

Surrey Heartlands Integrated Care System Area Prescribing Committee (APC)

Integrated Care Partnerships (ICPs) (Surrey Downs, Guildford & Waverley, North West Surrey, East Surrey & associated partner organisations.)

Title of paper:	Antimicrobial prescribing: Clostridioides difficile		
Meeting date:	3 rd November 2021		
Agenda item:	To be completed by APC secretary	Attachment(s):	
Author and contributors:	Sarah Watkin, Associate Director of Pharmaceutical Commissioning		
Paper type	Briefing: NICE Clinical Guideline		
For:	Agreement		
<p>Executive Summary: <i>(provide a short description of the subject matter and draw attention to the issues / facts and the proposal)</i></p> <p>In July 2021, NICE published new guidance on treatment of C.diff that included recommendations for prescribing vancomycin and fidaxomicin with implications for primary care. Both drugs have no current traffic light status, there is very limited use in primary care to date and both are costly for community pharmacists to stock. This paper outlines the rationale for considering vancomycin as GREEN for adults (BLUE for children), fidaxomicin as BLUE and suggests that routine supply by community pharmacy should be the normal access route but to consider if there is a need for additional central holding (similar to the palliative care drugs scheme).</p>			
<p>Summary: <i>(What is the APC being asked to do and why)</i></p> <ol style="list-style-type: none"> 1) Agree <u>oral vancomycin as GREEN</u> for treatment of C.diff in adults as per NICE clinical guideline. <u>BLUE</u> (on recommendation) for children. To be preparation specific? 2) Agree <u>oral fidaxomicin as BLUE</u> (on recommendation of microbiology specialist) for treatment of C.diff in adults and children as per NICE clinical guideline 3) Agree that routine access through community pharmacy is appropriate with communication out to indicate likely increase in requirement for vancomycin. Ask for feedback from GPs if timely supply is an issue. 4) Support the holding of vancomycin and fidaxomicin through a <u>locally commissioned service with community pharmacists</u> 5) Agree <u>bezlotoxumab as NON-FORMULARY</u> to prevent recurrence of <i>C. difficile</i> infection because it is not cost effective as per NICE clinical guideline. 			
<p>Accompanying papers (please list):</p> <ol style="list-style-type: none"> 1) N/A 			

Clostridioides difficile (C.diff): Antimicrobial Prescribing

Situation

In July 2021, NICE published new guidance on treatment of C.diff that included recommendations for prescribing vancomycin and fidaxomicin.

[Overview](#) | [Clostridioides difficile infection: antimicrobial prescribing](#) | [Guidance](#) | [NICE](#)

The inclusion of it in NICE guidelines implies that supply of both vancomycin and fidaxomicin can be made by primary care. Neither drug has a current PAD entry.

This paper outlines a possible implementation mechanism.

Background

New NICE guidelines for C.diff advise the use of oral vancomycin or fidaxomicin (appendix 1) – both of which have limited use to date in primary care and are costly:

Recommended treatment	Items in July 2021	Items in 12m to July 2021	Course	Cost
Vancomycin	8	83	125mg QDS x10d	£188
			500mg QDS x10d	£374
Fidaxomicin	0	2	200mg BD x10d	£1350

Other recommendations for consideration are:

- Do not offer **bezlotoxumab** to prevent recurrence of *C. difficile* infection because it is not cost effective.
- Consider a **faecal microbiota** transplant for a recurrent episode of *C. difficile* infection in adults who have had 2 or more previous episodes (see [NICE's interventional procedures guidance on faecal microbiota transplant for recurrent C. difficile infection](#))

Assessment

Safety

Fidaxomicin is a macrocyclic antibacterial that is poorly absorbed from the gastrointestinal tract, so is not used to treat systemic infections. It is taken orally to treat *C. difficile* infection. Common side effects when taken orally for *C. difficile* infection include constipation, nausea and vomiting. The manufacturer advises that it is preferable to avoid using fidaxomicin in pregnancy as a precaution (see [BNF information on fidaxomicin](#) and [fidaxomicin summary of product characteristics](#)).

Vancomycin is a glycopeptide that is taken orally to treat *Clostridioides difficile* infection. With oral use, the company advises monitoring serum vancomycin concentration in people with inflammatory intestinal disorders in which absorption may be enhanced. It also advises that serial auditory function tests may help to minimise the risk of ototoxicity in people with an underlying hearing loss, or who are having concomitant therapy with other ototoxic drugs. In renal impairment or in people having concomitant treatment with an aminoglycoside or other nephrotoxic drug, the manufacturer advises serial monitoring of renal function. The

manufacturer advises that vancomycin should be used in pregnancy only if the potential benefit outweighs the risk. Prolonged use of vancomycin may result in the overgrowth of non-susceptible organisms. Acquired resistance to glycopeptides is most common in enterococci, in which multiresistant strains have been seen (see [BNF information on vancomycin](#) and [vancomycin summary of product characteristics](#)).

Colour classification

Fidaxomicin is excluded from the national tariff and if supplied by acute trusts is usually funded on a cost per case basis. The inclusion of it in NICE guidelines implies that supply by primary care is suitable especially to avoid/reduce contact with other people and avoid travelling when acutely unwell.

The collaborative AMS group recommend that fidaxomicin is made BLUE (suitable for initiation in primary care on advice from a microbiologist). The rationale for blue rather than green was because of NICE indicating specialist advice (appendix 2) as follows:

- Adults - consider seeking prompt specialist advice before starting treatment
- Children - treatment should be started by, or after advice from, a specialist

There is also the high cost of fidaxomicin to consider.

Vancomycin is recommended as first line antibiotic suitable for first episode of mild, moderate or severe C.diff infection. There is no current colour classification on PAD and the APC are asked to consider if this needs a traffic light status for this indication and if it should also be made BLUE in light of the NICE 'consider seeking advice' (as above) or added as GREEN because it is lower cost and is first line treatment in uncomplicated patients.

Access in primary care

Community pharmacies do not routinely stock fidaxomicin due to the high cost and unlikely to stock vancomycin due to limited use and cost. Currently there is a high risk of wastage. In the six months to September 2021, the total number of C. diff across Surrey Heartlands was 114, with 67 being community cases but please note not necessarily treated in primary care (appendix 3).

Appendix 4 shows the possible impact on access to these drugs of community pharmacy delivery schedules. Both drugs can usually be obtained within half to one day of a patient presenting but there could be delays of up to three days. Most pharmacies have two deliveries a day (Mon to Fri and one on Saturday) although some are now on a single delivery model (one multiple has moved to this and there are probably a few others). Acute trust consultants have confirmed that short delay up to one day would not be clinically significant for community treated patients but quicker access to vancomycin as the first line choice would be appreciated to avoid delay in treatment of acutely unwell patients. Fidaxomicin as second line choice is less of an issue because a patient is likely to already be on vancomycin.

With the change in guidance it is proposed to communicate out to community pharmacies that they are likely to see an increase in prescriptions for oral vancomycin for treating C.diff

and they may want to consider holding a small stock. Vancomycin is split to supply specific courses so there may be split packs left for immediate part-supply when prescribing becomes more common place.

For the occasions when the ordering and/or delivery schedule of a pharmacy outlet will mean significant delay to access of vancomycin or fidaxomicin it is proposed that a locally commissioned service is developed which will provide to participants:

- Annual retainer for participation in the scheme
- Up front payment pay for minimum stock
- Reimbursement for stock replenishment after dispensing or expiry

Once a service specification is agreed, expressions of interest will be requested, and sites chosen based on locality/opening hours.

Preparations for oral administration

Fidaxomicin Tablets 200mg - *can be crushed and mixed with water or apple sauce for administration. May be crushed and mixed with water for enteral feeding.*
Granules for oral Suspension 40mg/ml – *not available until January 2022*

Vancomycin Capsules 125mg | 250mg
Injectable solution with IV needle & Luer syringe* OR with ENFit devices*
Imported oral liquid*

*Primary care availability questionable – for hospital only supply

Stakeholder views

Local microbiology teams were asked for views on traffic light classification and access in primary care of fidaxomicin and vancomycin. Views were received from SASH, ASPH & RSCH.

- **Support for BLUE traffic light for fidaxomicin** - being significantly more expensive and unfamiliar, seems sensible to prescribe after discussion only. It is not first line treatment, and it would be used in failure/ relapse/ recurrence cases only. As per the guidelines we should usually observe up to 7 days before we decide that vancomycin is ineffective and need changing to fidaxomicin. Most of the community C.diff cases, especially complicated ones, get discussed with us anyway. We agree that Fidaxomicin should be recommended by a microbiologist
- **Request for GREEN traffic light status for vancomycin** - for first episode cases with a positive C.diff toxin result, GP's should be able to start po vancomycin as per guidance without getting approval from microbiologist. Always happy to discuss with them if clinical advice is required. It would be a waste of their time and our time to be seeking permissions for non-severe or non-complex cases. As this is recommended as the first line treatment, its usage will be much more increased and should be readily available. This should include both capsules and the powder form. We agree vancomycin for uncomplicated CDI can be managed by GPs
- **Community pharmacy access** - long travel is not ideal if they can't get it delivered to them. Central stock similar to existing palliative care meds arrangement might be a good idea but as you mentioned, travelling much further might be an issue, and

particularly with symptoms expected in this patient group if no one else is available to pick these up for the patient or the distance they may be required to travel. A delay of a few hours/half a day is unlikely to be significant if the patient is well enough in the community and this is probably not dissimilar to how long patients presenting to secondary care may wait to initiate treatment but feel that longer than 1 day could be considered less appropriate and a significant delay to treatment. We should be aiming to start treatment as soon as a diagnosis is known so although not awful I think even a one day delay to treatment is not ideal- and certainly not a delay of 3 days

- **Fidaxomicin** – Half to 1 day is reasonable, I think. For first episode cases, it's not a major problem as they are on vancomycin anyway while the review for possible treatment failure is happening. A few hours of delay can be acceptable, but half a day might be too long
- **Vancomycin** - going to be used more commonly now and is first line treatment for CDT should be available quicker. Obviously, half a day is not going to do much harm due to the nature of this disease, unlike say sepsis! I would hope that the severely unwell will all be in hospital rather than community. Access to vancomycin without delay is key

Recommendation

- 1) Agree oral vancomycin as GREEN for treatment of C.diff in adults as per NICE clinical guideline. BLUE (on recommendation) for children. To be preparation specific?
- 2) Agree oral fidaxomicin as BLUE (on recommendation of microbiology specialist) for treatment of C.diff in adults and children as per NICE clinical guideline
- 3) Agree that routine access through community pharmacy is appropriate with communication out to indicate likely increase in requirement for vancomycin. Ask for feedback from GPs if timely supply is an issue.
- 4) Support the holding of vancomycin and fidaxomicin through a locally commissioned service with community pharmacists
- 5) Agree bezlotoxumab as NON-FORMULARY to prevent recurrence of *C. difficile* infection because it is not cost effective as per NICE clinical guideline.

Appendix 1

NICE section 1.2: Choice of antibiotic

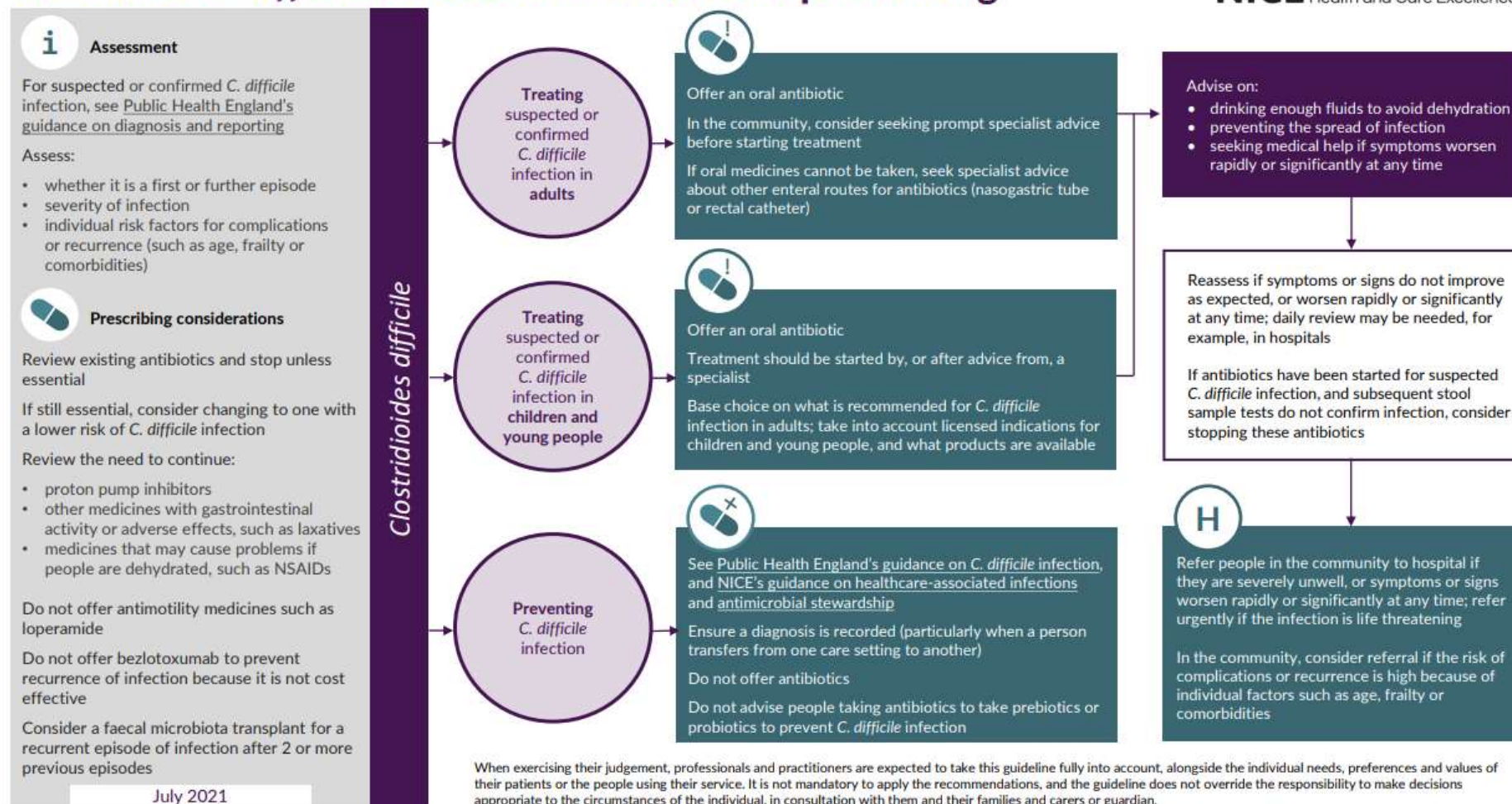
Table 1 Antibiotics for adults aged 18 years and over

Treatment	Antibiotic, dosage and course length
First-line antibiotic for a first episode of mild, moderate or severe <i>C. difficile</i> infection	Vancomycin: 125 mg orally four times a day for 10 days
Second-line antibiotic for a first episode of mild, moderate or severe <i>C. difficile</i> infection if vancomycin is ineffective	Fidaxomicin: 200 mg orally twice a day for 10 days
Antibiotics for <i>C. difficile</i> infection if first- and second-line antibiotics are ineffective	Seek specialist advice. Specialists may initially offer: Vancomycin: Up to 500 mg orally four times a day for 10 days With or without Metronidazole: 500 mg intravenously three times a day for 10 days
Antibiotic for a further episode of <i>C. difficile</i> infection within 12 weeks of symptom resolution (relapse)	Fidaxomicin: 200 mg orally twice a day for 10 days
Antibiotics for a further episode of <i>C. difficile</i> infection more than 12 weeks after symptom resolution (recurrence)	Vancomycin: 125 mg orally four times a day for 10 days Or Fidaxomicin: 200 mg orally twice a day for 10 days
Antibiotics for life-threatening <i>C. difficile</i> infection (also see recommendation 1.1.16)	Seek urgent specialist advice, which may include surgery. Antibiotics that specialists may initially offer are: Vancomycin: 500 mg orally four times a day for 10 days With Metronidazole: 500 mg intravenously three times a day for 10 days

Appendix 2

Clostridioides difficile infection: antimicrobial prescribing

NICE National Institute for Health and Care Excellence



Appendix 3

Surrey Heartlands C.diff cases provided by Senior Quality & Safety Manager

Cdiff	April	May	June	July	August	Sept
HOHA	7	7	8	12	7	6
COHA	5	2	3	3	5	1
COCA	4	4	7	3	6	3
COIA	3	4	1	6	2	5
Total	19	17	19	24	20	15

Appendix 4

Community pharmacy delivery schedules

Rx presented	Order and delivery information	Impact on patient
Mon-Thur	order before morning cut-off 11.30am will be delivered same day afternoon – some pharmacies only have one delivery per day so delivery could be next day	Half – one day wait
	order before afternoon cut-off 5pm will be delivered next day morning- or next afternoon if on a single delivery slot it	Up to one & half day wait
	Order after 5pm will be delivered next day afternoon – depends on cut off if they have a single delivery slot	One day wait
Fri	order before morning cut-off 11.30am will be delivered same day afternoon - some pharmacies only have one delivery per day so delivery would be next day	Half – one day wait
	order before afternoon cut-off 5pm will be delivered next day morning - depends on cut off if they have a single delivery slot	Up to one and a half day wait
	Order after 5pm will be delivered Monday morning or possibly afternoon if single delivery slot pm	Up to three days wait
Sat	orders will be delivered Monday morning or possibly afternoon if single delivery slot pm	Up to two & half days wait
Sun	order before afternoon cut-off 5pm will be delivered Monday afternoon or possibly Tuesday morning dependent on delivery schedule if only one delivery per day	Up to one and a half day wait
	Order after 5pm will be delivered Monday afternoon depends on cut off if they have a single delivery slot could be Tuesday morning	Up to one and a half day wait