

Microbiology Nuts & Bolts: Session 5: Fever in a returned traveler

Aims & Objectives

- To know how to diagnose and manage life-threatening infections
- To know how to diagnose and manage common infections
- To understand how to interpret basic microbiology results
- To have a working knowledge of how antibiotics work
- To understand the basics of infection control

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- 30-40% of patients admitted to hospital will receive an antibiotic
- It is critical to pick out those with life-threatening conditions in order to manage them appropriately and correctly in order to give them the best chance of survival
- It is also important to know how to diagnose and manage common infections so that complications do not occur and patients get better as quickly as possible
- Knowing about antibiotics ensures the correct ones are used for the correct indications, prevents prescribing errors and keeps patients safe
- Everyone working in a healthcare setting has a responsibility to protect patients from harm including cross infection from other patients

Paul

- 18-year old student on a gap year
- Returned from travelling 1 week ago
- Presents to his GP feeling unwell with a fever
- On arrival to admission unit:
 - Temperature 40°C
 - Blood pressure 135/85 mmHg
 - Heart Rate 100bpm
 - Respiratory Rate 30bpm
- How are you going to manage him?

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- It is often the young and previously fit and well who present with fever after they have been travelling
- The majority of these patients actually don't have something exotic, they have the same normal infections that people who haven't travelled will get e.g. UTI, influenza, pneumonia etc
- 20-70% of travellers to developing countries develop a fever
 - 1-5% seek medical attention
 - 0.1% need treatment
 - Only 0.001% (1 in 100,000) die from their infection

Travel History

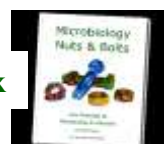
- Where have they been, for how long, and was it rural or urban?
- Have they had any contact with animals and insects?
- Have they been exposed to anyone else ill and how long ago was it?
- How long have they been unwell and when did it start?
- Have they received immunisations including both the primary childhood course and travel related?
- Did they take malaria prophylaxis? What and for how long?

All of the above informs your differential diagnosis

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- The most important part of the assessment of a patient with fever after travelling is the history, and in particular the details of where they have been e.g. it is not enough to just say someone has been to Thailand, you want to know exactly where in Thailand they have been as the types of infection risk can vary within a country



Differential Diagnosis

- Immediately life-threatening
 - Severe sepsis, pulmonary embolus, malaria, enteric fever (antibiotic resistant bacteria)...
- Common
 - Urinary tract infection (UTI), community acquired pneumonia (CAP), Dengue, HIV, Chikungunya, ...
- Uncommon
 - Leptospirosis, Melioidosis...
- How would you investigate this differential diagnosis?

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- The differential diagnosis for Paul includes a mixture of normal home grown infections as well as the more exotic diagnoses

Diagnosis	Investigations
Septicemia	• Urine, sputum and blood for the best of 3 different white blood cell (WBC) counts, blood count & ESR/CRP
UTI	• Urine for culture and sensitivity, blood for culture if severe
UTI with systemic signs	• Urine for culture and sensitivity, blood for culture if severe
UTI with systemic signs & risk factors	• Urine for culture and sensitivity, blood for culture if severe, consider HIV
UTI with systemic signs & risk factors & immunosuppression	• Urine for culture and sensitivity, blood for culture if severe, consider HIV, TB, CMV, PCP, Cryptococcus
UTI with systemic signs & risk factors & immunosuppression & recent travel	• Urine for culture and sensitivity, blood for culture if severe, consider HIV, TB, CMV, PCP, Cryptococcus, Leishmaniasis, Brucellosis, Q fever, Leptospirosis, Melioidosis
UTI with systemic signs & risk factors & immunosuppression & recent travel & immunosuppression	• Urine for culture and sensitivity, blood for culture if severe, consider HIV, TB, CMV, PCP, Cryptococcus, Leishmaniasis, Brucellosis, Q fever, Leptospirosis, Melioidosis, Dengue, Chikungunya, Malaria
UTI with systemic signs & risk factors & immunosuppression & recent travel & immunosuppression & recent travel	• Urine for culture and sensitivity, blood for culture if severe, consider HIV, TB, CMV, PCP, Cryptococcus, Leishmaniasis, Brucellosis, Q fever, Leptospirosis, Melioidosis, Dengue, Chikungunya, Malaria, Typhoid fever, Shistosomiasis, Babesiosis, Sickle cell disease
UTI with systemic signs & risk factors & immunosuppression & recent travel & immunosuppression & recent travel & immunosuppression	• Urine for culture and sensitivity, blood for culture if severe, consider HIV, TB, CMV, PCP, Cryptococcus, Leishmaniasis, Brucellosis, Q fever, Leptospirosis, Melioidosis, Dengue, Chikungunya, Malaria, Typhoid fever, Shistosomiasis, Babesiosis, Sickle cell disease, HIV, TB, CMV, PCP, Cryptococcus, Leishmaniasis, Brucellosis, Q fever, Leptospirosis, Melioidosis, Dengue, Chikungunya, Malaria, Typhoid fever, Shistosomiasis, Babesiosis, Sickle cell disease

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- In combination with a list of the type of infections that occur in different parts of the world, it is useful to have a list of the tests done for each condition
- The table of causes by region and the list of tests for those conditions are available in the book and on the website, Microbiology Nuts & Bolts.

Paul

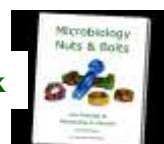
- Full history and examination
- Bloods
 - FBC, CRP, U&Es
 - Lactate
 - Blood Cultures
- Urine
 - Dipstick
 - MSU
- Sputum
- Chest X-ray
- Malaria antigen test PLUS thick and thin films x3
- Blood cultures for enteric fever & melioidosis - HIGH RISK
- Serology
 - HIV
 - Dengue
 - Chikungunya
 - Brucellosis
 - Q fever (Coxiella)
 - Leptospirosis
 - Melioidosis

Always send serum! Tests can always be added later

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- The tests represent a pretty standard initial screen for fever in a returned traveller.
- Whilst the list may appear long, it actually doesn't require a large number of samples:
 - 1x EDTA - for FBC and Malaria screen
 - 2x Clotted or lithium heparin - 1 for biochemistry, 1 for serology
 - Urine
 - Sputum
 - Blood cultures
- It is always worth sending a serum sample even if you don't know at the time what tests to request, ask for the sample to be saved (which can be done in most serology labs for up to 18 months) and give good clinical information (the lab will do the tests you should have asked for even if you didn't know what they were)



Paul

- Bloods
 - WBC $0.8 \times 10^9/L$
 - Platelets $90 \times 10^9/L$
 - CRP 112
 - Lactate 2.5mmol/L
 - U&Es - Urea 11, Creat 97
- Urine
 - Dipstick -ve leuc, -ve nitrites
 - Microscopy $>100 \times 10^6$ WBC, no epithelial cells
- How would you treat Paul?



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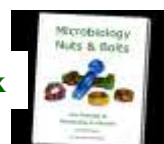
- It is essential to know the normal values of all tests within your hospital
- Full blood count (FBC)
 - The total white blood cell count can go up or down in infection
 - The differential white blood cell count can help to point to the type of organism but nothing is 100% (neutrophils = bacteria/fungi, lymphocytes = viruses, eosinophils = parasites)
 - Platelets are an acute phase reactant and go up in infection (they can go down in severe infections when disseminated intravascular coagulation DIC develops)
- CRP (C reactive protein)
 - Produced in liver in response to inflammation, often goes up in bacterial infection
 - >200 usually significant, otherwise need to know what the trend is i.e. increasing, decreasing
 - Beware, patients in liver failure do not produce much CRP – use other markers of liver synthetic function to guide you e.g. INR, Albumin
- Urea & Electrolytes (U&Es)
 - Antibiotics can only be prescribed safely if the patients kidney function is known
- Urine point of care includes a dipstick test
 - Leucocytes indicate the presence of white blood cells and hence inflammation in the urinary tract
 - Bacterial nitrites are breakdown products from the action of bacteria on Urea and indicate the presence of bacteria
 - Urine samples are prone to contamination so it is important to advise patients how to take a proper MSU
 - Part the labia or retract the foreskin, void the first part of the urine stream and discard, then catch the middle part of the stream.
 - The first part of the urine is prone to bacterial contamination from the urethra giving false positive results
- Chest X-ray is required by the British Thoracic Society in order to diagnose pneumonia in hospital

Paul

- Given oxygen and fluid resuscitated
- Started empirically on IV Ceftriaxone 2g OD PLUS IV Gentamicin 5mg/kg
- Initial malaria screen negative
- Would you do anything differently for Paul?
- IV Quinine was started despite negative malaria antigen test

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- Sometimes it is possible to wait before starting antibiotics in patients, and if they are cardiovascularly stable this is the right thing to do most of the time. Once antibiotics have been started it is very difficult to grow bacteria, and this compromises the ability to make a definite diagnosis
- Paul's observations though show that he is not stable and treatment needs to be started straight away
- Because the exact diagnosis is unknown, empirical treatment should be aimed at the most serious infections:
 - Ceftriaxone PLUS Gentamicin – sepsis including typhoid and paratyphoid
 - Quinine – severe malaria
- It is always prudent to discuss sick patients who have recently returned from abroad with the local Infectious Diseases Physicians, as this is their area of expertise



Next Day

- Diffuse maculopapular rash all over body
- Remains neutropaenic with low platelets
- Respiratory function worsens and develops pleural effusions
- Observations prior to ward round:
 - Temperature: 41°C
 - Heart rate 110bpm
 - Blood pressure 110/95 mmHg
- What are you going to do for Paul now?

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- Paul is very unwell, he is starting to go in to organ failure
- Senior support is required, as is Critical Care advice
- He should be discussed again with the local Infectious Diseases service, who will want an update on all of his latest results

- Further investigations:
 - Malaria antigen tests and blood films: negative x3
 - Blood cultures: negative
 - Urine culture: negative
 - Sputum culture: respiratory commensals only
 - HIV serology: negative
- What is the most likely diagnosis?
- How should he be managed?

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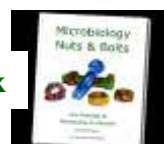
- Of the original differential diagnosis, the only one that causes all of Paul's symptoms (including the rash) which has not yet been excluded is Dengue
- It is important to be aware of the signs of the serious and potentially life-threatening versions of these types of infections: in this case if Paul has Dengue then the narrow pulse pressure suggests Dengue Shock Syndrome which has a mortality of up to 40%!
- If you don't know the warning signs then discuss the patient with an Infectious Diseases Physician and specifically enquire about what you should be looking out for then document it clearly in the patient's notes and let the rest of the team know.

- Transferred to critical care for closer monitoring and management of fluid balance
- Continued IV Ceftriaxone
- Stopped IV Gentamicin and Quinine
- Regular discussion with regional infectious diseases unit

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- Malaria has been ruled out, and there is little need to continue with empirical Gentamicin given that the blood cultures and urine are negative
- Typhoid and Paratyphoid have not been ruled, and given the nature of his rash it is possible that Paul has meningococcal sepsis which is now added to the differential diagnosis, and hence the Ceftriaxone is continued



- 5 days after admission serology confirms Dengue virus infection
- Diagnosis: Dengue Shock Syndrome
- Paul makes a slow recovery and eventually goes home 4 weeks later

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- Paul is confirmed as having Dengue
- There is no specific treatment for Dengue, supportive care is required
- Paul's physiological parameters are consistent with Dengue Shock Syndrome

Malaria

- Malaria is the most important potentially fatal disease in travellers returning from the tropics and in particular Sub-Saharan Africa
- Five main species of malaria:
 - Plasmodium falciparum (most common and most deadly)
 - Plasmodium vivax (benign)
 - Plasmodium malariae (benign)
 - Plasmodium ovale (benign)
 - Plasmodium knowlesi (rare - only found in some forested areas of South-East Asia)
- Incubation period
 - Falciparum malaria < 1 month for
 - Benign malaria up to 1 year or more

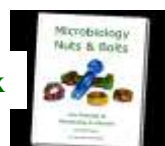
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- There are up to about 1500 cases of Malaria diagnosed every year in the UK
- It is recommended that all patients with Malaria diagnosed in the UK are admitted to hospital for 24 hours as they can deteriorate rapidly
- Once they are stable they can usually be managed as an outpatient with oral medication



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- Malaria is a disease of the tropics because this is where the Anopheles mosquito is found
- It is only the female mosquito that bites, the male is vegetarian!
- Biting tends to occur at dusk when the mosquito is most active
- Travellers to malaria areas should be advised about bite avoidance using insect repellents, wearing long trousers and shirts with long sleeves, sleeping under a mosquito net and taking malaria prophylaxis



Symptoms of Malaria

Central
- Headache

Systemic
- Fever

Muscular
- Fatigue
- Pain

Skin
- Rash

Stomach
- Nausea
- Vomiting

Skin
- Chills
- Sweating

Respiratory
- Dry cough

Spleen
- Enlargement

Severe disease

- >2% parasitaemia
- Cerebral malaria
- Pulmonary oedema
- Severe anaemia
- Hypoglycaemia
- Uraemia
- Lactic acidosis

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- Malaria is a potentially fatal infection
- Severe Malaria requires hospital admission, IV medication and usually critical care support
- Every doctor who might look after a patient with malaria should be familiar with the signs of severe infection

Relapsing fevers occur in Vivax and Ovale due to chronic infection of liver cells

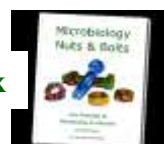
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- Some species of Plasmodia can cause relapsing fevers, and present months to years after the original infection
- They remain in the hepatocytes from where they are released intermittently and cause fever
- They can be difficult to diagnose because often there is no recent travel history to give a clue to the diagnosis

- **Antigen test**
 - Quick, easy to perform
 - Does not always differentiate species
 - Does not give parasite load
- **Microscopy**
 - Thick and thin films
 - Gives species and parasite load
 - Requires expertise and experience therefore difficult in UK
- **Need both tests combined**

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- The diagnosis of Malaria is made by testing EDTA blood samples on 3 consecutive days by antigen and thick and thin films
- It is important that patients stop their malaria prophylaxis whilst they are being investigated as this can interfere with making the diagnosis and the patient will not come to harm if the prophylaxis is restarted once the diagnosis has been excluded (don't forget to restart it!)
- The antigen diagnoses malaria and the films give the species and assess the severity, you need both



Enteric Fever

- Severe life-threatening infection in travellers returning from Asia
- Typhoid and Paratyphoid
 - Caused by *Salmonella typhi* & *Salmonella paratyphi*
- Incubation period 7-18 days (range 3-60 days)
- Vaccination:
 - Incomplete protection from Typhoid (Approx. 70%)
 - No protection from Paratyphoid

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- Enteric fever is a serious infection of the gastrointestinal tract that leads to sepsis and systemic infection, for which the mortality in untreated cases is up to 40%
- It is caused by *Salmonella typhi* and *Salmonella paratyphi*
- The first line treatment of enteric fever in hospital is IV Ceftriaxone, out of hospital PO Azithromycin is the most reliable
- Ciprofloxacin resistance is too high to recommended it's use first line (60% in Typhoid, 85% in Paratyphoid)

- Clinical features
 - Fever
 - Headache (may have meningism)
 - Constipation or diarrhoea
 - Dry cough
- Less commonly
 - Gastrointestinal bleeding
 - Gastrointestinal perforation
 - Encephalopathy

- Investigations
 - Blood cultures
 - Urine culture
 - Stool culture

All cultures are HIGH RISK for laboratory staff

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- Enteric fever can often be mistake for meningitis given the headache that often occurs, but in practical terms this does not stop you treating the patient appropriately because both infections are treated empirically with IV Ceftriaxone
- Pure cultures of *Salmonella typhi* and *Salmonella paratyphi* are potentially hazardous for laboratory staff to handle therefore all samples from patients where this is a possible diagnosis should be labelled "High Risk"

Dengue

- Arbovirus found throughout tropics mainly Asia and South America
- Incubation period 4-8 days (range 3-14 days)
- Transmitted by day-biting *Aedes* mosquito (especially *A. aegypti*)



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- Dengue is a viral infection transmitted by the *Aedes* mosquito which bites during the day (this is different to the *Anopheles* mosquito that transmits malaria when biting at dusk)
- Travellers to Dengue areas should be advised to cover up with long trousers and long sleeved shirts as well as use insect repellents during the day time, however they often don't as these areas tend to have hot climates and travellers find long clothes uncomfortable... you can only advised, you can't force them to comply!

- Classical dengue fever
 - Mild febrile illness
 - Headache, retro-orbital pain, myalgia, arthralgia and rash (changing from erythema to petechiae)
 - Rarely hepatitis, myocarditis, encephalitis or neuropathy
- Dengue haemorrhagic fever (DHF) – mortality 20%
 - Haemorrhages
 - Platelet count $<100 \times 10^9/L$
 - Evidence of plasma leakage (>20% increase in packed cell volume during illness) OR clinical signs of plasma leakage (e.g. effusions)
- Dengue shock syndrome – mortality 40%
 - Narrow pulse pressure $<20\text{mmHg}$ or systolic blood pressure $<90\text{mmHg}$

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- Dengue is often thought of as a mild self-limiting febrile illness but it is important to remember that Dengue can kill
- There are 4 main sub-types of Dengue, and the more you have had the more severe your Dengue becomes – it is actually the immune response that becomes more severe and damages the body
- It is worth telling patients who have had Dengue once about the risks of getting Dengue again in the future... next time they might actually cover up in the day time as advised
- Patients with severe Dengue need Critical Care support and should ideally be cared for by Infectious Diseases Physicians

- Investigations
 - Symptoms ≤ 4 days: PCR on whole blood (EDTA)
 - Symptoms >4 days: Antibody test for IgM on serum
- Treatment
 - Supportive care
 - Avoid NSAIDs as increased risk of bleeding

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- Dengue is diagnosed with a combination of molecular and serology tests
- The mainstay of Dengue treatment is good supportive care

Chikungunya

- Arbovirus found as part of ongoing epidemic in Mauritius and South & South-East Asia
- Incubation period 2-3 days (range 1-12 days)
- Transmitted by day-biting *Aedes* mosquito (especially *A. aegypti*)



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- Like Dengue, Chikungunya is a viral infection transmitted by the *Aedes* mosquito which bites during the day (this is different to the *Anopheles* mosquito that transmits malaria when biting at dusk)
- Travellers to Chikungunya areas should be advised to cover up with long trousers and long sleeved shirts as well as use insect repellents during the day time, however they often don't as these areas tend to have hot climates and travellers find long clothes uncomfortable... you can only advise, you can't force them to comply!

- Similar to classical dengue fever
 - Mild febrile illness
 - Headache, retro-orbital pain, myalgia, arthralgia and rash (changing from erythema to petechiae)
 - Rarely hepatitis, myocarditis, encephalitis or neuropathy
 - Arthralgia - often more prominent
 - Fever usually resolves in 5-7 days
 - Up to 30% have chronic arthropathy for months to years

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- Chikungunya does not appear to cause severe infections in the same way as Dengue, however long term joint problems are common

- Investigations
 - Symptoms \leq 5 days: PCR on whole blood (EDTA)
 - Symptoms $>$ 5 days: Antibody test for IgM on serum
- Treatment
 - Supportive care

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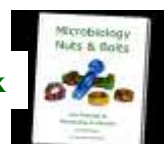
- Chikungunya is diagnosed with a combination of molecular and serology tests
- The mainstay of Chikungunya treatment is good supportive care

Treatment: Malaria

Treatment for <i>Plasmodium</i> Malaria OR Unknown Malaria Species	
Mild/Moderate (adult)	PO Quinine 600mg TDS for 7 days PLUS PO Doxycycline 200mg QD for 7 days OR PO Clindamycin 450mg TDS for 7 days
Severe OR $>$ 2% parasitaemia OR if ill by mouth	IV Quinine loading dose 20mg/kg (max 1.4g) THEN 10mg/kg TDS (max 700mg) PLUS PO Doxycycline OR PO Clindamycin (as above) If ill by mouth, start oral asap when able
If allergic to Quinine	PO OR IV Artesunate Discuss with Infectious Diseases Physician or Microbiologist as not easily available in the UK

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- Malaria treatment is based upon severity, but the British Infection Society recommend that all patients irrespective of how they are treated should be admitted to hospital for the first 24 hours because they can deteriorate rapidly
- Quinine is still the main treatment, although Artemether is becoming more popular
- Both Quinine and Artemether are derived from plants that grow in malaria areas – isn't nature clever?!



Treatment: Tropical Infections

Treatment of Other Tropical Infections
 (Discuss with an Infectious Diseases Physician or Microbiologist)

Dengue	No specific treatment, however observe carefully for signs of dengue haemorrhagic fever or dengue shock syndrome, as these may require critical care support and have a mortality up to 45% Dengue haemorrhagic fever = platelet count <100x10 ⁹ /L, PLUS objective evidence or clinical signs of plasma leakage (>20% increase in packed cell volume, effusions, hypoproteinaemia) Dengue shock syndrome = narrow pulse pressure <20mmHg OR systolic blood pressure <90mmHg PO Doxycycline 100mg BD for 7 days
Shistosomiasis	IV Captopril 2g OD for 14 days (patients can be converted to PO Clorazepate OR PO Atifenozin (depending on antibiotic sensitivities))

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- The most important aspect of treating patients with unusual tropical infections is to seek and take the advice of experts such as Infectious Diseases Physicians

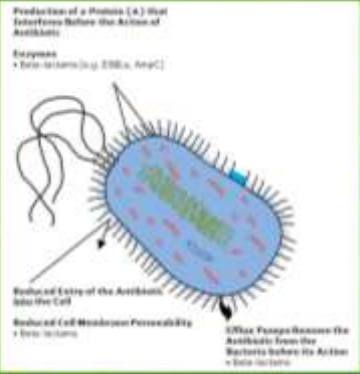
Caution: Global Antibiotic Resistance & Carbapenemases

- Carbapenems are the broadest spectrum antibiotics available
 - Ertapenem
 - Meropenem
 - Imipenem
 - Daripenem
- Carbapenemases are Beta-lactamase enzymes which hydrolyse carbapenems
- Confer resistance to ALL Beta-lactam antibiotics
- Often transferable on mobile genetic element e.g. plasmid



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- Antibiotic resistance is becoming a major world health problem, and people who travel can acquire resistant bacteria that may not cause symptoms and signs at the time but which become part of their normal flora
- 85% of infections are caused by a person's own bacterial flora getting in to a site where they should not be e.g. bowel flora getting in to the urinary tract to cause a UTI
- If a patient's bacterial flora is resistant to antibiotics then most of the infections that patient gets will be due to resistant bacteria
- The latest cause for concern around the world are Gram-negative bacteria such as *E. coli* and *Klebsiella* sp. that produce carbapenemases



Production of a Protein (A) that Interferes Before the Action of Antibiotics

Enzymes
 • Beta-lactams (e.g. ESBLs, AmpC)

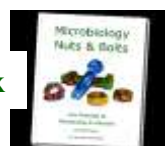
Reduced Entry of the Antibiotic into the Cell

Reduced Cell Membrane Permeability
 • Beta-lactams

Efflux Pumps Remove the Antibiotic from the Bacterium Before its Action
 • Beta-lactams

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- Bacterial resistance to the carbapenem antibiotics is usually due to either the production of an enzyme e.g. carbapenemase, or the combination of an enzyme e.g. AmpC, ESBL with the loss of a porin in the bacterial cell membrane (the combination lets less antibiotic in to the bacteria, and some of what does get in is then broken down by the enzyme)



- The "Big Five":
 - *Klebsiella pneumoniae* carbapenemase (KPC)
 - Verona integron-encoded metallo-beta-lactamase (VIM & IMP)
 - New Delhi metallo-beta-lactamase (NDM)
 - Oxacillin Carbapenemases (OXA)
- Should be considered in all patients transferred to UK from abroad
- Recent guidance supports screening and infection control precautions for these patients



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- There are recent guidelines from the DoH which are supposed to help us manage carbapenemase producing bacteria, but they are quite cumbersome and difficult to implement

- Treatment
 - Colistin PLUS carbapenem
 - Colistin PLUS Tigecycline
 - Colistin PLUS aminoglycoside (very nephrotoxic)
- Outcome
 - Mortality > 50% if active infection (true "Superbugs!")

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- The recommended treatments for the carbapenemase producing bacteria involve the combination of Colistin with another antibiotic
- If the bacteria is not too resistant to Meropenem (a carbapenem) then this can be combined with Colistin
- Tigecycline can be used for systemic infections and pneumonia caused by carbapenemase producing bacteria but not UTIs because Tigecycline is not active in the urinary tract
- The combination of Colistin with Amikacin (an aminoglycoside) is very effective at killing Gram-negative bacteria, unfortunately it is also very good at killing the patients kidneys and so is often only used as a last resort

Conclusions

- Keep fever in a returned traveller simple
- Take a detailed travel history to identify what they might have acquired
- Send the correct specimens for the potential diagnoses
- Remember "common things are common" don't forget UK acquired infections
- Don't forget to treat life-threatening infections whilst waiting for "tropical" investigation results!

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- Doctors often get confused about managing fever in a returned traveller but as long as a systematic approach is used then it need not be too difficult
- The most important part of managing these patients is to take a detailed travel history; it may not mean much to you but an Infectious Diseases Physician will want to know and it will probably mean more to them
- Patients who have returned from exotic locations can still get the home grown infections everyone else gets so don't forget to manage for those as well
- If in doubt and the patient is unwell, cover for the serious and life-threatening infections whilst waiting for results of investigations to come back

