Clostridiodes difficile

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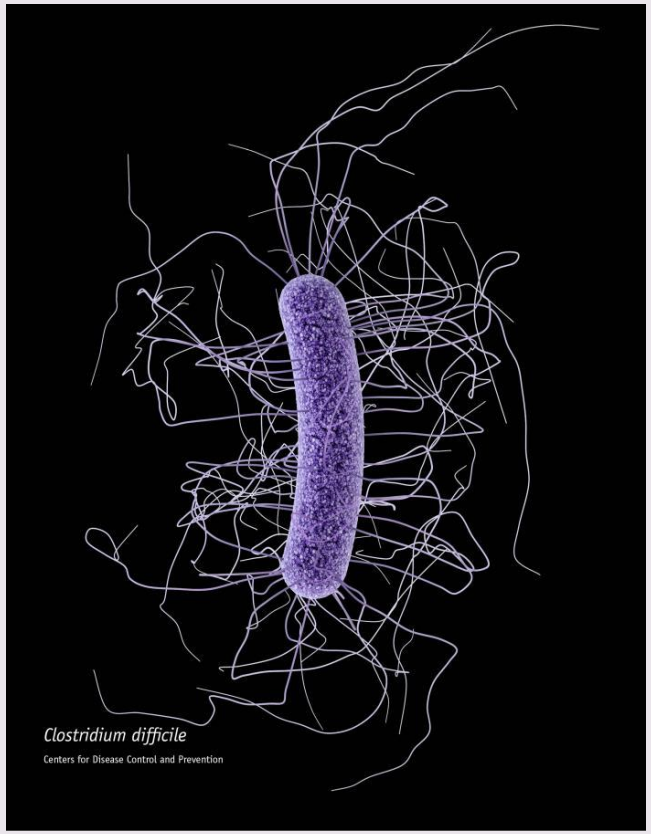


Introduction

- *Clostridiodes difficile (Clostridium difficile)* is the causative organism of antibiotic associated colitis
- Gram positive bacillus
- Can colonise the gastrointestinal tract or lead to fulminant disease
- Acquired by faecal oral route
- Clostridium difficile associated disease is most likely to occur following a change to the normal intestinal flora e.g. antimicrobial therapy.
- Significant cause of hospital morbidity and mortality in hospital patients

Epidemiology

- 1978 - Identified as the causative pathogen in the majority of cases of antibiotic associated colitis.
- Clindamycin usage implicated early on
- Increased antimicrobial consumption led to implication of other classes. e.g. cephalosporins, quinolones, broad spectrum penicillins.
- 2003-2006 Ribotype 027 :increased cases, severity, relapse, association with quinolone use.
- Increase in incidence and severity of healthcare associated C.difficile disease, particularly in patients over 65 years.

Epidemiology

- *C difficile* carriage rate approximately 10% in hospital/long term care facilities and estimated at 3% for healthy adults
- Asymptomatic carriers can shed spores and serve as a reservoir in the environment allowing for onward transmission via the faecal oral route in healthcare settings.
- New exposure and subsequent colonisation is thought to lead to CDI more often in new patients than in patients previously colonised.

Transmission

- Symptomatic and asymptomatic patients with *C difficile* act as a reservoir and can cause environmental contamination.
- Spores can be found on inert surfaces, hands , clothing, stethoscopes.
- Transmission more likely in an area where patients have diarrhoea related to active CDI than when patients have asymptomatic colonisation.

Risk factors - CDI can occur in the absence of any risk factors

- Age
- Hospitalisation
- Severe co-morbid illness
- Immunosuppression
- GI Surgery
- Gastric acid suppression

Antibiotic use and CDAD

- The consumption of antimicrobials disrupt the normal colonic flora and this allows C difficile to multiply and produce toxins.
- Use of broad spectrum agents, multiple antibiotic courses and increased course duration all contribute to the incidence of *Clostridium difficile* associated disease.
- Any antibiotic can predispose but those most frequently associated are the quinolones, clindamycin, broad spectrum penicillins and cephalosporins.
- Peri-operative antimicrobial prophylaxis confers a risk
- Antimicrobial usage may have occurred as late a ten weeks beforehand and occasionally there is no history of antimicrobial exposure.

Antibiotic Relative Risks for Provoking *Clostridium difficile* Infection

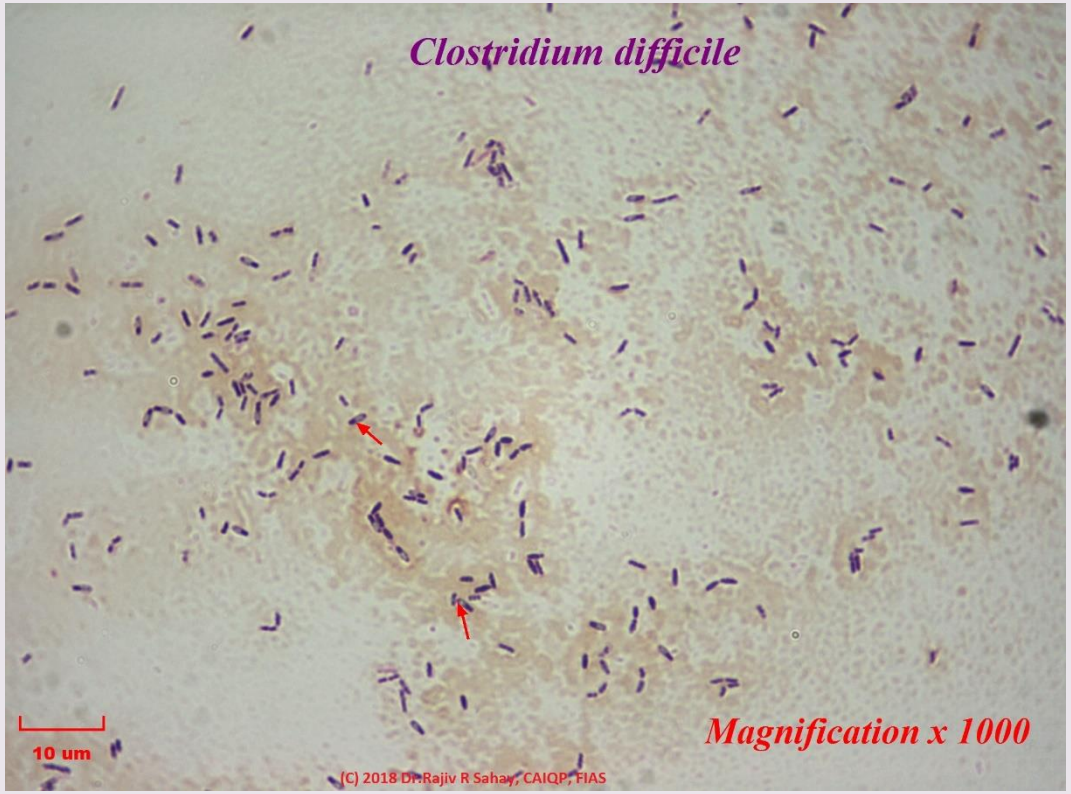
GIG CYMRU NHS WALES
Bwrdd Iechyd Prifysgol Abertawe Bro Morgannwg University Health Board

This document has been updated to reflect the findings of a comprehensive evidence review conducted by NICE in March 2015. NICE concludes that there is insufficient evidence to stratify antibiotics in terms of their risk for provoking *C.difficile* infection. Therefore all broad-spectrum antibiotics should be considered high risk. Narrow spectrum antibiotics should be utilised where ever possible and broad-spectrum antibiotics reserved for severe / resistant infections in order to minimise the risk to patients. Initial empirical broad-spectrum antibiotics should be converted to narrow-spectrum antibiotics on receipt of relevant culture and sensitivity results; this may be discussed with a Consultant Microbiologist when necessary.

High Risk (broad-spectrum)	Low Risk (narrow-spectrum)
Quinolones e.g. ciprofloxacin, ofloxacin, levofloxacin	Clarithromycin
Clindamycin	Erythromycin
3rd generation Cephalosporins e.g. cefotaxime, ceftazidime, Ceftriaxone	Amoxicillin
2nd generation Cephalosporins e.g. cefuroxime, cefaclor	Rifampicin
Co-amoxiclav	Doxycycline*
Co-trimoxazole	Glycopeptides e.g. vancomycin, teicoplanin
1st generation Cephalosporins e.g Cefalexin	Metronidazole
Carbapenems e.g. meropenem, imipenem, ertapenem	Benzyl penicillin / Penicillin V
Aminoglycosides e.g gentamicin, tobramycin, amikacin	Flucloxacillin
Piperacillin and Tazobactam	Nitrofurantoin
	Trimethoprim

*Doxycycline was the only antibiotic found to have no association with *C.difficile* infections in the 3 meta-analysis reviewed by NICE

Microbiology



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Gram positive bacillus
Anaerobe
Spore forming – endospore
Exists in vegetative state and spore form
May produce two toxins (A and B)

Toxins – A and B

- Both are exotoxins which act upon intestinal epithelial cells leading to tissue injury and diarrhea
- Toxin A ? enterotoxin, Toxin B ? cytotoxin
- Toxin B is the major virulence factor . X10 more potent than Toxin A.
- Mucosal damage and inflammation (colonocyte death, loss of intestinal barrier function, and neutrophilic colitis)
- However some strains of *C difficile* are non-toxigenic (10-30%) , colonise the GI tract and are not pathogenic.

Clinical manifestations

- Spectrum of disease: asymptomatic to fulminant.
- Symptoms include: diarrhoea, abdominal pain, nausea, anorexia, fever.
- Severe disease often associated with diarrhoea, lower quadrant or diffuse abdominal pain, abdominal distension, fever, hypovolaemia, lactic acidosis, hypoalbuminaemia, impaired renal function, raised wbc count.
- Fulminant disease may be associated with hypotension, shock, ileus, megacolon.

Recurrence of infection

- Up to 25% of patients may experience a recurrence within 30 days of completing treatment for CDAD.
- If they suffer a recurrence they are at greater risk of further episodes.
- Recurrence may be due to relapse or reinfection
- Relapse – initial strain
- Reinfection - new strain

Initial Management

- Early detection important
- If CDI is suspected, send a stool specimen to the microbiology lab and undertake the actions below immediately.
- Review CDI therapy if initial test result is negative. If symptoms continue despite a negative result, and clinical suspicion of CDI remains, send a further stool specimen for testing. Please check whether recent sample has been sent and result has been processed before sending another sample
- ACTIONS:
- Ensure patient isolated
- Review any current antibiotic treatment and stop if possible
- Stop or withold any PPIs / H2 antagonists, unless essential. See the acid suppression guidance Acid Suppression Therapy for further advice.
- Stop / avoid any anti-motility drugs (e.g loperamide)
- Assess severity of CDI using the severity Matrix
- Prescribe *C.difficile treatment* as per guidelines
- All of the above actions should be completed and documented via this case proforma (available via the Infection control intranet page) and filed in the medical notes

Clostridium difficile Infection (CDI) Disease Severity Matrix

All Oncology, Haematology, Renal and Immunosuppressed patients should be categorised as Severe and treated as such.

	Stools	WCC	Acute Rising Serum Creatinine	Temperature	Pain	Hypotension	CT or X-Ray Evidence
Mild CDI	< 3 episodes of Type 5-7 stool (using Bristol Stool Scale)	Not raised	Not raised	< 38.5°C	No	No	None
Moderate CDI	Between 3 to 5 episodes of Type 5-7 stool (using Bristol Stool Scale)	< 15 x 10^9/L	Not raised	< 38.5°C	No	No	None
Severe CDI Any patient with one or more severe parameters or **Any Oncology Haematology, Renal or Immunosuppressed patient**	Not reliable as indicator	Raised > 15 x 10^9/L	> 50% increase over baseline	> 38.5°C	Evidence of severe colitis	No	Abdominal or radiological signs present
Life-threatening CDI	Not reliable as indicator	Raised > 15 x 10^9/L	> 50% increase over baseline	> 38.5°C	Partial or complete ileus or toxic mega-colon	Present	CT evidence of severe disease

First Episode of infection	
First-Line antibiotic* for a first episode of mild, moderate or severe C.difficile infection	**Vancomycin:** 125mg orally four times a day for 10 days
Second-Line antibiotic* for a first episode of mild, moderate or severe C.difficile infection if vancomycin is ineffective**	**Fidaxomicin**: 200mg orally twice a day for 10 days
Antibiotics* for C.difficile infection if first- and second-line antibiotics are ineffective**	Seek microbiology / surgical opinion. Specialists may intitially offer: **Vancomycin:** up to 500mg orally four times a day for 10 days **With or without** **Metronidazole**: 500mg intravenously three times a day for 10 days

Life-threatening C.difficile infection (see severity matrix)	
Antibiotics for life-threatening C.difficile infection	Seek urgent specialist advice from microbiology/surgeons. Antibiotics that specialists may intitially offer are: **Vancomycin*****: 500mg orally/NG four times a day for 10 days **With** **Metronidazole:** 500mg intravenously three times a day for 10 days
Recurrent infections	
Antibiotic for a further episode of C.difficile infection within 12 weeks of symptom resolution (relapse)	**Fidaxomicin**: 200mg orally twice a day for 10 days
Antibiotics for a further episode of C.difficile infection more than 12 weeks after symptom resolution (recurrence)	**Vancomycin:** 125mg orally four times a day for 10 days **Or** **Fidaxomicin:** 200mg orally twice a day for 10 days

*if patient NBM or severe vomiting and showing no signs of life-threatening infection (see matrix) consider: Metronidazole IV 500mg TDS until able to continue on the recommended treatments above
**This is not usually possible to determine until day 7 because diarrhoea may take 1 to 2 weeks to resolve. Discuss with micro if a switch is needed before 7 days
*** If ileus present/consider: Use Vancomycin PR 500mg in 100ml Sodium Chloride 0.9% every 6 hours as a retention enema (for guidance see Administration advice: Vanc/Fidaxomicin) in place of oral/NG vancomycin i.e. with IV metronidazole

Do not offer antibiotics to prevent C.difficile infection
Do not advise people taking antibiotics to take prebiotics or probiotics to prevent C.difficile infection.

Other considerations

- Gastroenterology and/or general surgical review
- FMT - Faecal microbiota transplantation (to be considered after 2 or more previous episodes).
- Probiotics - the use of probiotics is not currently recommended by Public Health England as they found insufficient evidence to demonstrate their efficacy for treating or preventing *C. difficile* infection and state that further research is needed to determine which probiotics are the most effective [Public Health England, 2013].

Laboratory Diagnosis

- Suspect if a patient has three or more loose stools in a 24 hour period with no obvious explanation for the diarrhoea.
- Diarrhoea – Type 5-7 on the Bristol Stool Chart
- Send a stool sample to the Microbiology Laboratory for *C difficile* PCR
- PCR in Swansea– detection of toxigenic strains of C difficile (Toxin B gene)
- If positive sample tested for the presence of toxin using an ELISA.
- ELISA not as sensitive as PCR. May get a false negative result e.g. may be related to the amount of toxin in the sample.

Bristol Stool Chart

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on the surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces. **Entirely Liquid**

Infection Prevention and Control

- Contact precautions - gloves and plastic aprons
- Hand hygiene : soap and water rather than alcohol gel
- Single room with ensuite toilet (dedicated commode) – 48 hours after resolution of diarrhoea
- Cleaning and disinfection of equipment, single use equipment
- Environmental cleaning and disinfection
- Bed linen – alginate bag into red linen bag
- Antimicrobial stewardship

Ongoing management

- Daily clinical review
- Maintain stool chart
- Assessment of severity index on a daily basis
- Review of antibiotics, if continued review daily
- Proton pump inhibitor/H2 antagonist review
- Fluids
- Ensure compliance with infection prevention and control guidance

Ribotyping - yearly reports

- The standard procedure for PCR-ribotyping is culturing of C. difficile from fecal samples and subsequent typing. Ribotyping makes use of ribosomal RNA gene restriction pattern analysis to discriminate between bacterial isolates. Ribosomal RNA (rRNA) is present in ribosomes of all bacterial cells and is composed of molecules of three different sizes: 23S, 16S, and 5S. C difficile ribotyping is based on size variation of the 16S–23S rRNA intergenic spacer region (16S–23S ISR)
- A PCR ribotype was identified for 86% of C. difficile specimens reported in the 2017/18 routine surveillance data (Alll Wales).
- 86 distinct PCR ribotypes were identified in the 990 specimens with a ribotype; the 10 most common accounted for 71% of all specimens.
- PCR ribotype 002 was most common, accounting for 15% of all specimens
- 49 ribotypes in 256 specimens in Abertawe Bro Morgannwg UHB
- Can be used to help identify possible links in outbreaks, however PCR-ribotyping does not sufficiently discriminate to prove nosocomial transmission with certainty.
- Future use of WGS will help to better characterise the true epidemiology of C. difficile

Surveillance

- Mandatory reporting of PCR positive / toxin positive results
- Data compiled by Public Health Wales and distributed to Health Boards on a monthly basis
- Tabular and graphical representation of data
- Welsh Government targeted reduction programme with percentage reduction in cases per annum
- RCA of cases

Quiz
Principles of antimicrobial prescribing

(Antibiotic Guardian)

TRUE or FALSE?

- **Do not start antibiotics without clinical evidence of bacterial infection**
- **Broad spectrum antibiotic use promotes C. difficile infections**
- **Unnecessary or inappropriate antibiotic prescribing increases the emergence and spread of resistant bacteria**
- **Take appropriate cultures before starting antibiotics**

TRUE OR FALSE ?

- Always use IV antibiotics for 5 days before switching to oral
- IV antibiotics should be reviewed on a daily basis
- Antibiotics remove the need for surgical or other intervention

IV TO ORAL SWITCH

- Antibiotic therapy should be reviewed on a daily basis. For patients requiring initial IV therapy, in general a switch to the oral route should be made **within 72 hours**, when the patient has shown clinical improvement and is medically stable.
- Advantages of IV to PO switch
- Reduced risk of bacteraemia (including MRSA) from IV line
- Reduced risk of thrombophlebitis from drug/cannula
- Saves both medical and nursing time
- Increased convenience, comfort and mobility for patients
- Earlier discharge from hospital
- Significant cost reduction
- Reduced risk of administration errors
- Criteria for switching
- Patients receiving IV antibiotics should be switched to oral antibiotics if they meet **ALL** the following inclusion criteria and **NONE** of the exclusion criteria**:**

Inclusion Criteria

Clinical improvement observed

Oral route not compromised (vomiting, malabsorption, NBM, swallowing difficulties, unconscious, severe diarrhoea, steatorrhoea).
N.B. if PEG/NG feeding please consult your pharmacist.

Markers showing a trend toward normal:
•Temperature >36°C and <38°C for the last 24 hours
•Blood pressure stable
PLUS NOT more than **ONE** of the following:
•Pulse > 90 beats/min
•Respiratory rate > 20 breaths/min
•WCC <4 or > 12 × 10^9/L (If WCC is out of this range but the trend is towards normal this should not hinder switch if all other criteria met)

Suitable oral preparation available (see relevant section of the guidelines for advice on empirical oral switches)

- **Penicillin Allergy**
- **What is the nearest approximate percentage figure for the proportion of patients with penicillin allergy who may also be allergic to cephalosporins?**
- **a) 0.5–6.5%**
- **b) 5 – 10.5%**
- **c) 30%**
- **d) 50%**

- **Which antibiotic(s) can be used in a patient who has had an anaphylactic reaction to penicillin?**

a) Cefuroxime
b) Meropenem
c) Gentamicin
d) Ciprofloxacin
e) Clarithromycin
f) All of the above

Which of these drugs are penicillins or penicillin related?

Drug	yes	no	Drug	yes	no
Cotrimoxazole			Flucloxacillin		
Gentamicin			Clarithromycin		
Phenoxymethylpenicillin			Benzylpenicillin		
Co-amoxiclav			Cephalexin		
Augmentin			Vancomycin		
Erythromycin			Cefuroxime		
Ceftriaxone			Piperacillin/Tazobactam		
Meropenem			Tazocin		
Cefotaxime			Ciprofloxacin		
Amoxicillin			Doxycycline		

Which of the following are NOT effective in preventing the emergence or spread of antibiotic resistant pathogens

- **a. Adherence to hand hygiene**
- **b. Contact isolation during hospitalisation for patients colonised with MRSA**
- **c. Avoiding the use of antibiotics for viral infections**
- **d. Treating infections for a longer duration**

Which of the following is NOT a current example of clinically important antibiotic resistance?

a. Methicillin resistant Staphylococcus aureus

b. Penicillin resistant Streptococcus pyogenes (Group A Strep)

c. Fluoroquinolone resistant P. aeruginosa

d. Vancomycin resistant Enterococci

Which of these conditions have become harder to treat because of antibiotic resistance?

a. Gonorrhoea

b. Staphylococcal infections

c. Meningitis

d. All of the above

Which of the following conditions should generally be treated with antibiotic therapy in patients who are not immunosuppressed and not pregnant?

a. Acute bronchitis

b. Asymptomatic urinary tract infection

c. Cellulitis

d. All of the above

Which of the following is NOT a way that a bacterium can acquire antibiotic resistance

a. Acquiring resistance gene from its host's cells

b. On its own through evolution

c. From its parent cell

d. Exchanging DNA with another bacterium

Which of these antibiotics have useful clinical activity against Pseudomonas?

a. Ciprofloxacin

b. Co-amoxiclav

c. Ceftazidime

d. Cefotaxime

Which of these would be suitable to treat Gram positive cocci isolated from a blood culture?

a. Flucloxacillin

b. Vancomycin

c. Ciprofloxacin

d. Trimethoprim

Which of these conditions is an indication for therapy?

a. **A catheter specimen urine of a stroke patient positive with > 105 CFU/ml Candida species**
b. **b. A catheter specimen urine of a patient with heart failure, positive with > 105 CFU/ml Coliforms**
c. **c. Repeat isolation in a catheter specimen of urine of > 105 Candida species in an immunosuppressed patient**

Which of these blood culture results most likely represents a contamination and should NOT automatically be treated with antibiotics?

a. One of two blood culture bottles positive with Group A Streptococci

b. One of two blood culture bottles positive with a gram negative bacterium

c. One of two blood culture bottles positive with coagulase negative Staphylococci

d. One of two blood culture bottles positive with Klebsiella sp.

Which of these conditions needing IV antibiotics could be referred to an outpatient parenteral antibiotic therapy (OPAT) team?

a. **Resolving cellulitis needing a further 7 days therapy**
b. **An ESBL positive urinary tract infection**
c. **Meningitis – from day 2 of therapy**
d. **Osteomyelitis needing a further 6 weeks of treatment**
e. **All of the above**

Case Presentation

- Female 70 years old with stool sample 25/7/21 C.diff PCR+ tox +. No recent bloods. In Hospital A. Call to covering GP. Few days intermittent type 5 stool. Clinically stable, apyrexial. HTN, CKD3, prev ca breast, mixed dementia. Admitted with fall and confusion, developed shingles and post-herpetic neuralgia. Not yet seen today, will review shortly, informed IPC are coming to review. Advised - bloods inc FBC and U&Es, clinical review, if no concerns give fidaxomicin
- 7/9/21call - Patient has loose stool type 7 / 7 x a day, CRP 400, WCC 19, PCT not done, Abdomen soft but tender, No imaging available as in field hospital, Patient non specifically unwell. - Cdiff toxin +ve on 6/9/21 - Suggest fidaxomicin, needs imaging as well. Suggest surgical rv of abdomen. If concerns of managing in hospital then to treat in main 2ndry centre rather than field hospital.

- 10/09/2021 call with GP, on day 3 fidax for recurrent Cdiff. still multiple type 7 stools per day. but looks better in self. Stools had returned to normal after last episode but then had resp symptoms and was Paraflu pos but result went to Swansea and so several courses of Abx given for chest likely trigger for recurrence. Please raise in RCA as lack of result needs following up. Suggest continue with fidaxomycin 10 days, if still loose stool at the end consider tapering course of vanc. Please discuss with micro if any concerns and also if any other Abx needs to be started as might give vanc to try to prevent further episode.
- 21/09/2021 call from GP. Recovered from CDI, stools normal. Today pyrexia and rigors with single vomit. Pyrexial to 38.3, obs stable other than slight drop in O2 sats to 94%. Chest clear, abdomen SNT, no signs UTI, no evidence SSTI. Doesn't appear too unwell, nil specific evidence infection. Blood cultures and bloods done. Not keen to give abx given recent CDI. Advised - resp virus screen, hold off abx for now as with no specific clinical features would have to be broad spectrum, discuss with micro if deteriorates to consider targeted abx if needed

- 23/09/2021 GNB in blood culture pt in Hospital A. D/w nurse. GNB in blood cultures - suggest - transfer to acute hospital, start iv taz and po vanc and investigate for source of bacteraemia.

- 23/09/2021call from GP covering Hospital A. Patient was unwell on 2 days ago but wasn't started on Abx and has not had a temp since. increased urinary frequency but quite well. No abdo pain or tenderness, feels it is likely to be a urinary source. Concerned about C diff recurrance. Suggest - start iv gent and po vanc and rediscuss with sensitivities tomorrow - may be sensitive to co-trim which has good oral bioavailbility. The GP covering Hospital A will call micro tomorrow afternoon for a further discussion

- 24/09/2021 Call from GP at Hospital A. Patient has E coli bacteremia. Seems unwell. Not her usual self. Had gent yesterday. unable to do gent levels at the Hospital A (reliably and in a timely fashion) E coli is cotrim resistant. Suggest taz although i am aware not very friendly in terms of c diff risk. Patient is not for transfer to main hospital due to other comorbidities. Suggest taz and po vanc. with a view to monitoring stool frequenecy. Daily rv abdomen and monitor stools

- 27/09/2021 Patient seen today in Acute Hospital B's AMU for gent levels as unable to do these in Hospital A. D5 gent for E.coli bacteraemia for ?urinary source. Patient already back in Hospital A but FY1 on AMU has been asked what step down can be given as stopping gent today. Reported as well and improving. On PO vanc as well as known C.diff recently. E.coli R to co-trim and amox, S to co-amox and cipro. Advised could given cipro to 7 days total, continue to PO vanc and need to be aware of C.diff risk.

- 04/11/2021 - call from GP at Hospital A. Abx stopped end Sept, normal formed stool since. Worsened last few days, generally unwell, abdo pain and tenderness. BO x3 type 7 today. Clinically stable, abdomen SNT. Stool sample sent this morning, bloods done. Advised - vanc 125mg qds for presumed C.diff, monitor clinically, call if worsens, consider referral for FMT if C.diff confirmed
- 05/11/2021 - stool sample 4/11/21 C.diff PCR pos tox pos. Call to staff nurse C. Stable. BNO today. Isolated. Advised - continue vanc, need to d/w GP next week re further treatment ?FMT