

## Microbiology Nuts & Bolts: Session 6: Sepsis

### 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

### Geoff

- 66 years old
- Presents with shortness of breath
- Recent admission due to MI
- On examination
  - Temperature 35.5 °C
  - Crackles throughout precordium
  - Heart Rate 120bpm
  - B.P. 120/75
- How should Geoff be managed?

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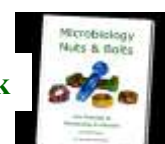
- A vague history but allows the process of diagnosing the patient to begin
- There are non-infectious reasons for crackles in the chest therefore it is important not to become too fixated on a diagnosis without considering all possibilities
- All doctors should know the limitations of the tests they do including basic observations not just laboratory tests
- Normal temperature is 36.5°C to 37.5°C
  - Often a tympanic temperature which is actually a peripheral temperature not a core temperature
  - Can vary from core by up to +/- 1°C
  - Works by infrared looking at the tympanic membrane therefore any obstruction in the ear can lead to a false temperature result
- Worryingly Geoff is hypothermic and tachycardic, and he has a potential focus of infection in his chest, he is septic and needs urgent treatment

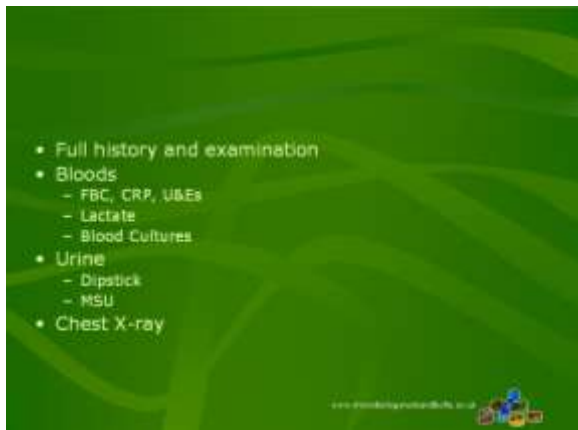
### Differential Diagnosis

- Immediately life-threatening
  - Severe sepsis, pulmonary embolus, myocardial infarction...
- Common
  - Urinary tract infection (UTI), community acquired pneumonia (CAP), aspiration pneumonia...
- Uncommon
  - Infective endocarditis...
- How would you investigate this differential diagnosis?

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- Formulating a differential diagnosis appears to be going out of fashion but it is essential if diagnoses are not to be missed
- A systems approach (e.g. respiratory, cardiac, Gastrointestinal, genitourinary, neurological, skin, bone, joint, etc) can be fitted to a template of life-threatening, common, uncommon in order to complete the differential but considering the life-threatening first ensures these are dealt with as early as possible
- It is not a static process but can change throughout a patients management as new information becomes available and their clinical condition changes





- 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
- Lactate
  - High lactate indicates inadequate tissue perfusion and anaerobic metabolism, and can be a sign of severe sepsis
- 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



- Patient has raised high white blood cells and CRP indicating a significant inflammatory problem and therefore a likely infection
- U&Es shows a degree of renal failure and may make antibiotic dosing problematic
  - The urine microscopy indicates a possible UTI but requires a culture before being diagnostic as many patients with a systemic inflammatory response will have pyuria
- The chest x-ray shows a device in the upper left chest wall and multiple small shadows throughout the lung fields
  - There are two main types of implantable device seen on chest x-rays, permanent pacemakers (PPM) and implantable cardioverter defibrillators (ICD)
  - PPM usually has 2 wires but can occasionally have



- only 1
- ICD has 1 wire but it is surrounded by insulation at certain key points to prevent it defibrillating structures it shouldn't when it goes off such as where it enters the atrium and passes through the atrioventricular valve (as in this patient's chest x-ray)

- What is the diagnosis?
- How would you manage Geoff now?
- What are the common bacterial causes of sepsis?


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- This chest x-ray appearance would be unusual for a pneumonia but would be consistent with multiple pulmonary emboli
- The ICD leads are implanted in the right side of the heart and therefore if infective and a vegetation forms, micro-emboli would go to the lungs (unless there was a ventriculoseptal defect)
- It is likely that Geoff has an infected ICD, and therefore essentially a right-sided endocarditis
- Treatment should be directed at right-sided endocarditis and the ICD removed if possible
- The common causes of sepsis are the Gram-negative bacilli and cocci as well as Staphylococcus aureus

## Sepsis

### Definitions

- Sepsis: clinical evidence of infection plus evidence of systemic response to infection
- Sepsis syndrome: sepsis plus evidence of altered organ perfusion
- Severe sepsis: sepsis associated with organ dysfunction, hypoperfusion or hypotension



- Sepsis is a clinical diagnosis, not a laboratory one
- Severe sepsis occurs when there is also end organ dysfunction and this can be diagnosed through the use of laboratory tests
- For more information see [www.survivingsepsis.org](http://www.survivingsepsis.org)

## Sepsis

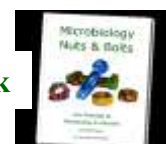
### Definitions

- Sepsis: clinical evidence of infection
- Severe sepsis: sepsis associated with organ dysfunction, hypoperfusion or hypotension

**For every hour delay in treatment mortality increases by 7% up to 6 hours (42%)**



- Every hour counts when treating septic patients and early intervention really does save lives
- Resuscitation and antibiotics should be given as fast as possible, ideally within an hour of arrival in the hospital



## Febrile neutropaenia & sepsis

- Neutrophils  $< 0.5 \times 10^9$  PLUS temperature  $> 39^\circ\text{C}$  once or  $> 38^\circ\text{C}$  twice
- Need bactericidal antibiotics specifically targeted against Gram-negative bacteria and *Staphylococcus aureus*
- Antibiotics should be administered within 1 hour
- If possible try to take blood cultures before antibiotics but DO NOT delay antibiotics unnecessarily - Medical emergency
- Empirical treatment when source unknown NOT treatment when source known e.g. Community Acquired Pneumonia

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- Sepsis in a patient who is already neutropaenic is a different clinical entity to sepsis causing neutropaenia and yet many doctors make the mistake of assuming that if you are septic and neutropaenic then you should always be treated as neutropaenic sepsis
- The distinction is important because the causes can be different
- Sepsis in a patient who is already neutropaenic can be due to opportunistic micro-organisms as well as those which can cause sepsis in immunocompetent patients
- Sepsis which is overwhelming and induces neutropaenia itself is usually caused by the Enterobacteriaceae, *Neisseria meningitidis* or *Staphylococcus aureus* and the neutropaenic aspect is a sinister sign and shows that the patient is unable to cope with the infection
- Both are emergencies requiring urgent management

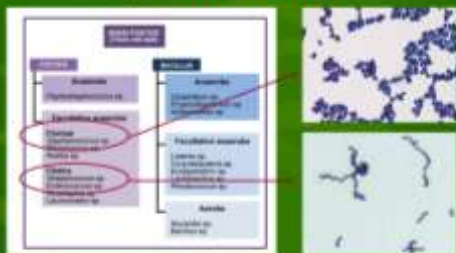
## Culture: classification of bacteria



Cause of sepsis can originate in any body organ

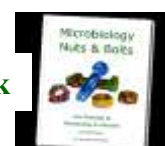
- Any bacteria can cause sepsis but the most common are the Enterobacteriaceae, *Neisseria* sp and *Staphylococcus aureus*

## Classification of Gram-positive cocci

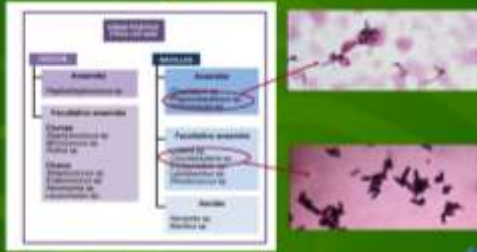


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- Most microbiology text books list numerous biochemical tests to aid in distinguishing Staphylococci from Streptococci but these are of no use to ward doctors
- In practical terms Gram-positive cocci can be distinguished by:
  - Staphylococci form clumps
  - Streptococci form chains



## Bacterial Identification: Gram-positive bacilli



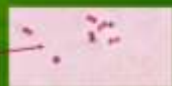
- The most clinically significant Gram-positive bacillus is *Listeria monocytogenes*
- The more common isolates are the skin bacteria such as the Diptheroids and Propionibacteria which are common blood culture contaminants

## Bacterial Identification: Gram-negative bacilli



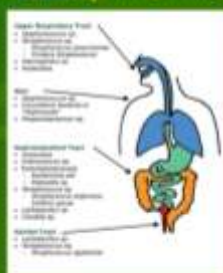
- The Enterobacteriaceae and *Pseudomonas* sp. are the most common clinical isolates from the Gram-negative bacilli
- The main distinguishing features for these two groups are that the Enterobacteriaceae are Facultatively anaerobic (i.e. will grow both aerobically and anaerobically) whereas *Pseudomonas* sp. are aerobic only
- In clinical terms if a blood culture has a Gram-negative bacillus in both the aerobic and anaerobic bottle it will be an Enterobacteriaceae, whereas if it's only in the aerobic bottle it may well be a *Pseudomonas* sp.

## Bacterial Identification: Gram-negative cocci

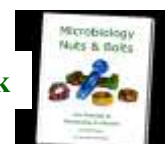


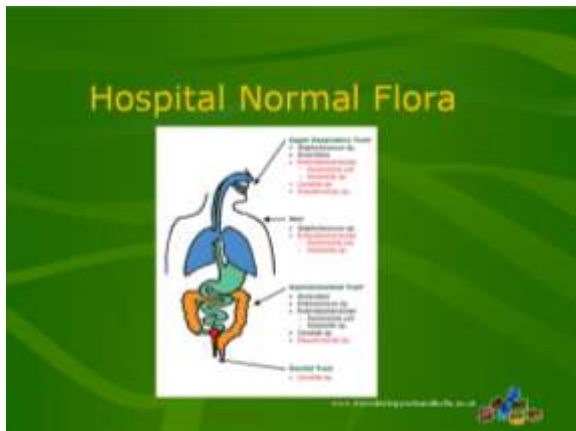
- There are 2 main *Neisseria* sp. which can cause disseminated infection and sepsis though in the UK it is really only *Neisseria meningitidis* that we see
- Some countries (such as the USA) appear to have a strains of *Neisseria gonorrhoea* which is more likely to disseminate and cause sepsis than the UK strains

## Community Normal Flora

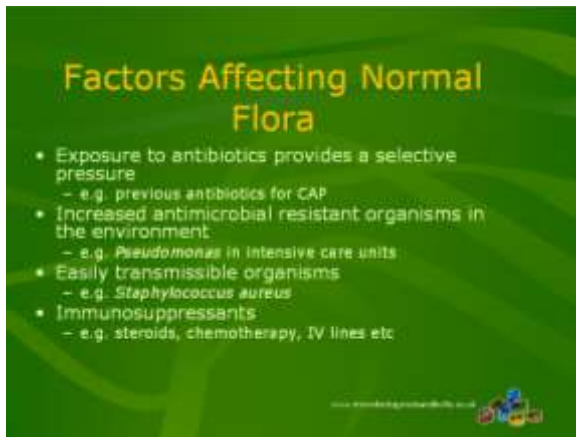


- If a septic patient grows a bacteria from their blood culture then knowing normal flora allows you to focus attention on the likely originating part of the body and hence a potentially reversible cause e.g. *E. coli* is likely to originate in an intra-abdominal organ such as the urinary tract, biliary tree or bowel





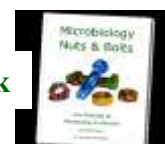
- It is important to remember that normal flora starts to change in hospitalised patients and so the causes of sepsis from specific body sites also changes



- There are many circumstances that can affect a patient's normal flora
- Understanding how this happens can allow predictions to be made as to how the flora will change and therefore how this will influence the types of bacteria causing infections
- Antibiotics will tend to remove sensitive bacteria from the flora leaving the resistant ones behind, for this reason if antibiotics have been used as prophylaxis for a procedure any infection occurring immediately after the procedure is likely to be resistant to those antibiotics



- The CT scan suggests multiple pulmonary metastases but this is unlikely to have occurred out of the blue
- Remember, most support services like pathology laboratories and radiology are only as good as the information they receive, in this case the radiology lab were given no information about the patient being septic and were only asked to look for a lung pathology
- Always provide as much clinical information as you can when liaising with support specialties, it is in the interest of both you and your patients



## Culture: how is a blood culture processed?

- Taken using aseptic technique into broth culture
- Automated system scans bottles every 10 minutes looking for logarithmic growth
- If positive (usually 24-48 hours)
  - Gram film Same day
  - Identification by MALDI-TOF Same day
  - Agar culture 24 hours
  - Sensitivity testing 24 hours

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- Most healthcare staff are under the mistaken belief that microbiology laboratories do something special with blood cultures when they arrive in the lab and that they will be ready in 48 hours
- In fact the system is completely automated
- The blood culture bottles are loaded on to an automated incubator and left
- The incubator scans the bottle every 10 minutes looking for logarithmic growth (the incubator is actually looking for logarithmic CO<sub>2</sub> production from replicating bacteria causing a pH change in the bottle)
- Once this growth phase occurs the bottle is taken off the incubator and further work including Gram's stain and culture on agar begins, as well as identification by mass spectrometry (MALDI-TOF – Matrix-assisted laser desorption/ionisation time of flight))
- Most significant blood cultures will signal within 48 hours but it is entirely dependent on the amount of organism that went in to the bottle, whether the patient was on antibiotics and the species of bacteria in question
- Most laboratories will telephone out all positive blood cultures when a result is available

## Antibiotic sensitivity testing

- Laboratory cut-off based upon physiologically achievable antibiotic levels in a normal person (i.e. 60-70kg)
- Takes 24-48 hours depending on antibiotic tested
- Methods
  - Disc diffusion
  - Etest MIC

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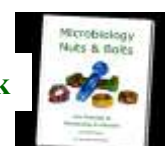
- Antibiotic sensitivity in UK laboratories is usually tested for using the BSAC method where antibiotic impregnated filter paper discs are put on agar inoculated with bacteria and then incubated overnight
- The size of the zone where the bacteria have been unable to grow is then measured and compared to a known standard value
- The value is related to the combination of antibiotic, bacterial species and body site
- Most antibiotic resistance is relative, i.e. it is not possible to get enough antibiotic into the body site to treat the organism however some is absolute e.g. MRSA is completely resistant to the Beta-lactam antibiotics
- For more serious infections such as infective endocarditis antibiotic advice is based upon the minimum inhibitory concentration (MIC) which is the lowest concentration required to prevent the bacteria from growing, usually test for with the Etest method where an antibiotic graduated impregnated strip is placed on the agar and the MIC corresponds to where the bacteria intercept the strip

## How do you choose an antibiotic?

- What are the common micro-organisms causing the infection?
- Is the antibiotic active against the common micro-organisms?
- Do I need a bactericidal antibiotic rather than bacteriostatic?
- Does the antibiotic get into the site of infection in adequate amounts?
- How much antibiotic do I need to give?
- What route do I need to use to give the antibiotic?

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- In this case the patient clearly needs antibiotics
- Because he is so unwell he needs antibiotics that will kill the bacteria as quickly as possible
- The antibiotics should be bactericidal and should be given intravenously in the high doses

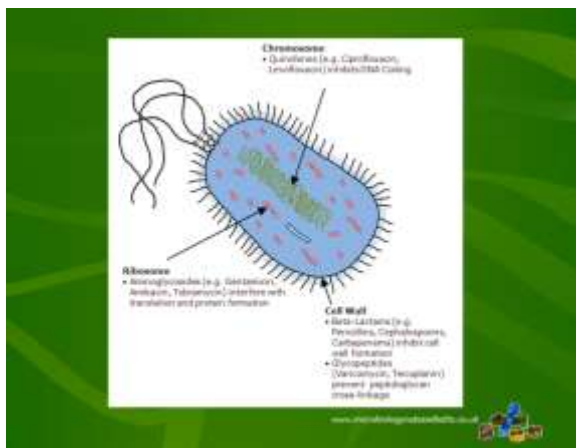


In reality...

Infection	Antibiotic	Mechanism of action	Side effects	Contraindications	Precautions
Respiratory	Penicillin V	Inhibits cell wall synthesis	None	None	None
UTI	Trimethoprim/Co-trimoxazole	Inhibits folic acid synthesis	Nausea, diarrhoea	None	None
UTI	Fluoroquinolones	Inhibits DNA gyrase	None	None	None
UTI	Nitroimidazole	Inhibits pyruvate dehydrogenase	None	None	None
UTI	Polymyxins	Disrupts cell membrane	None	None	None
UTI	Carbapenems	Inhibits cell wall synthesis	None	None	None
UTI	Monobactams	Inhibits cell wall synthesis	None	None	None
UTI	Vancomycin	Inhibits cell wall synthesis	None	None	None
UTI	Tetracyclines	Inhibits protein synthesis	None	None	None
UTI	Macrolides	Inhibits protein synthesis	None	None	None
UTI	Chloramphenicol	Inhibits protein synthesis	None	None	None
UTI	Sulfonamides	Inhibits folic acid synthesis	None	None	None

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- Empirical antibiotic guidelines vary a little between hospitals based upon local epidemiology, therefore it is important to know your own guidelines
- They are empirical, that is they are designed to initiate treatment when the cause is unknown, they are not definitive for a specific cause
- Once the cause of an infection is known the antibiotics should be changed to specifically target that infection, the guidelines have done their job by that time and are no longer required



- The mechanisms of action of antibiotics causes a lot of confusion (and the similarity of names makes it even worse – anything ending in “mycin” is derived from a fungus and has nothing to do with the class of the bacteria!)
- It can be helpful to split them into groups as this at least reduces the list to a more manageable size:
  - Mainly act on the cell wall
    - If no cell wall or unable to penetrate Gram-negative cell membrane to cell wall then no activity i.e. glycopeptides have no Gram-negative activity
  - Mainly act on the ribosome
    - Gentamicin acts on the ribosome but actually also displays concentration dependent killing of bacteria so is very useful in sepsis
  - Mainly act on the chromosome
    - Quinolones interfere with DNA coiling and are broad spectrum and cidal, however there is some evidence that they promote mutation and therefore resistance in bacteria

- ### Other considerations
- Are there any contraindications and cautions?
    - e.g. quinolones with methotrexate
  - Is your patient allergic to any antibiotics?
    - e.g.  $\beta$ -lactam allergy
  - What are the potential side effects of the antibiotic?
    - e.g. Aminoglycosides and hearing and balance disturbance
  - What monitoring of your patient do you have to do?
    - e.g. Teicoplanin levels and full blood count
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- It always worth checking if a patient is allergic to whatever drug you are going to give them although be sure they are describing an allergy not just a recognised side-effect
- Some antibiotics have common or severe side effects and doctors should be familiar with these and warn patients about them, as part of the informed consent to treatment process
- Many antibiotics also require monitoring for these side effects and this should be checked in the BNF at the time of prescribing
- Patients given aminoglycosides such as gentamicin should be assessed for hearing and balance disturbance as well as renal failure




## Geoff

- Started on IV Co-amoxiclav and Clarithromycin
- Continued to deteriorate
- Discussion about putting on Liverpool Care Pathway (LCP) as metastatic malignancy
- Noted that the implantable cardioverter defibrillator (ICD) was implanted 3 weeks before he became unwell at time of MI
- Blood culture isolate identified as *Staphylococcus epidermidis*
- What is the most likely diagnosis?
- How should Geoff be managed?



- The ICD is still the most likely source of this patient's infection, and the "metastases" are almost certainly septic emboli
- He should be started on a high dose of a glycopeptide such as Teicoplanin or Vancomycin
- An Echocardiogram will show if the ICD is definitely infected as will serial blood cultures
- If the ICD is the source it will need to be removed, but this is often easier said than done

- Urgent echocardiography confirmed vegetation on ICD wires
- Diagnosis Infective Endocarditis
- CT scan actually showed multiple mycotic pulmonary emboli
- ICD removed
- Antibiotics changed to IV Teicoplanin 10mg/kg every 72 hours
  - Why is he dosed every 72 hours?




- The diagnosis is confirmed and the treatment has been started
- The Teicoplanin is only dosed every 72 hours because the patient is in renal failure and it will take him much longer than normal to clear the antibiotic from his blood
- From a treatment perspective this doesn't matter, he will remain therapeutic throughout

## Antibiotic dosing in renal failure

- Many antibiotics require dose reduction in renal failure
- eGFR is not an accurate predictor of renal function
- Use Cockcroft Gault equation
  - Actual body weight or Ideal Body Weight (IBW) if weight > 20% above IBW
  - Also use IBW for patients with oedema & ascites

Antibiotic	Renal Clearance	Renal Impairment
Amoxicillin	Renal	Reduce dose
Amoxicillin/Clavulanate	Renal	Reduce dose
Azithromycin	Renal	Reduce dose
Clarithromycin	Renal	Reduce dose
Clindamycin	Renal	Reduce dose
Doxycycline	Renal	Reduce dose
Erythromycin	Renal	Reduce dose
Gentamicin	Renal	Reduce dose
Meropenem	Renal	Reduce dose
Moxifloxacin	Renal	Reduce dose
Nafcillin	Renal	Reduce dose
Netilmicin	Renal	Reduce dose
Pivmecillinam	Renal	Reduce dose
Rifampin	Renal	Reduce dose
Spectinomycin	Renal	Reduce dose
Tetracycline	Renal	Reduce dose
Trimethoprim	Renal	Reduce dose
Vancomycin	Renal	Reduce dose
Zidovudine	Renal	Reduce dose

Male:  $CrCl = \frac{1.23 \times (140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{Serum creatinine (}\mu\text{mol/L)}}$   
 Female:  $CrCl = \frac{1.23 \times (146 - \text{age}) \times \text{weight (kg)}}{72 \times \text{Serum creatinine (}\mu\text{mol/L)}}$



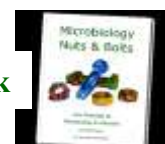
- Most antibiotics are affected in some way by renal failure
- Where doses are concerned it is important to use a calculated GFR because eGFR does not take body mass or even ethnic origin into account and so can be very different from an actual value
- It is safest to use a calculated GFR to aid the prescribing of antibiotics in renal failure and to consult renal dosing guidelines

## Geoff

- Calculated GFR
  - 56 years old
  - Weight 66kg
  - Creatinine 196
  - Calculated GFR = 31 ml/min
- Geoff received 4 weeks of IV Teicoplanin and made a full recovery
- Following treatment his "pulmonary metastases" disappeared!



- Unsurprisingly with the correct treatment Geoff got better
- It is really important to keep an open mind about a diagnosis and not to be afraid to question what is happening, that is good medical practice



## Caution: Vancomycin resistant Enterococcus (VRE)

- Vancomycin resistance in Gram-positive bacteria is rare
- In VRE the genes for resistance are carried on a transposon which did not originate in Enterococcus
  - Avoparcin used in animal husbandry
- Theoretically possible to transfer resistance to other bacteria e.g. MRSA creating VRSA
- This would be almost impossible to treat in the blood stream!
- All patients with VRE should be isolated if possible



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- Vancomycin Resistant Enterococcus (also known as Glycopeptide Resistant Enterococcus) has a resistant mechanism on board which is capable of transferring to other bacterial species
- As a result it is capable of making an organism like MRSA resistant to Teicoplanin or Vancomycin which are the current mainstays of treatment with these bacteria
- Since VRSA/GRSA would cause severe diseases with a high mortality we isolate patients with GRE in most UK hospitals
- GRE itself doesn't cause many infections and is pretty low grade even when it does
- GRE is thought to have arisen through the previous unrestricted use of the glycopeptide Avoparcin in the swine industry, and is a clear link between our bacterial flora and the food we eat

## Conclusions

- Sepsis is a clinical diagnosis
- Sepsis can be caused by almost any bacteria but is usually caused by:
  - Gram-negative bacilli e.g. E. coli, Klebsiella sp etc
  - Staphylococcus aureus
- Bactericidal antibiotics are chosen to treat the likely bacteria
- Many antibiotics need dose adjustments in renal failure based upon a calculated GFR
- Antibiotic resistance is becoming an increasing problem for patient care

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- Sepsis is a clinical diagnosis and a medical emergency
- There are lots of potential causes and it is important to try and diagnose the underlying cause in order to try and treat patients effectively
- Sepsis requires aggressive treatment with antibiotics but these may need dose adjustment if the patient is in renal failure
- Antibiotic resistance is an increasingly problem and has recently been put on the UK National Risk Register by the Chief Medical Officer (CMO) as a mark of just how serious the problem is

