Overview of Evidence on Oral Vancomycin Prophylaxis for *C. difficile* Prevention

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Background: Data for oral vancomycin are limited to a single randomized trial and several observational cohorts – all with significant limitations (see Table 1). Not all studies found evidence of benefit: in fact, the largest single observational study found no reduction in *C. difficile* incidence with prophylaxis.(1) Within the limitations of existing heterogenous and low-quality data, prior meta-analyses suggest a potential benefit for oral vancomycin prophylaxis.(2) Well-conducted trials are still needed.

Several studies also raise important unresolved issues:

-Highlighting the importance of adjustment for immortality time bias, one case series found that 31% of subjects developed *C. difficile* within the 8 weeks following discontinuation of prophylaxis. This raises the key question whether prophylaxis actually prevents rather than just delays disease onset.(3)

-On meta-analysis, vancomycin actually showed an *inverse* dose effect: higher total daily doses correlated with reduced benefit – suggesting lower dose regimens might be preferred.(2)

-Oral vancomycin may also select for vancomycin-resistance *Enterococcus faecalis*.(4)

For the interested reader, a recent *New England Journal* Clinical Decisions feature succinctly outlines pro- and con- viewpoints regarding oral vancomycin prophylaxis.(5)

Summary: Evidence for oral vancomycin prophylaxis remains limited – hinging mostly on observational data with significant risk of selection bias and failure to account for immortality time bias or potential for delayed infection.

-Clinicians may consider oral vancomycin prophylaxis in select situations, such as cases with a history of recurrent or severe *C. difficile* infection requiring high-risk systemic antibiotics.

-Vancomycin 125 mg PO once or twice daily is likely as effective or more effective than higher doses.

Table 1: Summary of Existing Studies on Oral Vancomycin Prophylaxis

Study	Design	Outcomes	Quality
Johnson et al CID 2020(6)	Randomized open-label trial Inclusion: high CDI risk (age >60, hospitalization in preceding 30 days, systemic antibiotic receipt) Intervention: vancomycin 125 mg	Hospital-onset *C. difficile*: 0/50 with prophylaxis vs 6/50 control (p=0.03) Healthcare facility associated *C. difficile*: 0/50 with prophylaxis vs 2/50 control (p=0.49)	MODERATE -Inclusion criteria based on perceived risk without consideration of *C. difficile* history -Very small event numbers -Missing telephone follow-up for >50% of subjects

	PO daily during antibiotics to 5 days post Follow-up: telephone at 4 weeks, chart review at 3 months N=50 in each arm	*Note that benefit was limited to hospital-onset period and was lost in longer HCFA period.	-Missing chart review follow-up for 12-16% of subjects -No statistical accounting for missingness or censoring -Failed to account for immortality time bias
Van Hise et al 2016(7)	Retrospective cohort Inclusion: prior *C. difficile* & hospitalized with systemic antibiotic receipt Intervention: vancomycin 125-250 mg PO once or twice daily Follow-up: 4 weeks N=71 at 125 mg dosing, 42 at 250 mg dosing, 132 in control arm	C difficile recurrence 4.2% with prophylaxis vs 26.6% with control (p<0.01)	LOW -High risk of selection bias (observational & retrospective) -Follow-up period is much shorter than usual & risks missing delayed cases which have been documented after PO vancomycin -Failure to account for immortality time bias -No description of completeness of follow-up
Carignan et al 2016(8)	Retrospective cohort Inclusion: systemic antibiotic receipt after *C. difficile* episode within preceding 90 days Intervention: vancomycin 125 mg PO Q6h for 84% Follow-up: 90 days N=227 receiving prophylaxis, 324 without	aHR 0.47 with prophylaxis (p<0.01) On subgroup analysis, prophylaxis was not effective after initial *C. difficile* episodes – only after recurrences	LOW -High risk of bias (observational) -Empirical re-treatment (without testing) was counted as a *C. difficile* case, introducing bias in outcome ascertainment -Groups differed in number of prior CDI episodes and use of vancomycin taper -Failure to account for immortality time bias
Splinter et al 2018(9)	Retrospective matched cohort	0/12 with prophylaxis vs 2/24 control (p=0.54)	LOW

	Inclusion: renal transplant with history of *C. difficile* & receiving systemic antibiotics Intervention: vancomycin 125 mg PO Q12h Follow-up: 4 weeks N=12 with prophylaxis, 24 in control		-High risk of bias (observational & retrospective) -Very specific population -Extremely small numbers -Short follow-up -Failure to account for immortality time bias
Knight et al 2019(10)	Retrospective cohort Inclusion: prior *C. difficile,* hospitalized on systemic antibiotics Intervention: vancomycin 125-250 mg PO Q6h Follow-up: up to 12 months N=32 with prophylaxis, 59 control	6.3% with prophylaxis vs 28.8% in control (p=0.01)	LOW -High risk of selection bias (observational and retrospective) -Limited description of follow-up, outcome ascertainment or missingness (appears to have been limited to electronic chart review at 1 center) - Failure to account for immortality time bias -Small numbers -No standard prophylaxis regimen
Zhang et al 2019(3)	Retrospective case series Inclusion: Recurrent *C. difficile* infection but not a candidate for FMT or failed FMT Intervention: 125 mg PO once daily (after initial 14 day treatment course)	Although no *C. difficile* occurred while on prophylaxis, 31% still developed *C. difficile* within 8 weeks of prophylaxis discontinuation	LOW -Case series with no control arm -Narrower inclusion criteria -Variable follow-up - Failure to account for immortality time bias

	Follow-up: up to 19 months N=20		
Caroff et al 2019(1)	Retrospective cohort (including propensity matching) Inclusion: adults with *C. difficile* in the past 30-150 days receiving systemic antibiotics Intervention: not specified (variable vancomycin regimens used) Follow-up: 3-6 months N=193 receiving prophylaxis, 567 controls	9.8% vs 9.4% (no benefit on naïve or adjusted analyses)	MODERATE -One of the better-adjusted studies, but still some risk of residual confounding & selection bias -Irregular inclusion criteria -No set intervention - Failure to account for immortality time bias
Zacharioudakis et al 2020(4)	Retrospective cohort Inclusion: CDI history and systemic antibiotic receipt Intervention: vancomycin 125 mg PO Q12h Follow-up: 1 month N=264	Breakthrough *C. difficile* infection occurred in 6.4% receiving prophylaxis; recurrence occurred in 8.3% following prophylaxis *Did observe an increase in VRE rates among vancomycin recipients: 16.2% had VRE isolated following prophylaxis vs 6.2% prior	LOW -Observational and retrospective (risk of selection bias) -No control group used for *C. difficile* outcome -Short follow-up - Failure to account for immortality time bias
Morrisette et al 2019(11)	Retrospective cohort Inclusion: HSCT/heme malignancy and prior *C. difficile*	OR 0.14 (95% CI 0.007-0.994) with prophylaxis (p=0.049)	LOW -Observational with risk of selection bias

	Intervention: vancomycin 125 mg PO Q12h up to 7 days post antibiotic Follow-up 8 weeks N=21 prophylaxis, 29 controls		-Mean age differed between prophylaxis and control groups -Short follow-up - Failure to account for immortality time bias -Limited and specific inclusion criteria (Heme malignancy population only) -Small numbers with high uncertainty -High study fragility index (e.g., just 1-2 additional cases might have altered results)
Najjar-Debbiny et al 2024(12)	Retrospective cohort Inclusion: adults receiving systemic antibiotics within 2-8 weeks of prior *C. difficile* Follow-up: 4-8 weeks N=107 prophylaxis, 327 control	HR 0.51 (95% CI 0.27-0.97) with prophylaxis	LOW -Observational and retrospective (risk of selection bias) -Short follow-up -Failure to account for immortality time bias -High study fragility index (note how confidence interval approaches 1)

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