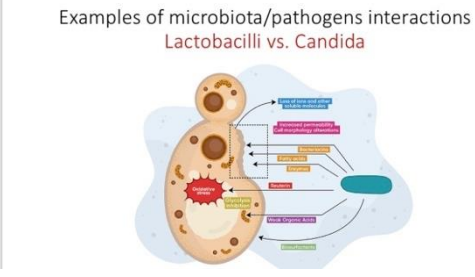
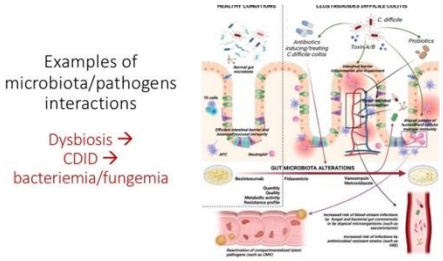


Fig.19

Fig.20



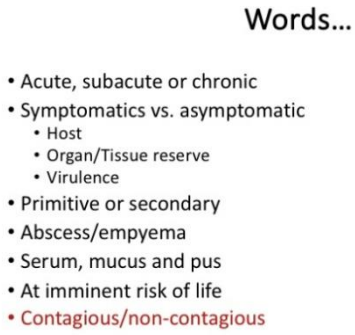
associated with several complications such as toxic megacolon and death.
Because of the changes clostridium creates in the gut microenvironment, we have passage of bacteria from the gut to the blood, so we start with dysbiosis because of antibiotic treatment, we create clostridium infection, clostridium facilitates the passage of bacteria from the gut to the blood.
The interaction between the bacteria inside and outside the gut is very important and it has clinical consequences.

BASICS OF INFECTIOUS DISEASES

WORDS

These (*fig.21*) are all words we are going to use, such as acute, subacute or chronic, symptomatic versus symptomatic is linked to the host; some infections are asymptomatic, for many years people have no symptoms or an infection, but it changes the immune system. Primitive and secondary are very important when we do consult with a patient, often they ask us what is the cause of fever or what is the cause of raised CRV, we need to understand if there is an infection and if that infection comes only from that organ or tissue.

Fig.21



People use the word infectious as a synonym of contagious, infection means there is a microorganism, contagious that is going to be spreading from person to person.

SPREAD

Fig.21

An infection can be spread by **contiguity**, there is usually a small way of entry in the skin, and it usually just get down the skin into the dermis and just spread horizontally, so contiguity, and grows and grows until we don't do something about it.
It can spread by be a **hematogenous** spread when we talk about endocarditis, we see that the infection can just be spread to the blood circulation.
The last one is **lymphatic** spread, the main infection is actually drained by the lymphatic vessel so if you have an infection in the extremities, hands or feet, the lymphatic vessel usually drains out the bacteria or the microorganisms to the lymph nodes. When you have an lymphatic spread you have an infection somewhere in the lymph nodes, that enlarge. In this case (*fig.21*) it's cat scratch disease, in which after cat scratch or bite bartonella enters the skin, and from the skin it's drained by lymph nodes so usually people present fever, sometimes scratch or bites and the lymph nodes in particular the axillary lymph nodes are enlarged.

TRANSMISSION ROUTES

Fig.22

1. Airborne and droplets: Influenza, Tuberculosis, Neisseria meningitidis
2. Contact: Erisipela, VZV, scabies
3. Sexual: HIV, Syphilis, Chlamydia
4. Oro-fecal: HAV, *Salmonella typhi*, *Vibrio cholerae*
5. Vector: Malaria, *Borrelia burgdoferi*, Leishmania

How can microorganisms actually spread from person to person? The first one is **the airborne droplets,** we already talked about tuberculosis, neisseria meningitis and influenza.
There are very different patterns of spread, so just to remind you this slide we used for tuberculosis (*fig.23*):

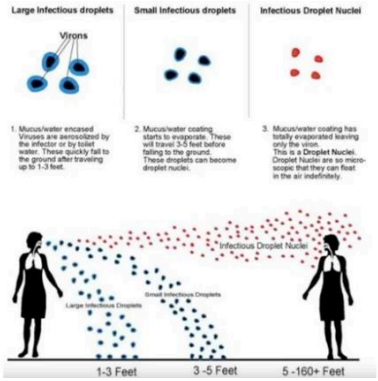


Fig.23

droplets-> 1m, meningitis;
small droplets-> tuberculosis, usually 1 to 2 meter but in close groups it can stay in the air and viruses can spread like air or aerosol it gets to all of us in the same room. Very different kind of distance.
The second one (*fig.22*) is by **contact**: erisipela potentially can be spread by touching; VZV -> in lesions you get a lot of viruses that can be spread by touching them; also scabies can be spread like that. Concerning varicella, if you remember it usually it is a disease in children and young people, and when you have varicella but also chlamydia you also have the virus in the mouth, in the lungs, so the spread is both by contact and airborne.
If you have a patient with varicella you isolate both by air and contact. If we have a patient with zoster we just isolate by contact. We exempt immunocompromised hosts because from the skin varicella virus goes back blood and to lungs, and from lungs in the mouth. So immunocompromised hosts can spread the zoster by airborne transmission.
We talked about STIs, we talked a little bit about **oro-fecal** transmission, we talked about HAV, we will talk about salmonella and Vibrio, and finally we will talk a little bit about **vectors** when we talk about we will spend some time talking about malaria.
Today we will talk about ticks, some borrelia and we will talk also about leishmania. So, these (*fig.22*) are the most important paths of transmission.

ARTHROPODS

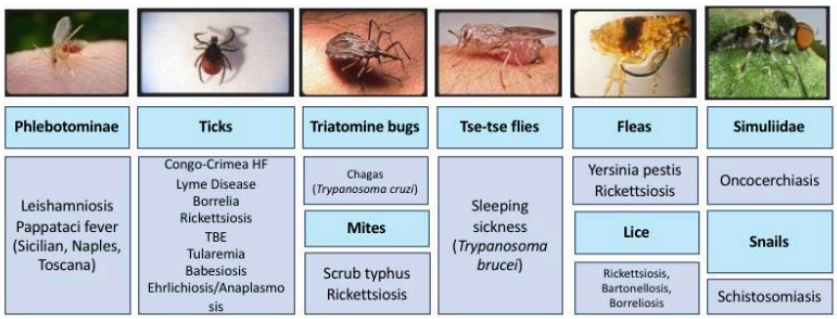


Fig.24

When we will discuss about arboviruses, that are viruses spread by arthropods, we all think about mosquitoes because they are the most common ones, then we will talk about zika etc, but just let me remind you there are much more arthropods in the world and they can spread a lot of things.
Phlebotominae (*fig.24*) it's pappataci, it can spread a few viruses and leishmania; **ticks** can spread a lot of things, we'll just touch borrelia and we can see all these (*fig.24*); **triatomine bugs** transmit Chagas disease in South America; **mites** can sometimes bring rickettsia and Scrub typhus; **tse-tse flies** cause sleeping sickness (we don't see many cases); **fleas** can spread Yersinia pestis; there are also **lices**; **Simulliidae** can cause oncocercgiasis; **snails**, we'll talk about them when we talk about (*unintelligible*). So Arthtopods are really a lot of families they can spread a lot of things.

TOSCANAVIRUS

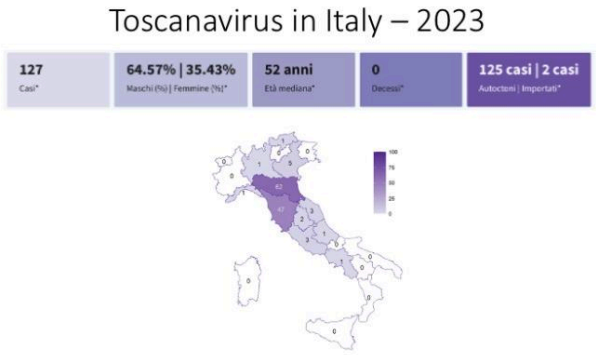


Fig.25

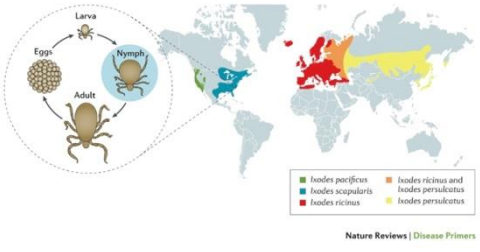
Phlebotomus transmits 3 viruses: sicilian virus, naples virus and toscana virus.
Because they were discovered in these areas, there are certain areas in which phlebotomus can reach and spreade a disease. Let's give you an idea of the cases (*fig.25*): last year we had tuscanavirus most of all in Emilia and Toscana. They are very mild, very quick to resolve.

TICKS

Fig.26

These are ticks in different stages, you can see they are very small. Usually before eating blood, ticks are so small you don't see them (usually around one millimeter) when they feed on blood it will be at one centimeter and don't stimulate feeding.

Fig.27



There are several different ticks they transmit different things. Ixodes is the soft tick, it's usually in wild animals. There are different types in the world.
It's a disease (*fig.28*) that in Europe it's kind of common. There are some countries in which we have more than 10 cases for 100.000 inhabitants, in Germany for example they sell the ticks remover in the supermarket.

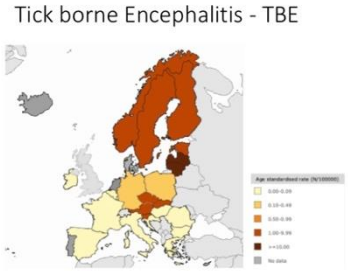


Fig.28

VECTORS

Fig.29

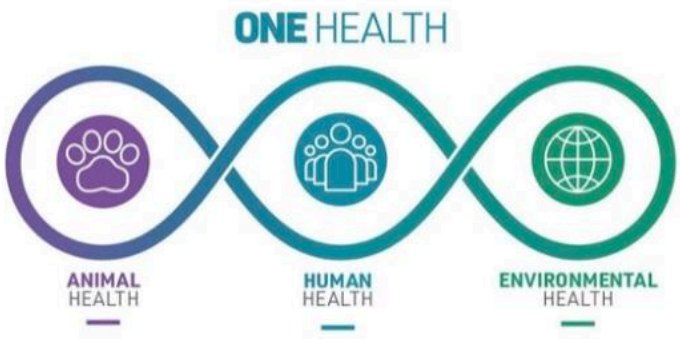
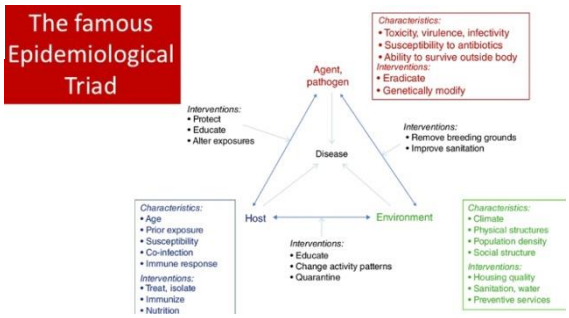
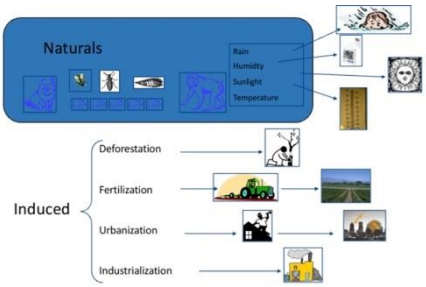


Fig.30



We already started talking about **vectors,** so I'm just gonna talk about of one health, it's the idea of just bringing together animal health human health and environmental health. It actually comes from this (*fig.30*), a very famous **epidemiological triad**.

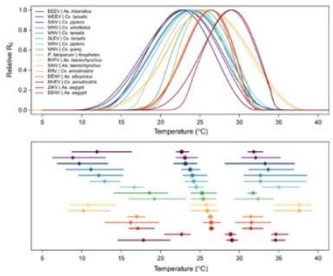
Fig.31



We have at the same time, the **host** with all the features (age, sex, comorbidities, genetics, etc), we have the **pathogen**, the agent that can change a lot depending on pathogens differences in terms of virulence and so on, and the **environment.**

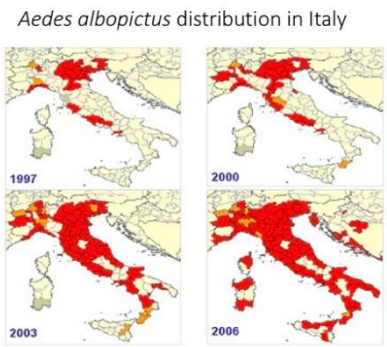
The features of the environment are important for understanding these interactions. Some changes are important think of like rain, humidity, sunlight, temperature, some are actually induced by humans in forestation, in urbanization etc.

Fig.32



This example (*fig.32*) is just how mosquitoes are used at transmitting disease according to temperature, so if the change in temperature keep on with the same as we've seen in the last 20 years, in the next 5 years we'll see a lot of malaria because mosquitoes are very effective between 20 and 30 degrees. If the temperature keep on increasing from 25 to 40, we'll see a lot of dengue, chikungunya and Zika, because mosquitoes can adapt to very high temperature.

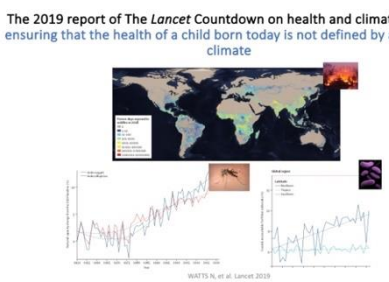
Fig.33



In 1997 the vector of dengue was just in certain areas of Italy, in only 10 years it was in he entire country, now is in the the whole middle and south of Europe.

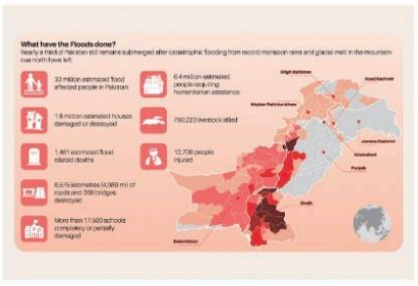
There's this very interesting report by the Lancet it's called "*ensuring that the health of a child born today is not defined by a changing climate*". It's a very important piece of paper, and it talks about all these the only change in climate that might affect health.

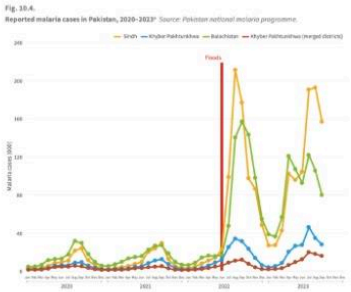
Fig.34



It talks about infections, about mosquitoes, about vibrio colerae. The increase the temperature of sea water increases the amount of vibrio we've found.

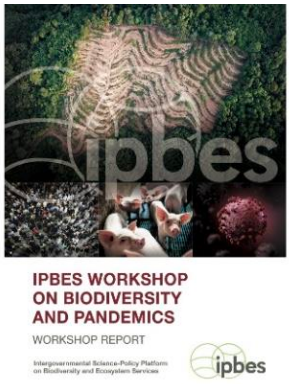
Fig.35





Sometimes climate is not induced by humans, that's what happened in Pakistan in 2022 big flood (*fig.35*), like one third of Pakistan was actually under water, that's (*fig.35 right*) the cases of malaria just in the months after the flood. The pools of water everywhere they bring much more mosquitoes, more malaria.

Fig.36

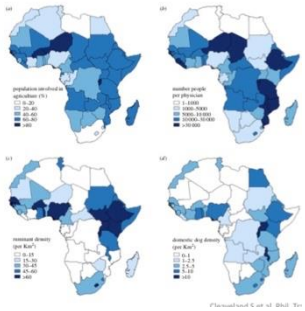


If you like this kind of topic that's (*fig.36*) a report of the WHO UN committee on biodiversity and pandemics it's really interesting because there are probably 1.7 million unknown viruses, half of them have the potential to infect humans and we only know 10,000.

Animals they cannot increase the changes in the environment caused by humans, that can actually increase the risk of pandemics. Land use change, forestation agricultural expansion, urbanization, biodiversity, climate change what is the threat for natural wildlife? After ebola epidemics in West Africa it was forbidden to bring animals from Africa to the other parts of the world legally, so they were brought illegally so the controls increased a lot. Someone suspected that COVID19 was actually due to the import of birds and bats from Africa to Asia.

Most of the diseases we see now are actually associated with animals, so the more you get next to animals the higher risk you have to get this disease or the virus that might be asymptomatic in animals, like rabies.

Fig.37



That's the density of physicians (*fig.37B*), so number of people per physician, and certain countries you see there are more than 3,000 people per one or two, this (*fig.37D*) is the density of dogs, this (*fig.38*) is the expenditure for rabies and every six seconds one person dies of rabies. Numbers are terrible, we absolutely not do enough, we're not investing money for rabies.

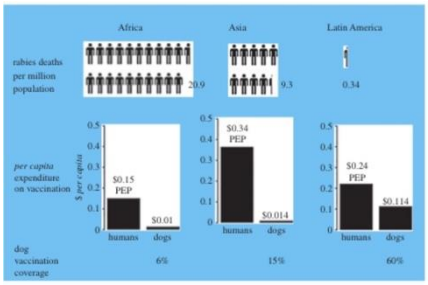


Fig.38

We already talked about the pox so we're not going to go there, but again pox tells you something about how close we get to wild animals and how quickly we move around the world.

In terms of resistance, antibiotic resistance is very important. We're going to talk about MDR pathogens, we talk about NDM metalloprotease (they're called NDM since they were found in the river next to New Dehli NDLE in an antibiotics factory). Probably, in the production process, several antibiotics were just released in the river.

That's (*fig.39*) a cartoon that tells something about how much antibiotics that are unnecessary are used, which are a lot. What happens when someone takes ciprofloxacin? People urinate, 95% of the times, and urine goes to rivers, it goes to the soil, so the rivers are full of antibiotics, the soil is full of antibiotics. What is done with animals? Intensive breeding includes the use of antibiotics for infections prevention, there are a lot of antibiotics in meat. This was just to describe how antibiotics are used.

MDR pathogens are really increasing, it is an estimation, a lot of people are dying of MDR infections.

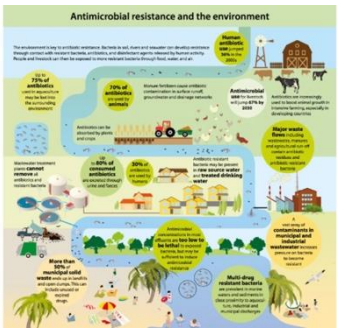


Fig.39

POPULATION CHANGES

There are also population changes. There are older people in countries such as Italy, Italy is a very old country, and that's one of the reasons why there was such a high mortality with COVID-19, for example we will talk about the change in the elderly, and there are also more complex patients: immunosuppression now is very wide, there are hundreds of drugs that can induce immunosuppression, we also have aggressive treatment of diseases. We use a lot of different protheses, think of a joint prothesis, now every person above the age of 70 has for example a knee prosthesis.

We have an increasing worldwide prevalence of diabetes and obesity, both conditions include some changes in immunosuppression: all of these examples include risk of infections.

In chemotherapy for instance, what happens? Usually there is mucositis, because all cells are killed, including cancer cells and gut cells, leading to malabsorption, but also bacteria cross the barrier from the gut to get to the blood, hence people will get bacteremia and sepsis.

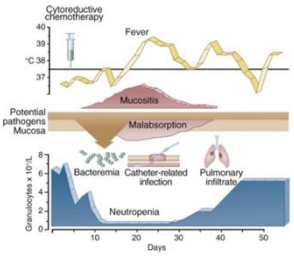
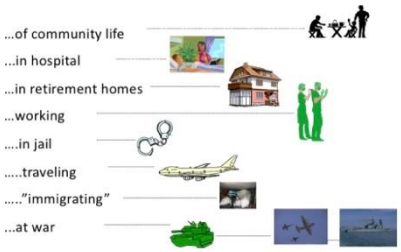


Fig.40

SETTINGS AND INFECTIONS

Fig.41



Settings are also important. When we will talk about resistance, community life infections are really
different from hospital ones, and there is an average category called healthcare-associated infections, so
those in which people living at home that often undergo dialysis for example, long-term facilities for elderly
are all considered to be in the average. But, for example jail, jail is a setting in which you have a very high rate of infections, why? Why are there more infections in jail? First of all, often there are many people that are physically close to each other, also, sex and rape happen in jail, drugs use happens in jail.

Switzerland, in the year 2000, since the rate of HIV infections and other STDs was too high, decided to give free condoms and free syringes.

We talk about tropical diseases and immigration, we talk about war: every time we talk about war, we talk about STDs, soldiers often have sex with sex workers, rapes are part of the picture unfortunately, STDs are really common, but that's not the only thing. Wars also mean migration, displacement of people; what happened to the latest cholera epidemic in the world? 3 million people had cholera in Yemen.

THE "CHAIN OF INFECTION"

Fig.42

This involves the breaking of the chain of infections. So, these (*fig.42*) are all the things that we need to
consider, we have host factors, environment, pathogen, portal of entry, so the things to know in order to
figure out what to do to break these chains.

(The professor states that the students can read the factors on their own fig.43A,B,C,D,E).

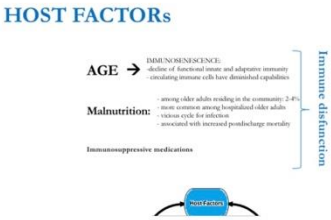


Fig.43A

Fig.43B

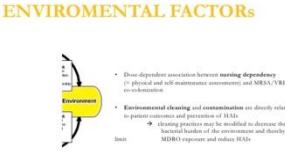


Fig.43C

Fig.43D

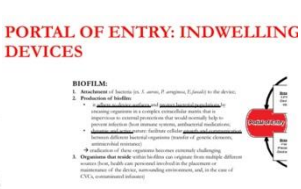


Fig.43E

TRANSPORTATION CLUSTERS

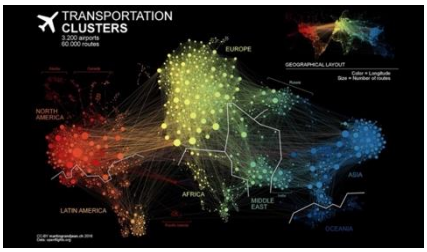


Fig.44

It's important to see how microorganisms move around the world, it has a political implication.
This (*fig.44*) is a transportation cluster, so how many people are moving around the world in one year, just to give the density: of course, it's more dense in Europe, North America, Asia, etc.. It's estimated that around
1.5 billion people every year move from their country to another.

NEW HYBRID CORONAVIRUS RESPONSIBLE FOR SEVERE HUMAN DISEASES

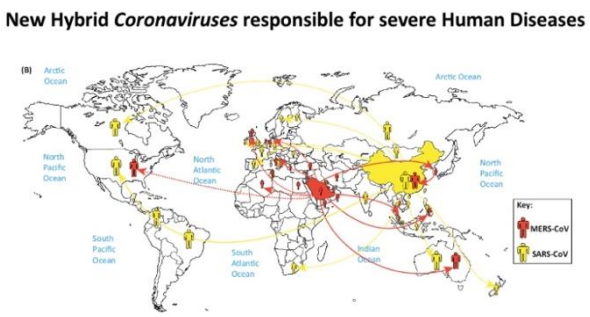


Fig.45

This (*fig.45*) is the example of coronaviruses, there is SARS-1and MERS (Middle East Respiratory Syndrome). There is the one from China, the yellow one, then MERS, which is less spread but still it went to all continents. I think you've heard about the idea that "migrants bring diseases", is it true? A study was carried out in Europe concerning this topic, and they wanted to see how many cases of non-autoctonous infections were associated with migration and how many were associated with tourists: they found 274 high risk non-autoctonous infections in Europe, and 90-92% were related to travelling, this is because integration of minor populations communities is really low, so the chances of spread are really low.
Pathogens can also migrate with animals. We can talk about West Nile, that's what happened with the West Nile virus. We didn't have West Nile, birds came from east of Africa/Middle East mostly, a migration of birds happened and things changed.

ZIKA VIRUS

We will talk about Zika virus. Zika virus probably started in Africa, it was discovered in 1947 in Africa and then it spread to the Pacific then it went all over the world. Then only when it got to South America we discovered a serious complication of Zika: microcephaly, brain malformation if Zika virus is contracted in pregnancy.
We didn't know that. We had epidemics before, all over the 60s, in the Pacific area. It could be not even reaching like thousands of millions of people so this can't change the pathogenesis and the genetics of people are different so that's how virus interact: with the brain changes, with animal changes, with different areas and there's also changes in prevention.
In the three countries in red (*fig.46*) we have less coverage of measles vaccination, so where the second dose of measles vaccination is less than 4% (the one usually done in teenagers). The three countries are France, Italy and Romania. Greece doesn't provide vaccination. Think: which are the four countries with the highest incidence of measles in Europe? France, Italy, Romania and Greece.
Prevention strategies and vaccination are really important inprevention of these infections.

Fig.46

But things can change quickly. I just took last week a look at the WHO website (they have an epidemics web page in which they tell you which are the disease outbreaks around the world) andjust to give you an idea, last week we had Avian influenzaA(H5N1) in Vietnam, also different strands of influenza in China,we had psittacosis in Europe, we had several cases of yellow fever in Congo, Ghana and Central Africa, we had Nipa Virus in Bangladesh (Nipa Virus is really nasty, probably transmitted by rats and flying foxes and it can give respiratory symptoms, can have high mortality and MERS). So very big changes of outbreaks in the world.

EMERGING INFECTIONS

I want to talk a little bit about emerging infections, you've probably heard about it. Emerging infections are defined as those recently discovered or re-emerged in different geographic areas. They can be new infection, can be unrecognized, etc.

That's (*fig.47*) the slide that Anthony Fauci, the US president counselor, prepared in 2017 for presenting why the US should invest money in ID, because 4 years ago this method almost ended. But now we have emerging viruses, now we do it always (spread, animals, etc) and also our past ability to identify viruses and other pathogens.

Plague. I think, I didn't think I've ever seen one like plague again like 4 centuries ago. Actually, this is the last epidemic we had, they had in Madagascar or Ebola. We briefly touched on Ebola on the fact that we discovered that Ebola can be transmitted sexually,so months after the epidemics, male survivors can spread Ebola by sex. That's something we absolutely had no idea about.

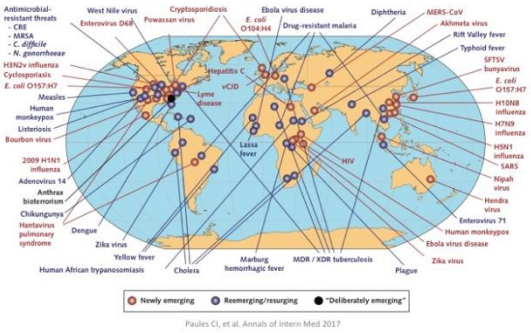


Fig.47

CRIMEA-CONGO HEMORRAGIC FEVER

The last example I wanted to give you is the Crimea-Congo hemorragic fever. It's a virus, usually every year we have a few cases in the Middle East, Central Asia and South Africa. It's transmitted by ticks, specific ticks: it's called the *Hyalomma.* It's a very aggressive tick so it's not just a tick that stays there on the plants and if you pass there you just get a tick, they follow people because they want to infect them.

So what happened? Well, in 2016 one Spanish guy, just went into a thorough walk next to Avila in the center of Spain. He went home and 3 days afterwards he developed high fever, confusion, sepsis and died in 48 hours. He was brought to ICU and the nurse that first was taking care of him the ER actually got infected too.She survived and this time they were able to diagnose the virusand they discovered that since 2010 the *Hyalomma* ticks in that region had the virus in them.

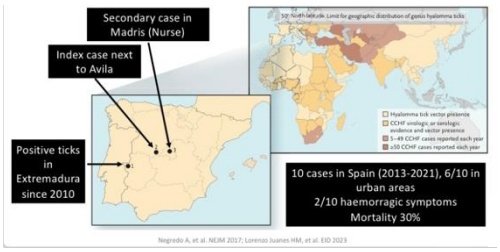


Fig.48

So the virus was there for at least 6 years before we saw the first case. Why is it important? Well, mostly because the virus was found in Italy in 2017 in a bird (in a tick) and just a few months ago, October 2023 a cow tick was found to be positive in the Alps between France and Italy. So the virus is here and we need to be prepared because we can have episodes of hemorrhaging feverdue to the Crimea-Congo hemorrhaging virus.

So again, the important part of this is the change that there's needto be: some of that depends on humans some on climate, some on animals but the only way to to be prepared is actually to perform surveillance and take a look at the disease, birds animals, etc.

FEVER OF UNKNOWN ORIGIN (FUO)

We will not have much time to go through fever of unknown origin. It's a chapter, I think really fascinating because you just think of all the causes of fever, the definition, reason to change. That's a very important angle to watch and actually they touch on all the infection causes. For the first time, they included metagenomics so again, if you're not able to diagnose the cause of fever try to go for **NGS**, next generation sequencing, try to find whatever pathogen you might find. It's the first time that it's*(metagenomics)* included in any algorithm so probably in the future we'll do the headings.
So we have no idea unless we just don't look at the microbiome in an unbiased way because we don't have a test for this one and the same for others.

ID CONSULTATION IN PRACTICE

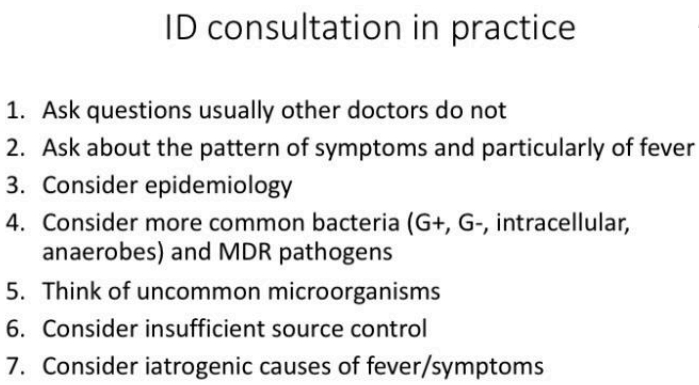


Fig.49

It's a bit wide. I would like to do more practice and somehow talk to you about what's an ID consultation in practice, what we do when we consult. So the first thing is actually we ask questions
that usually other doctors don't do: for example that's a list of the questions (*fig.50*) I usually ask when I'm consulting. So:

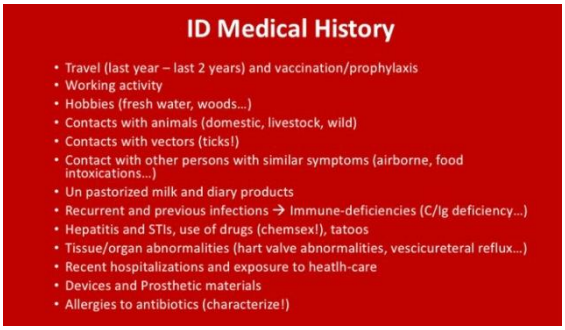


Fig.50

• **travel** (we discussed about areas not only the Tropics, even areas in Europe: Chykunguya Virus in Europe, Borrelia Burgdoferi etc
• **vaccination/prophilaxis** I don't know if you've already read some medical history but often we don't have that history, we only have that for COVID. But what about pneumococcus, meningococcus etc.?
• **hobbies** potential exposure to certain potentially toxic substances in lungs. Working can be important and hobbies as well, people that do hobbies with fresh water like kayaking for instance, or swimming in lakes and rivers they can be exposed to things that live in fresh water.
Leptospirosis for example is transmitted by the urine of rodents, so that's a risk you need to understand, or by just walking in the woods you can get tick bites. Contact with animals, domestic animals can be important, let's think about cat-spread disease, dog ticks, animals can have fleas, you can get in contact with wild animals such as a fox or a bat or a raccoon.
• That is a very stupid question, but does any person in your complex have the **same symptoms** as you? Very basic basic question about spread, contact spread or respiratory spread of disease.
• We can ask about **food intoxication**, one of the classic thing is like a wedding or a large banquet in which all people start having gastrointestinal symptoms at the same time. We can also somehow track the food itself, there are certain toxins that are more typical in like egg derivates or creams…
• One question we always do is "are you fond of **diary products**?" , because it's usually done with unposterised milk salmonella, listeria, TB can be transmitted by dairy products.
There is a question about requirements and previous infections that's important you have several infections at the same time sinusitis, otitis, pneumonia etc., but one cause is actually **immunodeficiency**, in immunology you study all the severe immunodeficiency, the congenital ones, we talked about HIV but there

is a lot of moderate immunodeficiency, complement deficiency, they can be a cause of repeated infection and often patients don't have those measures to understand the cause.

• **Hepatitis and STIs**: we try to ask questions about sex, the way that we discuss it's not all that easy but it's important to understand the risk and the prevention. We talk about drugs; you will see that it's really common to ask a patient, we ask if they smokes or we ask if they drink alcohol. We don't often ask if they use drugs and you know there's so many drugs there's all the talk of chemsex, so we go back to sex and drugs. We ask about tattoos, it's important in terms of risk of HIV and other blood-borne diseases.

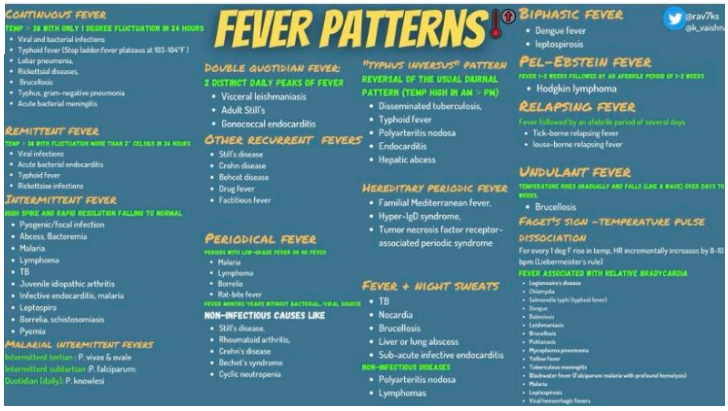
• A question we might get is **tissue organ abnormalities**, one respect for endocarditis, very strong one is having had another endocarditis in life, once you have damaged the valve the risk of getting second endocarditis is much higher. Same thing with TB, people might be at a high risk of aspergillosis, because of the previous damage to the structure.

• Risk of **hospitalization**. Why do we ask if the patient was hospitalized in the last three months? There's a common infection and colonization, so it's important that we consider these risks in terms of treatment.

• We ask about **devices and prosthetic materials,** we have now a patients hospitalized that use an aortic prosthesis because and the prosthesis got infected. Well he actually had is spondylodiscite and the infection spread fro the vertebrae to the prosthesis, but you can't just cut the aorta and then just put that there so this infection will not be able to be eradicated, because it has a device that cannot be changed and that is infected so in this case we will use suppressed treatment, so we try to keep on the treatment for a very long time.

• The last point is actually **allergy to antibiotics**. It's something we ask but I invite you to ask precisely, because people will tell that they are allergic to amoxicillin because they had diarrhea, everyone has diarrhea with antibiotics because of dysbiosis of microbioma etc. That's not allergy and in that case we will not use the galactose, so please characterize antibiotic allergy. In case we need certain antibiotics it's important that we talk to the allergologist and try to desensitize. There are several protocols, you can start with a low dose but if you increase the dose you get to a normal dose, you don't stop and people can tolerate. Don't do that if they have edema, but in milder cases you can do it.

Fig.51



The second point (*fig.49*) is **the pattern of symptoms and particularly of fever.** That's (*fig.51*) something I found on the internet it's well done. There are so many different kinds of fevers: intermittent fever, remittent fever, continuous fever…

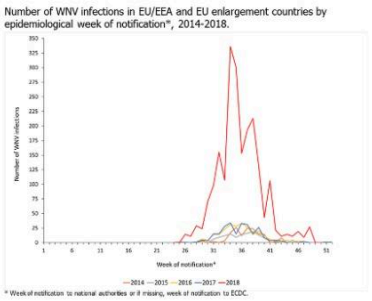
When we think of malaria as having fever between 2 or 3 days you will never see it, it's a historical thing in people who have not treated malaria and have had like high fever every 2 or 3 days, but it's not as impossible to see.

Another example is undulant fever: it's fever just going up and very slowly going down, very well tolerated by patients and you will smell the livestock smell in the patient. Brucellosis is there but I think in like 20 years I only saw one patient diagnosed like this because of undulant fever and this kind of smell. Fever patterns can be important in terms of just giving you a hint on what to do.

Look at number 3 (*fig.49*) **consider epidemiology:** we talk about trouble, of course we are understanding where people were, understanding epidemiology is important for how to change it. Now we started measuring and trying to diagnose dengue in all patients presented with fever, why? Because we know that last year we had 81 cases of dengue in Italy. People never heard about it, now dengue is autoctonous, so if you don't know it you will not just ask a test but miss dengue. Sometimes it is really uncommon, for exmple we had a patient that had malaria, and had never been out of Italy. That was really really uncommon and unfortunate.

I think using epidemiology can really help, you but you need to be updated on your own.

Fig.52 Epidemiology: time and space



That's (*fig.52*) the cases of West Nile Virus in Europe, well in 2018 there was a very high rise, but the important thing is that they were just from May to October, so zero cases in the other months, no mosquitos. But its changed with ticks. Now we have ticks from March to November.

Point number 4 (*fig.49*) is **consider more common bacteria,** so when we have to cover and start the treatment we need to think which is the most common cause of these? You will have books telling you all the protocols, such as triaxon plus azythromycin for pneumonia, ciprofloxacin for gastritis, fosfomycin for UTIs... You will have these kind of protocols and it's correct, but the important thing you have to think is which are the most common cause of that kind of infection, the most important thing is when we talk about (*unintelligible*) they are caused by 90% of stafilococci. When you go deeper, to necrotizing facsitis you do have a lot anaerobs, because in the fascia you don't have oxygen, so anaerobs are more important. Think about the most important ones, gram+, gram-, atypical pneumonia, we think legionella, we think chlamydia we think some other ones. Think of the more common groups of bacteria but also consider which patient might be colonized and infected by MDR. These are the maps (*fig.53*), when we talk about MDR bacteria, you see that Italy is really bad it is red in almost all maps, that means the prevalence of resistant bacteria is the highest in Europe. It is the case for example of vancomycin resistant enterococci (*fig.53 left*), which we have about 20-50%. This (*fig.53 right*) is the Klebsiella pneumoniae, 20-50%. If you do have Klebsiella think how many of my patients might have the resistant form? I need to understand the epidemiology.

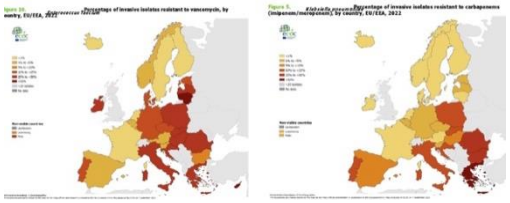


Fig.53

Q: unintelligible
A: There are several reasons, I think probably the best one is infection control. If you go to any hospital you will see you see how many doctors and nurses actually do wash correctly their hands before renting the room after touching something in the room after getting out of the room before putting gloves on and after taking out the gloves. I see people just putting intravenous devices with bare hands. I think this infection control is really bad. The second thing is about age, Italy is one of the oldest countries, elderly are high risk of resistant ones.
The important thing is to see not only the country level, but the regional, hospital level and even the patient level is very different. Patients that are admitted to urology wards have the highest risk of having the urine tract colonized by resistant bacteria, they go in and out of surgery… it's important to get an idea of which are the bacteria in in your hospital, in your ward, This is not really done systematically but it should.

Number 5 (*fig.49*) is actually think of abnormal things. We often are called when the doctors try anything so all the antibodies and see the patient with fever and raise CRP or whatever and ask us what clould that be. Thinking about **uncommon microorganism** is important. I just put here (*fig.54*) stuff that again we don't have time to think of, but Q fever is caused by coxiella burnetii, an uncommon pathogen transmitted by interactive animals, with unexplained fever an negative hemoculture.
Mucormycosis is a very uncommon fungus usually seen in severe immuno-compromized hosts.
Think of uncommon things is important and think of something that is not a bacteria.

Fig.54

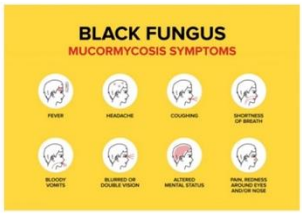
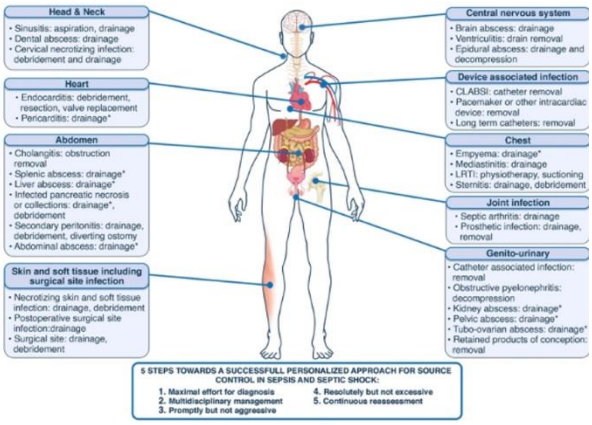


Fig.55



Last but not least consider **inefficient source control**. These (*fig.55*) are all infections that are not controlled, so even if you do the right antibiotic treatment for the right duration but if you are not able to clear the primary focus patients will have relapses or will still keep on with fever and raise inflammation. People can have sinusitis, in certain cases you don't aspirate, people will just keep on without curating. It's not really clear because sometimes they don't have many symptoms. Endocarditis is a very difficult diagnosis because you read in the books that people have fever and a heart murmur. Half of my patients have heart murmurs and fever so we will not do the diagnosis, so we need to think of a potential cause of endocarditis. I have a patient now that came in with bilateral pyelonephritis, young man, 40 degrees of fever, sepsis and I see in the scan and he has bilateral pyelonephritis. He's a male, he is young, it's really uncommon to have pyelonephritis and much more uncommon to have a bilateral pyelonephritis. That's the case in which I think of the endocarditis and embolization through the bloodstream.

The abdomen is very important in surgery. most of the patients in surgery might have deep infection tissue, like abdominal abscesses, no symptoms, just fever, and if you don't drain the abscess people have relapses.

For what concerns intravenous devices we will talk about bloodstram infection, BSI. If a patient has a central venous catheter, we need to understand if the bacteria comes from the central venous catheter or not. There are certain things we can do to understand and if the central venous catheter is infected, we need to remove it.

That is the last slide (*fig.56*), and it's about **iatrogenic cause of fever**. Sometimes we're told when people are taking ropenem, vancomycin, tetracyclin, acetomycin, fluconazole and fever is still there. We just go through the case, try to understand, read the source somewhere, there are drugs that can cause fever, even antibiotics. Sometimes what we do if the patient is not septic is remove all antimicrobial treatments, we wait for 48 to 72 hours to repeat all the cultures and we see the fever range. Fever can be caused by all these drugs (*fig.56*), look here many antibiotics can cause fever carbapenems, erythromycin, penicillins.

Table 3. Medications that Can Cause Fever of Unknown Origin

Anticonvulsants	**Cardiovascular drugs**
Barbiturates*	Captopril (Capoten)
Carbamazepine (Tegretol)	Hydralazine
Phenytoin (Dilantin)	Hydrochlorothiazide
Antihistamines	Methyldopa
Cimetidine (Tagamet)	Nifedipine (Procardia)
Ranitidine (Zantac)	Procainamide
Antimicrobials	Quinidine
Carbapenems*	**Nonsteroidal anti-inflammatory drugs**
Cephalosporins*	Ibuprofen
Erythromycin	Salicylates
Isoniazid	Sulindac (Clinoril)
Minocycline (Minocin)	**Others**
Nitrofurantoin (Furadantin)	Allopurinol (Zyloprim)
Penicillins*	Heparin
Rifampin	Meperidine (Demerol)
Sulfonamides*	Phenothiazines

**—The literature does not identify individual drugs in these classes.*

Information from references 20, 21, 25, and 26.

Fig.56