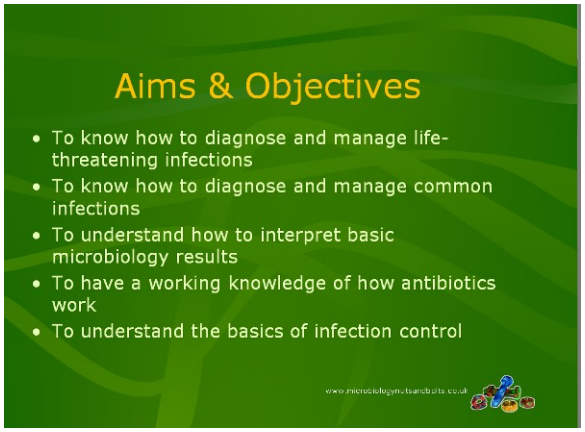
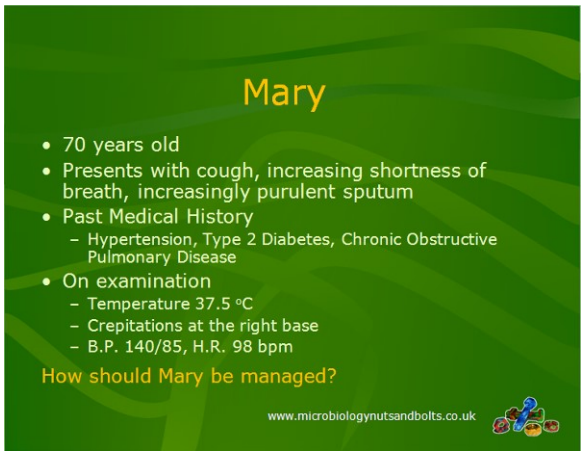
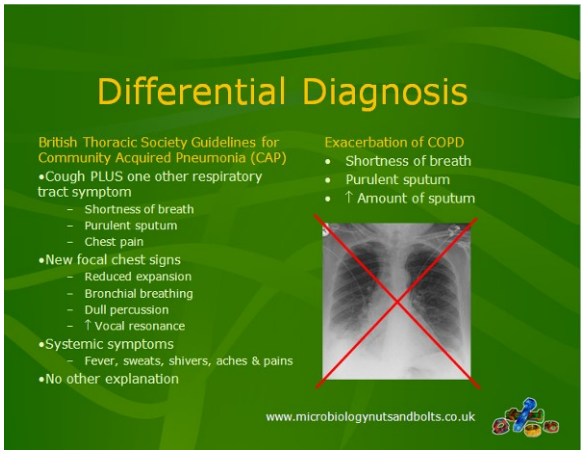
Microbiology Nuts & Bolts: Session 4: Primary Care Infections



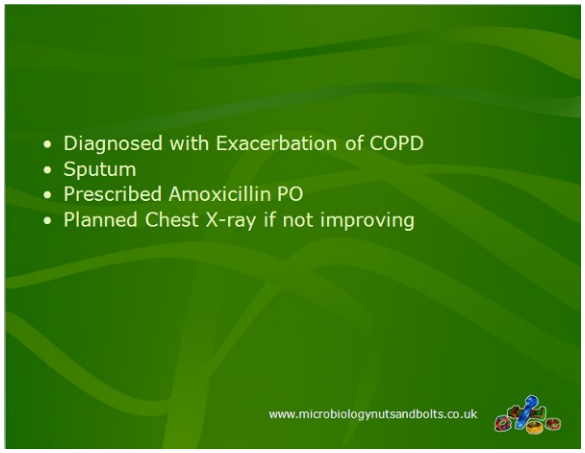
- Many consultations in primary care are for potential infections, where it can be difficult to distinguish those that need treating with antibiotics and those which do not
- It is important to know how to diagnose and manage common infections so that complications do not occur and patients get better 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



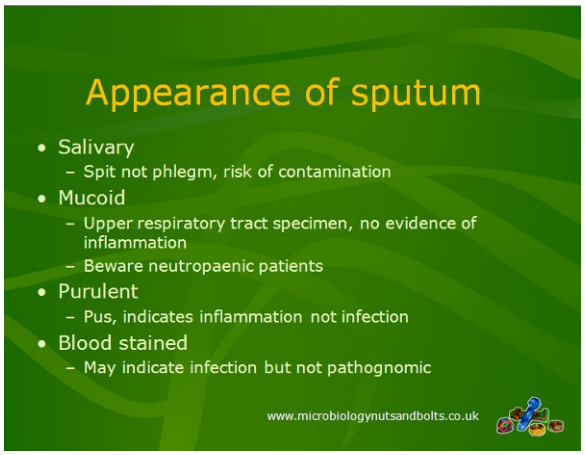
- This is a common history both in primary and secondary care, both in terms of presenting symptoms as well as co-morbidities
- If taken correctly her temperature is the upper end of normal and her cardiovascular system observations are normal
- The presence of crepitations on auscultation indicates interstitial changes such as fibrosis or fluid, not consolidation
- Given her past medical history of chronic obstructive pulmonary disease, shortness of breath but no symptoms of pneumonia it would be reasonable to treat Mary for a non-pneumonic exacerbation of COPD



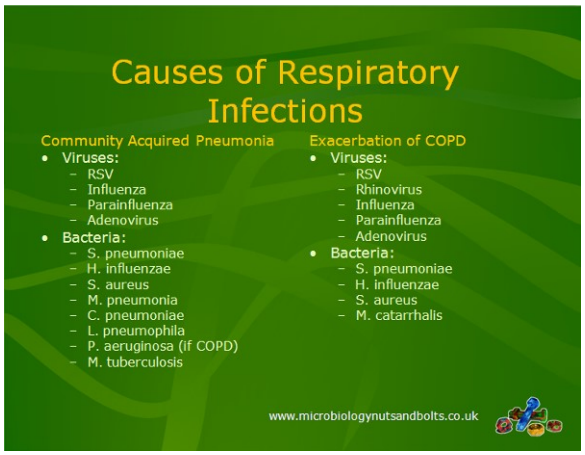
- The British Thoracic Society (BTS) have published guidelines that cover the diagnostic criteria of community acquired pneumonia in primary care as well as exacerbations of COPD



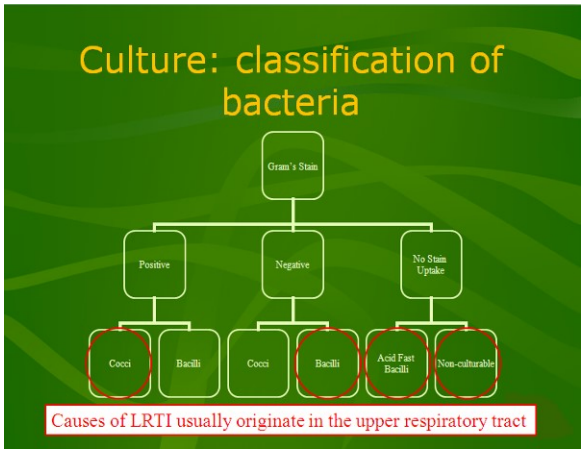
- The treatment with Amoxicillin is reasonable and would cover the common bacteria which cause exacerbation of COPD which are covered later
- Alternative treatments could be PO Clarithromycin or PO Doxycycline



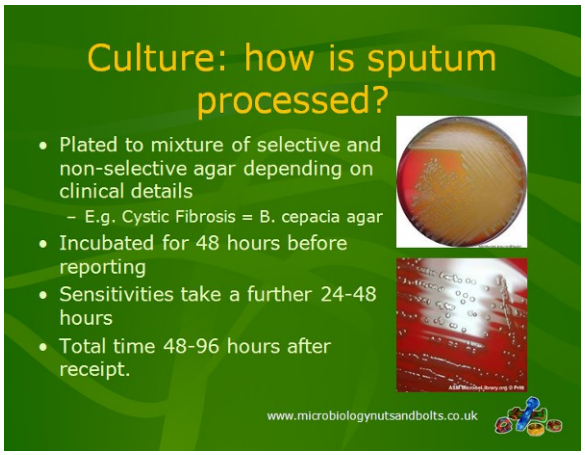
- As with other tests it is important to have a system for looking at microbiology results
- Microbiology results should be looked at in the following order if available:
  - Appearance
  - Microscopy
  - Culture
- For sputum results the appearance gives guidance on the likelihood of any cultured bacteria being from the upper respiratory tract or not
- Too many patients get treated for what is essentially normal flora and this is a mistake!



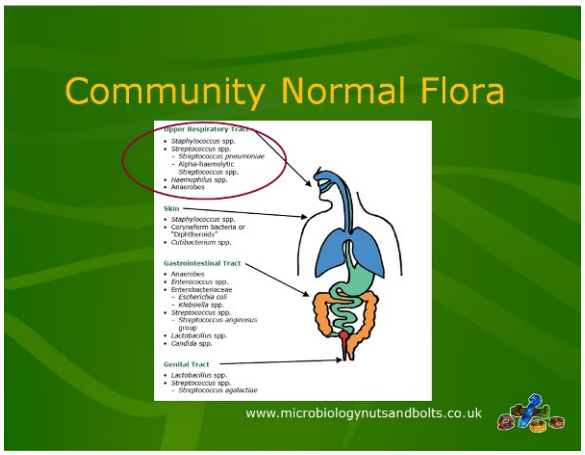
- Viruses are a common cause of respiratory tract infections, in over 25% of patients
- When caused by bacteria, exacerbation of COPD is usually caused by bacteria from the upper respiratory tract getting down in to the chest



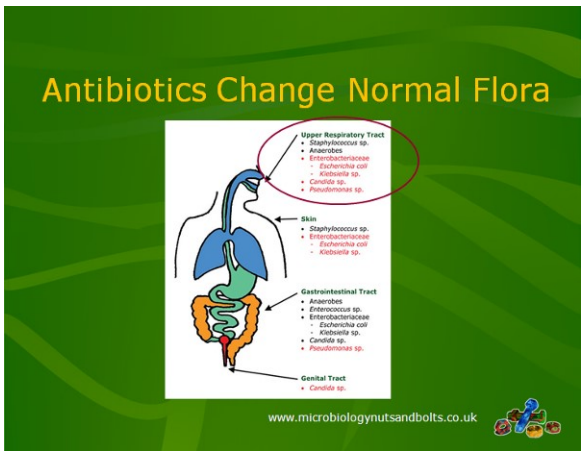
- The types of bacteria which commonly cause community acquired pneumonia usually originate from the upper respiratory tract
- Gram positive cocci
  - Streptococcus pneumoniae
  - Staphylococcus aureus
- Gram negative bacilli
  - Haemophilus influenzae
- Non-culturables ("atypicals")
  - Mycoplasma pneumoniae
  - Chlamydia pneumoniae
  - Legionella pneumophila
- Acid fast bacilli
- Mycobacterium tuberculosis



- Most microbiological tests are based on the clinical information on the request card
- If adequate clinical information is not provided the correct tests may not be done e.g. if the request card does not say cystic fibrosis the lab will not look for Burkholderia cepacia
- In addition, clinical information allows the lab to spot high risk samples that may be hazardous to the health of the laboratory staff when they are processing them Sputum samples can take up to 96 hours to give a result which is only helpful in the event of either de-escalating antibiotics or knowing what to change to if the patient does not respond to initial treatment

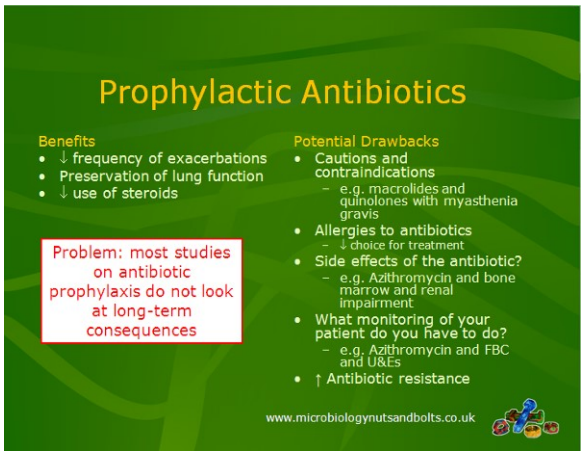


- The normal flora of a human body consists of 10^{14} bacteria (that's approximately 15,000 times the number of humans on the Earth!)
- Knowing the common bacteria that colonise the human body allows:
  - Prediction of the causes of infection from any body site because 85% of infections are caused by the patient's own flora getting in to a site it should not be e.g. pneumonia caused by bacteria from the upper respiratory tract
- Prediction of the origin of an infection when a bacteria is found in a normally sterile site e.g. E. coli in blood cultures from either urine, bowel or Biliary tract

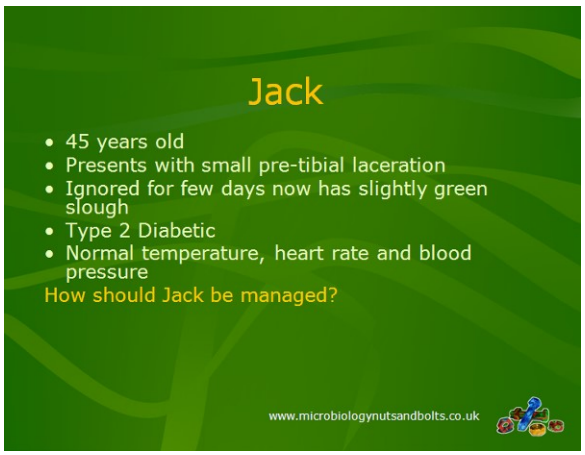


- The normal flora of a patient changes in hospital around 4 days after admission
- The upper respiratory tract becomes colonised with Gram-negative bacteria from the bowel
- This is the reason that different antibiotics are used to tract hospital acquired pneumonia (HAP) from community acquired pneumonia (CAP), NOT because one is more severe than the other
  Note – it is also not correct to escalate from CAP antibiotics to HAP antibiotics because the causes are different and the antibiotics are chosen to treat these different antibiotics, they are different clinical conditions

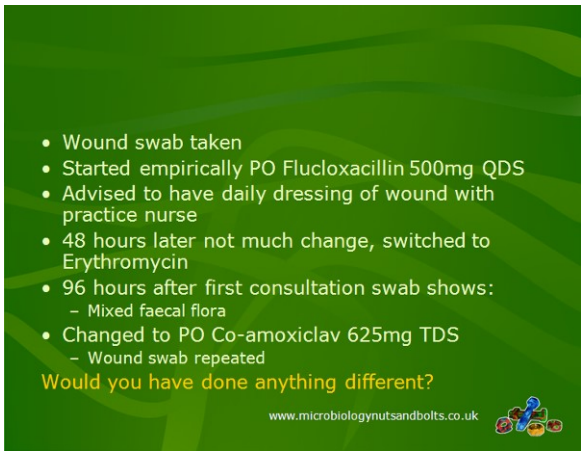
- Although Mary has grown an organism resistant to the treatment she is on she is getting better and it is important to treat the patient not the result



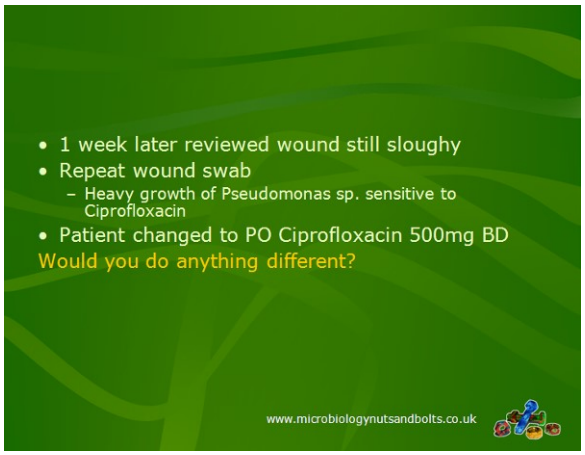
- There is no proven role for prophylactic antibiotics in trying to prevent infections in COPD, essentially you would be trying to eliminate and control the upper respiratory tract flora and this is not meant to be sterile, all the antibiotics would do is make these bacteria more resistant



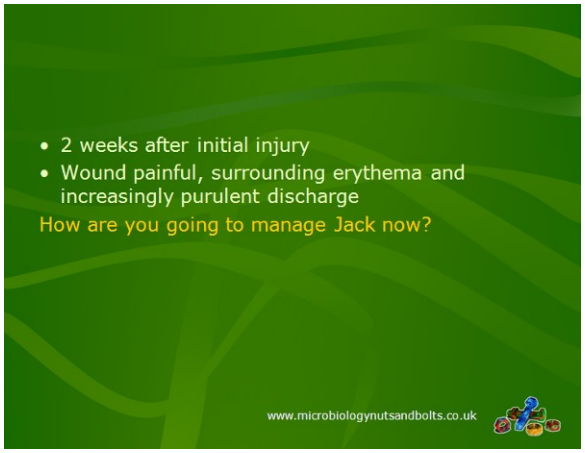
- As a diabetic Jack is particularly at risk of skin and soft tissue problems, including infection, ulceration and vascular insufficiency
- Green discolouration is often cited as evidence for the presence of Pseudomonas aeruginosa, and this is sometimes the case. Pseudomonas produces a chemical called pyoverdin which is green and pyocyanin which is turquoise, leading to the greenish colour, however the presence of Pseudomonas does not necessarily mean there is an infection
- The correct management of Jack's ulcer would be to debride it and keep it clean



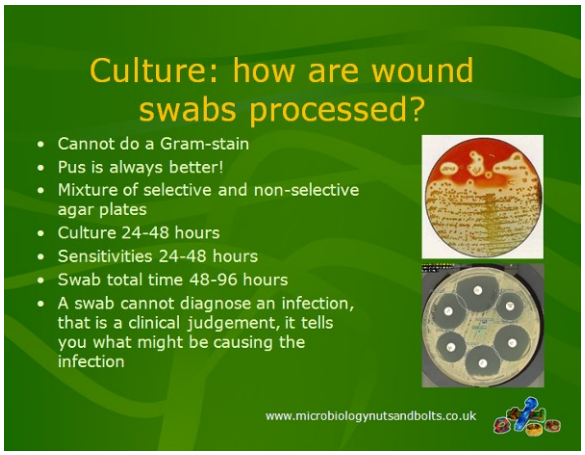
- Unfortunately Jack was given antibiotics despite having no evidence of infection
- The culture result is consistent with colonisation of the wound not infection, most wounds on the lower limb become colonised with bacteria that like warm moist sites, such as the enteric bowel flora
- The presence of bacteria does not necessarily indicate the need for antibiotics



- Yet again Jack is given antibiotics despite no evidence of infection



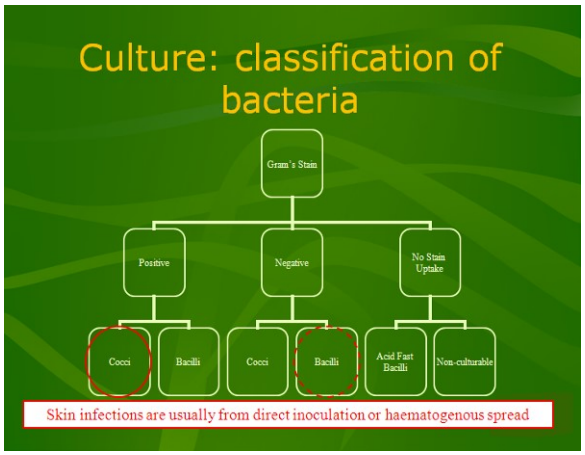
- Now Jack's ulcer is inflamed and infected
- At this stage antibiotics are indicated but given that he has had multiple different antibiotics in the recent weeks the chances of him having an infection with a nice sensitive bacteria are limited



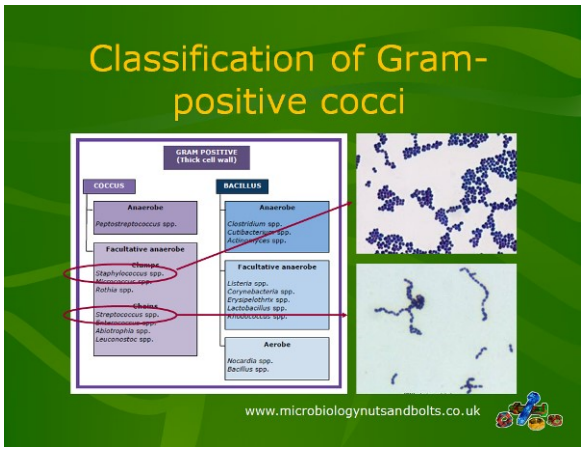
- The laboratory is often asked to do Gram stains on swabs but this is not a good idea as it contaminates the swab and rarely generates any meaningful results
- Pus on the other hand can be stained to give goods results
- It is one of the microbiology frustrations that surgeons will wash out litres of pus from an abscess but only send a swab to the lab… don't be this kind of doctor… put some pus in a sterile universal and send that to the lab instead

- Wounds swabs can indicate the presence or absence of bacteria, but they cannot distinguish infection from colonisation, this is based upon the clinical picture
- Infection is the presence of inflammation and tissue damage caused by bacteria

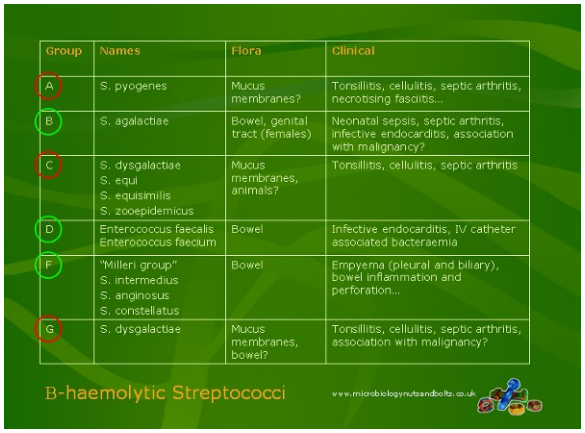
- Most skin and soft tissue infections are caused by either Staphylococcus aureus or the Beta-haemolytic Streptococci



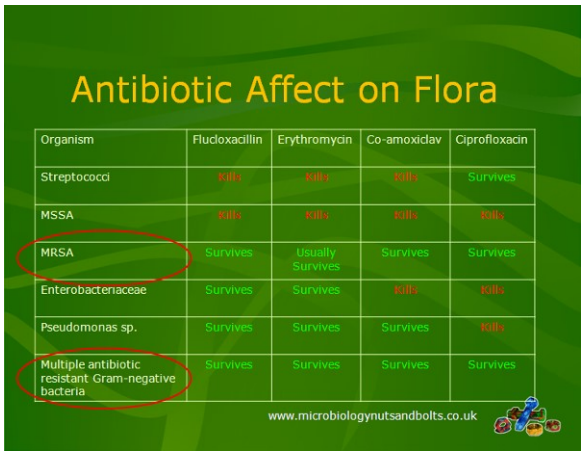
- Very occasionally bacteria such as Pseudomonas aeruginosa do cause serious infections of skin and soft tissue, but usually this is in the context of burns and skin grafts



- Most skin infections are caused by Gram-positive cocci, notably Staphylococcus aureus and the Beta-haemolytic Streptococci
- 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

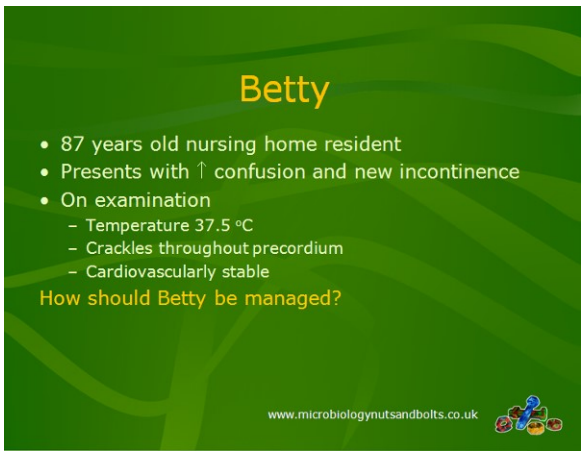


- Beta-haemolytic Streptococcal grouping causes a lot of confusion but can be made simpler by considering different types together
- Beta-haemolysis refers to the type of red blood cell breakdown that the bacteria gives on blood agar in a laboratory, but there are 3 types of haemolysis
  - Alpha-haemolysis = partial haemolysis causing a green discolouration on blood agar (Viridans Streptococci, Viridans means green)
  - Beta-haemolysis = complete breakdown of the blood allowing you to see through the blood agar plate (see image in next slide)
  - Gamma-haemolysis = this is a very misleading term as in fact there is no haemolysis at all (also called non-haemolytic)
- Consider Groups A, C and G together because they all cause very similar infections of the upper respiratory tract, skin, bone and joint
- Consider Groups B, D and F together because they all originate in the gastrointestinal tract

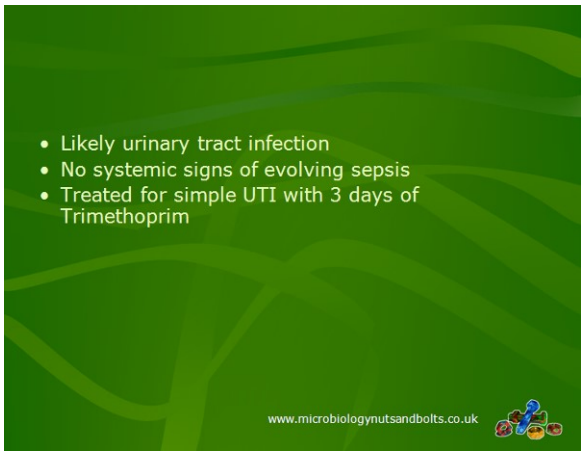


- Knowing how antibiotics impact and influence the normal flora of the human body allows you to predict what is going to happen in a patient, and therefore if they do develop an infection, what the cause of that infection is
- In Jack, the multiple courses of unnecessary antibiotics he had will have selected out Meticillin resistant Staphylococcus aureus or resistant Gram-negative bacteria
- In the context of a skin and soft tissue infection the most significant of these is the MRSA, as Staphylococcus aureus is the most common cause of these types of infections

- As predicted Jack's infection was due to MRSA
- It is unlikely that Jack would have developed an infection if his normal flora wasn't adversely affected by the antibiotics he was given when he didn't have an infection



- There are many things that could be causing this problem in Betty, but the most common is a urinary tract infection
- It is reasonable to start her on a course of Trimethoprim or similar to cover for a simple UTI



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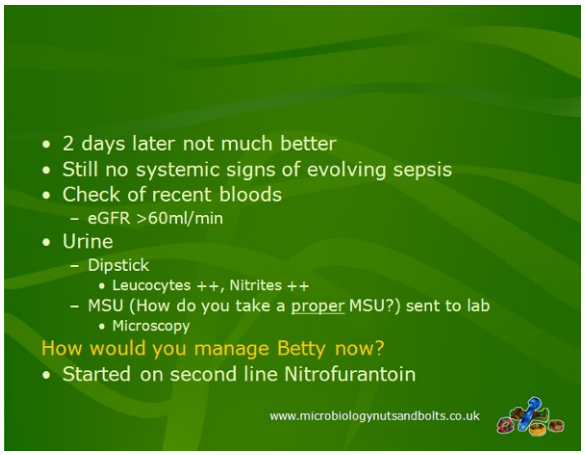
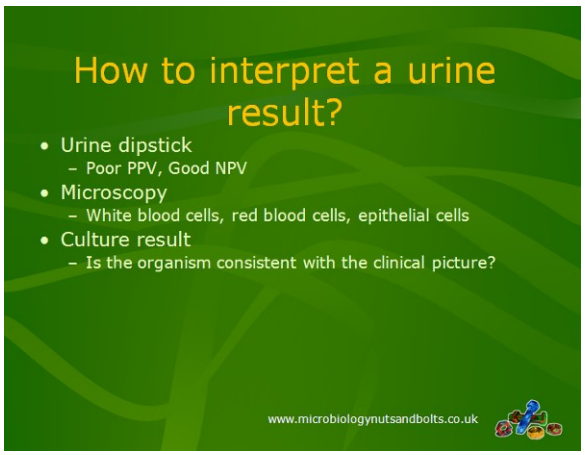
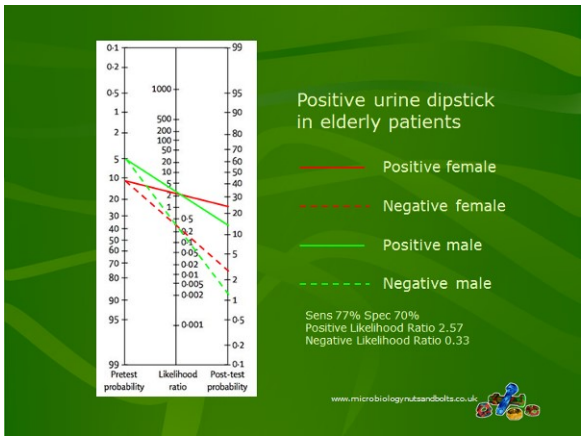


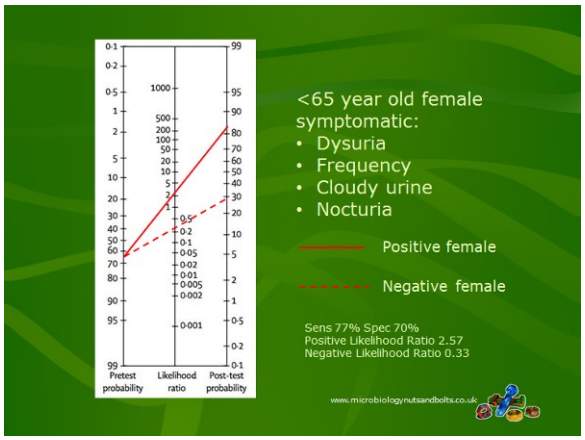
- At this stage it is sensible to take a midstream urine sample in order to check that Betty does not have an infection with a Trimethoprim resistant bacteria
- Urine point of care includes a dipstick test
  - Leucocytes indicate the presence of white blood cells and hence inflammation in the urinary 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



- As with other tests it is important to have a system for looking at microbiology results
- Urine dipsticks are good for excluding UTIs in normal immunocompetent adults but beware patients who cannot mount an immune response or who can have significant UTIs without a white blood cell response:
  - Neutropaenia
  - Pregnancy
  - Children
  - Anatomical abnormalities of the urinary tract
- Too many patients get treated for what is essentially normal flora and this is a mistake!



- The Fagan Nomogram is a statistical tool for evaluating the effectiveness of a test
- A positive urine dipstick in an elderly female patient with a fever is only about 25% predictive of a UTI; that means 75% of patients with a positive urine dipstick DO NOT HAVE A UTI
- A negative urine dipstick in the same type of patient means that 97% DO NOT HAVE A UTI
- Urine dipsticks are a screening test for ruling out a diagnosis of UTI, they are not a diagnostic test for proving a patient does have a UTI



- In comparison to the urine dipstick above, the combination of dysuria, frequency, cloudy urine and nocturia in a female < 65 years old is better at predicting a UTI than a positive urine dipstick.

Microscopy of urine

- White blood cells
  - >100 x10^6/L definitely significant
  - >10 x10^6/L significant if properly taken MSU (rare!)
- Red Blood Cells
  - Poor correlation with UTI, used by urologist and renal physicians
- Epithelial cells
  - Indicator of contact with, and therefore contamination from, the perineum

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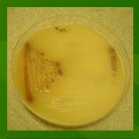
- A high WBC in the urine is consistent with a UTI but other systemic inflammatory conditions can give rise to pyuria e.g. pneumonia, appendicitis, etc
- The presence of epithelial cells in a urine sample indicates that the urine has not been taken correctly and has been in contact with the skin of the perineum with the risk that anything that has grown may actually be a contaminant from the perineal flora
- Positive bacterial culture in the presence of epithelial cells or the absence of white blood cells is consistent with possible contamination and should be regarded with caution when planning patient treatments (it may be better to repeat these samples with a carefully taken specimen)

Culture: how is urine processed?

- Day 1 Automated Microscopy
  - If values not significant reported as negative
  - If values significant or specific patient group cultured with direct sensitivities
- Day 2
  - Reported with identification and sensitivities
- Patient groups always cultured
  - Cancer and haematology
  - Pregnant
  - Urology
  - Children < 5 years old



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- Most microbiological tests are based on the clinical information on the request card
- If adequate clinical information is not provided the correct tests may not be done e.g. if the request card does not say that the patient is pregnant then a full culture may not be performed
- In addition, clinical information allows the lab to spot high risk samples that may be hazardous to the health of the laboratory staff when they are processing them
- Most laboratories receive urine samples in boric acid containers which helps to stabilise bacterial growth and the white blood cell count for 24-48 hours before being tested however if less than about 8mls of urine is put in these containers then the concentration of boric acid may be high enough to actually kill the bacteria
  - If you are submitting a small volume sample e.g. from a child, use a normal sterile white universal and indicate this on the request form

2 days later

- Much more confused, still incontinent
- Very distressed
- Vomiting, diarrhoea
- Urine result
  - Microscopy >100 x10^6/L WBC, no epithelial cells
  - Culture E. coli
  - Resistant to Amoxicillin, Co-amoxiclav, Trimethoprim, Cephradine, Ciprofloxacin
  - Sensitive to Nitrofurantoin
  - Further results to follow

How would you manage Betty?
What further results are to follow?

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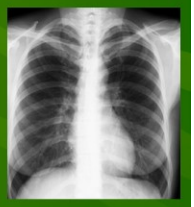
- Betty's condition has clearly worsened, but why?
- It is easy to assume that she has developed a pyelonephritis or more severe UTI but there might be other reasons
- In this instance the E. coli is sensitive to Nitrofurantoin and so it is important to consider why the Nitrofurantoin is not working
- Nitrofurantoin is a pro-drug which is activated in the urinary tract, it is not systemically active
- In renal failure the pro-drug builds up in the blood stream causing toxicity, the symptoms of which are confusion, vomiting and diarrhoea
- The further test result to follow is a test for the reason why the bacteria are so resistant, and some further sensitivities

- Admitted to secondary care for IV antibiotics
- Started on Piptazobactam for sepsis, probably UTI
- Further result on MSU
  - E. coli ESBL positive

What is an ESBL?
What should Betty be treated with?
Why didn't Nitrofurantoin work?



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- An ESBL is an Extended-spectrum Beta-lactamase enzyme
- The most reliable antibiotic class for treating these resistant bacteria are the carbapenems such as Meropenem, Imipenem and Ertapenem
- The Nitrofurantoin didn't work because she was in renal failure but it wasn't noticed

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

The following antibiotics require dose modification in the presence of renal impairment

◄ Severe impairment (CrCl <10ml/min) ►		
◄ Moderate to severe impairment (CrCl <20ml/min) ►		
◄ Mild to severe impairment (CrCl <50ml/min) ►		
Aciclovir (IV)	Aciclovir (oral)	Amoxicillin
Amikacin	Ampicillin	Amphotericin (IV)- Fungizone
Gentamicin (once-daily adjust frequency)	Azetreonam	Cefotaxime
Meropenem	Benzylpenicillin	Erythromycin
Nitrofurantoin	Ceftazidime	Fluconazole
Streptomycin	Cefuroxime	Metronidazole
Teicoplanin	Ciprofloxacin	Rifampicin
Tetracycline	Clarithromycin	
Tobramycin	Co-amoxiclav	
Vancomycin	Co-trimoxazole	
	Ethambutol	
	Sulphonamides	
	Pip/Taz	
	Trimethoprim	

Male: $CrCl = \frac{1.23 \times (140 - \text{age in years}) \times \text{weight in kg}^{*}}{\text{Serum creatinine } (\mu\text{mol/L})}$

Female: $CrCl = \frac{1.04 \times (140 - \text{age in years}) \times \text{weight in kg}^{*}}{\text{Serum creatinine } (\mu\text{mol/L})}$

- 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 in to 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 consultant renal dosing guidelines

How might weight effect Betty's GFR (ml/min)

Female, Age 87, Creatinine 75

Weight (kg)	eGFR	Calculated GFR	Variance
45	63	33	-30
50	63	37	-26
55	63	40	-23
60	63	44	-19
65	63	47	-16
70	63	51	-12
75	63	55	-8
80	63	59	-4

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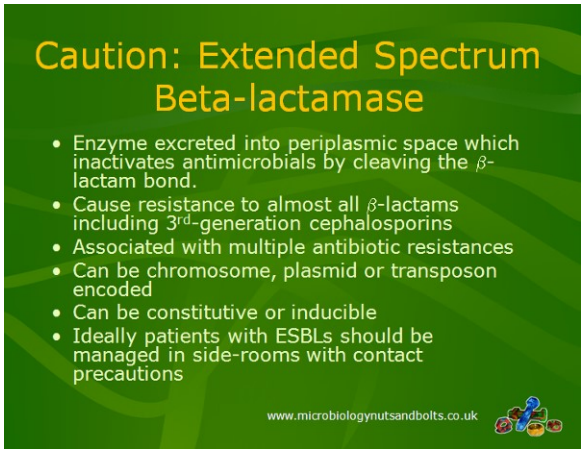
- It is important not to overestimate the renal function of patients who are elderly and have little muscle mass
- In elderly patients, even relatively small changes in muscle mass can have profound effects on CrCl

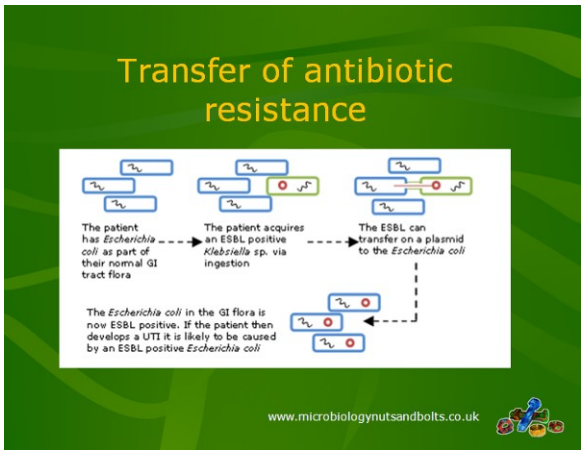
- Betty was started on the correct antibiotic at a reduced dose because she is in renal failure

- Unsurprisingly, with correct treatment Betty improved and her Nitrofurantoin toxicity resolved
- Unfortunately there are no simple oral agents to treat this infection and Betty will require IV antibiotics to finish her treatment

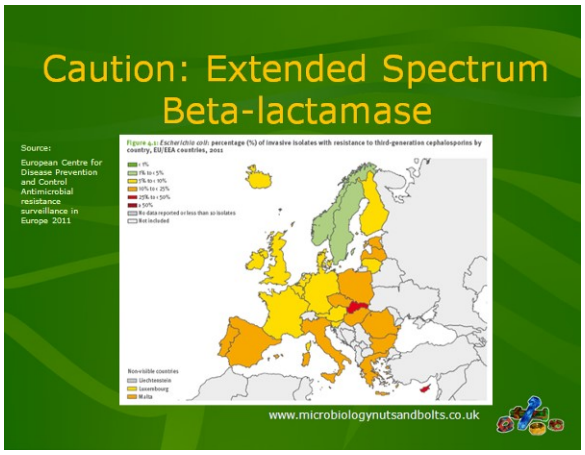
- It is likely that Betty has now changed her normal flora such that the predominant facultative anaerobic bacteria in her gut (E. coli) is resistant to many antibiotics
- Every time she develops an infection due to E. coli it is likely to be her own E. coli causing the problem, and this is now resistant to antibiotics
- This is going to lead to problems with choosing empirical therapy for infections in the future



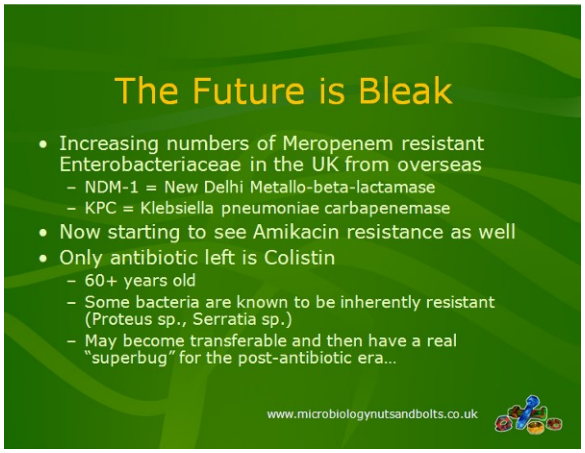
- The extended-spectrum Beta-lactams are the 3rd generation cephalosprins such as Ceftriaxone, Cefotaxime and Ceftazidime
- These enzymes breakdown all of the commonly used Beta-lactams giving resistance to all except the carbapenems such as Meropenem, Imipenem and Ertapenem
- They can be associated with multiple resistance mechanisms
- Constitutive resistance is expressed all the time whereas inducible resistance is only expressed when induced by the presence of the antibiotic
    - Inducible resistance can be difficult to spot on laboratory tests and so a high degree of suspicion should exist when patients fail to respond to what appears to be effective treatment



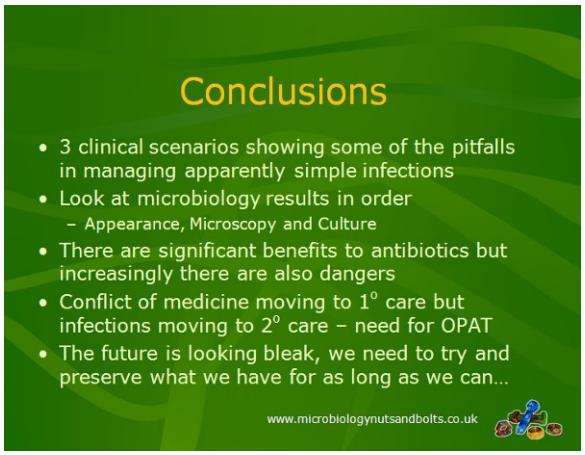
- The genes encoding the production of ESBLs are usually carried on a mobile genetic element called a plasmid
- A plasmid is a circular piece of DNA that sits outside of the bacterial chromosome but which can be reproduced and transferred to other bacteria
- In this way antibiotic resistance can be spread from species to species, which is what has happened with ESBL-positive E. coli – the ESBL genes came from a different Gram-negative bacterial species called Kluyvera spp.



- The presence of ESBL positive bacteria is increasing worldwide with up to 10% of community E. coli isolates in UTIs now expressing the enzyme
- It is though that the bacteria may be in the food chain and a number of specific sources have been proposed
- They represent a real public health threat and this is becoming the focus of Department of Health attention with regards to antibiotic resistance



- Antibiotic resistance is an increasing problem for healthcare
- There are no new antibiotics being developed against Gram-negative bacteria, and we have only just seen the first new class of antibiotic discovered within the past 30 years (Teixobactin)
- Antibiotic development is not cost effective for pharmaceutical companies, short courses of restricted medications makes them expensive, and then hospitals won't use them
- Something needs to change…



- A knowledge of clinical microbiology can significantly benefit your patients
- Prescribing antibiotics is not completely without risk, and these should be weighed against the potential benefits to the patient
- OPAT = Outpatient Parenteral Antibiotic Therapy, the giving of intravenous antibiotics in an outpatient setting for infections, with the same standard as given for inpatients