

Clinical Finding Form (CLiFF)

Branch Baseline

ICL118_Vaginal Yeast Infection

Vulvovaginal Candidiasis (VVC) is a yeast infection of the vulva and/or vagina mainly caused by *Candida albicans*. *Candida albicans* is normally a harmless yeast infection that can be found in the mouth, intestinal tract, or vagina. It can lead to symptoms when overgrowth occurs, and this can often follow administration of systemic antibiotics that kill off the normal flora in these locations. VVC is characterized by pruritis, discomfort/pain, abnormal vaginal discharge, dysuria, and/or dyspareunia. Signs can include swelling, redness, fissures, excoriations. Up to 75% of women will have at least one episode of VVC in their life and 40-45% will have 2+ episodes. On the basis of clinical presentation, microbiology, host factors, and response to therapy, VVC infections can be labeled as complicated or uncomplicated. Uncomplicated VVC infections, by definition, include: sporadic or infrequent VVC, mild-to-moderate VVC, and likely to be *C. albicans* in non-immunocompromised women. Complicated VVC can be recurrent, severe, nonalbicans species, or women with immunocompromising conditions including HIV infection, diabetes, debilitation, or immunosuppressive therapy. 10-20% of VVC may be complicated by these criteria (CDC 2015). Of all infectious vaginitis, 20-25% is caused by candida, while 40-50% is caused by bacterial vaginosis (BV), and 15-20% is caused by trichomoniasis. Pre-flight screening and treatment should prevent trichomoniasis while BV will likely be investigated in a future CLiFF.

INCIDENCE DATA INCLUDED IN THE MODEL

The model imports the following incidence information from the MEDPRAT Evidence Library Database: incidence data category, space adaption status, EVA status, incidence data type, incidence and occurrence distribution data and incidence data characteristics. Data category defines the type of data available for incidence calculations (i.e. raw data vs. adjusted data). Space adaptation identifies medical events that where onset occurs in the first 5-7 days of flight and does not reoccur. EVA-related incidence values identify medical events that occur only during an EVA. Incidence values types vary by data category and define the number of medical events per person-year (rates) or medical events per person at-risk (proportion) for each medical condition. Incidence values can be modified by crew characteristics such as gender sex and certain crew medical history characteristics. Modifying characteristics are noted below and incidence values are listed individually for each characteristic. Distributions are assigned to medical events incidence values and occurrences in the model. For each crewmember in a given trial, the incidence and number of occurrences of each medical condition are randomly selected from these probability distributions. Detailed descriptions of the distributions are included in the MEDPRAT Technical Description Document.

INCIDENCE DATA

SPACEFLIGHT LITERATURE

There is no record of VVC occurring in spaceflight. This may be due to underreporting or absence of data collection.

ANALOG LITERATURE

Two analog studies were evaluated. Nice in 1989 evaluated VVC aboard U.S. Navy ships. 83 cases were reported with an incidence rate of 14.16 per 1000 person-months. This leads to a reported incidence rate of 0.1699 (95% CI: 0.1362, 0.2096). Hanna 1992 evaluated gynecologic complications during Operation Desert Storm. 74 cases of VVC were reported among ~10,000 females deployed for 4-6 months, however, there is not enough data to give us a true incidence rate.

TERRESTRIAL LITERATURE

Three studies were revealed in our effort. The first was Foxman 2000, which surveyed 2000 women over 2 months. There were 127 self-reported cases over 333.33 person-years leading to an IR of 0.381 (95%CI: 0.3189, 0.4518). Goncalves 2016 and Tibaldi 2009 were also evaluated however, they mainly deal with prevalence rate and do not have the data in order to calculate IR.

OVERALL INCIDENCE SUMMARY

INCIDENCE

mean 0.2553 and SD 0.01771

INCIDENCE SUMMARY

This is a condition relevant to only females. The Bayesian posterior distribution for the incidence rate given the evidence (Nice 1989 and Foxman 2000) under an uninformative prior is Gamma(shape=207.81, rate=813.98) with mean 0.2553 and SD 0.01771.

TABLE 1. INCIDENCE MODEL

Incidence Details

Incidence Type

General

Segment

All

Env. Exposure

NA

Sex

Female

Crowns

Any

Contacts

Any

Pregnancy

Any**Incidence Distribution**

Occurrence Dist

Poisson

Incidence Dist.

Gamma

Mean

0.255301

SD

0.01771

Gamma

(Shape): 207.81**(Rate): 813.98**

TABLE 2. INCIDENCE LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Nice, 1989	Analog	3
Hanna, 1992	Analog	2
Foxman, 2000	Terrestrial	3
Goncalves, 2016	Terrestrial	2
Tibaldi, 2009	Terrestrial	2

Our search was first limited by the fact that most studies discuss prevalence rather than true incidence. The two studies that were used in the composite decision were Nice, 1989 and Foxman, 2000. The terrestrial study is limited by recall bias as it is a survey-based analysis. Interestingly, the incidence in the analog study population was half of that of the terrestrial population. Underreporting of a female-specific issue in the military is highly possible. Thus overall, our confidence in this incidence rate is neutral to low.

CREWMEMBER SELECTION/PREVENTION

DISQUALIFYING CONDITIONS

Refer to Medical Evaluation Documents (MED) Volume A, Medical Standards for ISS Crewmembers, International Space Station Program, Rev 3.4 (2016).

PREFLIGHT PREVENTATIVE MEASURES

All astronauts undergo a pre-flight gynecologic exam in which VVC can be recognized and treated, however there are not specific pre-flight measures for prevention of VVC.

BEST CASE SCENARIO DEFINITION

Uncomplicated vulvovaginal candidiasis, with mild to moderate, sporadic, or infrequent vulvar irritation, including itching and discomfort of the vulvar skin and vaginal epithelium, vaginal discharge, and/or discomfort with voiding which responds to all azole treatment regimens including single-dose oral, and intra-vaginal therapy.

WORSE CASE SCENARIO DEFINITION

Complicated, severe, or recurrent vulvovaginal candidiasis requiring extended oral treatment.

CONDITIONS INCLUDED, BUT NOT EXPLICITLY STATED (CNES)

None.

BEST CASE/WORST CASE PROBABILITY COMMENTS

While the CDC estimates that 10-20% of VVC is complicated per their definitions as stated in the introduction above, the incidence of worst case VVC per the definitions of this CLIFF are likely lower, especially given the astronaut population's lack of immunocompromising medical problems meeting such criteria. Our literature search did not reveal an incidence of severe infection in the absence of immunocompromising factors or recurrence, however multiple studies report recurrence rates of 8-8.5% (Foxman, 2000, Grigoriou, 2006). Thus, a conservative WC scenario rate of 10% is reasonable in light of this data and the known potential for immune system dysregulation in space (Crucian, 2018).

TABLE 3. BEST/WORST CASE PROBABILITY LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Foxman, 2000	Terrestrial	3
Grigoriou, 2006	Terrestrial	3
CDC, 2015	Terrestrial	2

Neutral to some confidence levels were chosen for these sources as they are all terrestrial and not engineered for determining the WC definition established for this CLIFF. However, the large population data is large and robust and informs a reasonable WC rate.

TABLE 4. CLIFF TREATMENT & OUTCOME TABLE BY CLINICAL PHASE

Case Scenario	Composite Incidence	Condition Probability %	CP1: Diagnosis		CP2: Treatment			CP3: Condition End State				
			TI%	Duration	TI%	Duration		TI%	RTDC	LOCL		
			Preset	Preset	Preset	Min	Max	Preset	Min%	Max%	Min%	Max%
Treated Best Case (TBC)	mean 0.2553 and SD 0.01771	90 - 90	100	0.666	5.76668	24	168	0	0	0	0	0
Treated Worst Case (TWC)		10 - 10	100	0.666	5.76668	72	4380	0	0	0	0	0
Untreated Best Case (UTBC)	N/A	N/A	N/A	0.666	5.76668	72	8760	0	0	0	0	0
Untreated Worst Case (UTWC)	N/A	N/A	N/A	0.666	5.76668	336	8760	5.76668	0	0	0	0

TABLE 4 KEY

Composite Incidence: The same composite incidence will be used for both TBC and TWC. For EVA conditions: events per EVA (events/EVA). For space adaptation conditions: events per person (events/person). For non-spaceflight conditions: events per person year (events/py).

Condition Probability: The probability that CLIFF condition progresses to a worst case scenario. Best case scenario: 100%-Worst Case.

Clinical Phase General Comments:

- TI% = Task Impairment %. Task Impairment is the % of tasks that the crewmember is incapable of performing without impairment secondary to the medical condition.
- Durations are defined in hours.
- Removal to Definitive Care (RTDC): The probability the entire crew aborts the mission and returns to earth. This is considered as a condition end state result if any of the following criteria are met: 1) the potential for LOCL, 2) potential for significant permanent task impairment, or 3) potential for intractable pain.
- Loss of Crew Life (LOCL): The probability of death of affected crewmember due to medical condition.

Clinical Phase 1: Initial Assessment and Diagnosis:

- Covers only the initial assessment and diagnosis of the affected crewmember to define his or her medical condition. While the affected crewmember is being assessed, he or she is not able to perform any assigned tasks, thus Task Impairment (TI) during this phase is considered 100%. In the untreated case, there is no diagnosis performed, therefore Task Impairment and Duration will always be "not applicable."

Clinical Phase 2: Stabilization, Treatment, and Convalescence:

- The affected crewmember is receiving any appropriate initial or follow-on treatment for his or her medical condition to allow the crewmember to recover as much as he or she is able to recover in the spaceflight environment. Clinical phase 2 also encompasses relapses or recurrences of the same original medical condition in Clinical Phase 1. The duration of Clinical Phase 2 is expressed as minimum and maximum hours.

Clinical Phase 3: Condition End State:

- Reached once the affected crewmember has recovered from the medical condition as much as he or she is able to recover in the spaceflight environment amongst treated and untreated best and worst case scenarios. This may or may not be recovery from the given medical condition to the full extent possible. If this "recovered" state results in Removal to Definitive Care (RTDC) or Loss of Crew Life (LOCL) this will be noted in the condition end state results.

SCENARIO OVERVIEW COMMENTS

As discussed below, diagnostic resourcing for this condition will be limited. Fortunately, VVC can often be diagnosed with signs and symptoms alone. Management of BC scenario VVC should also be straightforward and possible with the assumption of azole therapies, however, recurrent VVC refractory to azole therapy may require therapies beyond available resourcing.

TREATED BEST CASE (TBC) SCENARIO COMMENTS

Treated best case scenario may involve a single dose or oral fluconazole or 3-7 days of topical azole therapy. By definition it would not require RTDC or LOCL.

TREATED WORST CASE SCENARIO (TWC) COMMENTS

These data represent ACOG guidelines for treatment of the defined WC scenario. The broad range is reflective of the fact that contained within the WC definition is both a severe infection and a recurrent infection. Complicated or severe yeast infections are treated for 3-14 days, while recurrent infections are treated with weekly fluconazole for up to 6 months. RTDC and LOCL are not expected.

UNTREATED BEST CASE (UTBC) SCENARIO COMMENTS

While about 50% of VVC infections in the placebo arm of VVC treatment studies saw clearance by 7-days, BC infections can certainly clear spontaneously in as early as 3 days. However, even in BC scenarios, such infections can continue to be symptomatic even as late as 48-52 weeks (Stein, 1993; Bro, 1990; Sobel, 2001; Brand, 2018). While untreated VVC is not likely to cause RTDC or LOCL, it is also less likely to resolve on its own and the constant irritation is more likely to lead to task impairment.

UNTREATED WORST CASE (UTWC) SCENARIO COMMENTS

As with untreated BC scenarios, there is the possibility of self-resolution, however, this is exceedingly less likely in the setting of severe or recurrent yeast infections. There is not data to guide the minimum duration of self-resolution of a WC yeast infection, and thus 14 days was chosen by expert clinical opinion. Despite the symptoms of severe or recurrent VVC, RTDC or LOCL are not expected. While hospitalization may occur in the setting of severe candida infections, this is likely in a population with severe medical comorbidities that would not represent the astronaut population. Sepsis from a yeast infection would also not be expected in the astronaut population from VVC, however, candida septicemia would be accounted for in the sepsis CLIFF.

TABLE 5. CLINICAL PHASE II DURATION LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
Stein, 1993	Terrestrial	2
Bro, 1990	Terrestrial	
Sobel, 2001	Terrestrial	
Brand, 2018	Terrestrial	
ACOG, 2020	Terrestrial	
Pappas, 2016	Terrestrial	

All data is based on terrestrial trials of treatment of candidiasis with placebo arms. However, for some durations, there is no clear data to guide decision making. Furthermore, confidence in duration is also limited by the wide variance of pathology noted in the WC definition.

TABLE 6. RTDC LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
N/A	N/A	2

Even with hospitalization as a surrogate, our search did not reveal any significant increase in RTDC for VVC.

TABLE 7. LOCL LEVEL OF CONFIDENCE (LOC)

Citation	Source	LOC Value
N/A	N/A	2

Our search did not reveal any mortality data from VVC.

CAPABILITY RESOURCE TABLE (CRT) OVERVIEW

Overview

Vulvovaginal Candidiasis (VVC) usually is caused by *C. albicans* but can occasionally be caused by other *Candida* species. Typical symptoms include vaginal pruritus, soreness, dyspareunia, external dysuria, and abnormal vaginal discharge. 5-20% of women may have severe VVC or recurrent VVC. Severe vulvovaginitis would include symptoms of extensive vulvar erythema, edema, excoriation, and fissure formation. Recurrent VVC is usually defined as four or more episodes of symptomatic VVC within 1 year. The pathogenesis of recurrent VVC is poorly understood, and most women have no apparent predisposing or underlying conditions. *C. glabrata* and other nonalbicans *Candida* species are observed in 10%–20% of women with recurrent VVC. Conventional antimycotic therapies are not as effective against these nonalbicans species as against *C. albicans*.

CNES: None

Diagnostic Scope and Resourcing

A diagnosis of *Candida* vaginitis is suggested clinically by the presence of external dysuria and vulvar pruritus, pain, swelling, and redness. Signs include vulvar edema, fissures, excoriations, and thick curdy vaginal discharge. Terrestrially, the diagnosis can be made in a woman who has these signs/symptoms and either 1) a wet preparation (saline, 10% KOH) or Gram stain of vaginal discharge demonstrating budding yeasts, hyphae, or pseudohyphae or 2) a culture or other test yields a positive result for a yeast species. However, these tests are unlikely to be practical during spaceflight. *Candida* vaginitis is notably associated with a normal vaginal pH (<4.5), thus the availability of a pH strip can help distinguish between VVC and bacterial vaginosis which can present similarly. For a severe or recurrent infection, vaginal cultures would be obtained terrestrially to confirm clinical diagnosis and identify unusual species, including nonalbicans species, particularly *Candida glabrata*, however, this is beyond the scope of our diagnostic capabilities.

Clinical Phase 1 Duration and Rationale

This version of IMPACT presumes physician level knowledge, skill, and ability will be present on the mission. The CRT working group SME consensus duration is as follows:

CP1 BC (Treated or Untreated): 0.666 hours
CP1 WC (Treated or Untreated): 0.666 hours

The highest scope of practice is 3 (experienced ED/ICU nurse) in that the diagnosis and distinguishing factor between CVV and BV will need to be made by history and physical without the addition of laboratory tests to assist.

Treatment Scope and Resourcing

Terrestrially, a short-course topical formulation (i.e., single dose or regimen of 1–3 days) can treat uncomplicated VVC and result in relief of symptoms and negative cultures in 80%–90% of patients who complete therapy. Severe or recurrent CVV caused by *C. albicans* (our worst-case scenario) will also respond well to short duration oral or topical azole therapy. However, to maintain clinical and mycologic control, some specialists recommend a longer duration of initial therapy (e.g., 7–14 days of topical therapy or a 150mg oral dose of fluconazole every third day for a total of 3 doses [day 1, 4, and 7]) to attempt mycologic remission before initiating a maintenance antifungal regimen. Maintenance therapy after acute treatment includes 150mg oral fluconazole weekly for 6 months. Importantly, a vaginal applicator would need to be included with these topical modalities. 30%–50% of women may have recurrent disease after maintenance therapy is discontinued. Unless previously affected by recurrent VVC infections pre-flight, it is unlikely that an astronaut would develop recurrent VVC that is refractory to the above. Thus, further treatment beyond this is beyond the scope of this condition.

Communications and Support Needs

For the WC, consultation with ground specialists to facilitate treatment and healing could be necessary given the limited diagnostic capabilities in-flight

IMM CLIFF RECONCILIATION COMMENTS

The previous CLIFF and many of the sources were also utilized in the investigation for this effort.

LIMITATIONS SUMMARY

A major limitation of this effort is the paucity of data regarding incidence of VVC in spaceflight and analog populations. There is robust terrestrial data, however, given that the symptoms are easily recognizable by patients themselves, they are often treated with over the counter medications. Thus, terrestrial data is often based off past survey data given ambulatory visits would underrepresent incidence. Survey data is limited by recall bias. The WC vs. BC scenario decision is limited by the broad definition which includes both severe infections and recurrent infections. Duration data can adequately evaluate treated scenarios but the duration must be broad as well because of constraints imposed by the duration. Untreated best case scenarios can be found by looking at placebo-controlled RCTs, however, untreated worst case duration is impossible because this is a setting where no one would ever not treat. One interesting finding is that the level of task impairment remains the same regardless of best case or worst case, treated or untreated. While this is likely true, the duration of CP2 displays the difference in severity between conditions.

TABLE 8. TASK IMPAIRMENT CALCULATION BASED ON AFFECTED HUMAN SYSTEMS TASK CATEGORIES (HSTC)

Clinical Phase 2: Treatment												
	Affected HSTCs											
	Cognitive - Simple	Cognitive - Complex	Communications	Inter-personal Skills	Vision	Hearing	Cardio-pulmonary	Dentition	GI	GU		
Treated Best Case (TBC)										6		
Untreated Best Case (UTBC)										6		
Treated Worst Case (TWC)										6		
Untreated Worst Case (UTWC)										6		
	Affected HSTCs (Continued)								TI Calculation		TI Score	
	Hand (Dom)	Hand (Any)	Upper Extremity	Lower Extremity	Ambul & Standing (g)	Translation & Stabilization (microgravity)	Don/Doff Equipment	Pressure Ops	Total Tasks Impaired By Condition	Total Human System Category Tasks Full Mission	TI Decimal	TI %
Treated Best Case (TBC)								211	217	3763	0.0576668	5.76668
Untreated Best Case (UTBC)								211	217	3763	0.0576668	5.76668
Treated Worst Case (TWC)								211	217	3763	0.0576668	5.76668
Untreated Worst Case (UTWC)								211	217	3763	0.0576668	5.76668
	Affected HSTCs (Continued)								TI Calculation		TI Score	
	Cognitive - Simple	Cognitive - Complex	Communications	Inter-personal Skills	Vision	Hearing	Cardio-pulmonary	Dentition	GI	GU		
Treated Best Case (TBC)												
Untreated Best Case (UTBC)												
Treated Worst Case (TWC)												
Untreated Worst Case (UTWC)										6		
	Affected HSTCs (Continued)								TI Calculation		TI Score	

	Hand (Dom)	Hand (Any)	Upper Extremity	Lower Extremity	Ambul & Standing (g)	Translation & Stabilization (microgravity)	Don/Doff Equipment	Pressure Ops	Total Tasks Impaired By Condition	Total Human System Category Tasks Full Mission	T1 Decimal	T1 %
Treated Best Case (TBC)									0	3763	0	0
Untreated Best Case (UTBC)									0	3763	0	0
Treated Worst Case (TWC)									0	3763	0	0
Untreated Worst Case (UTWC)								211	217	3763	0.0576668	5.76668

TABLE 8 KEY

Human System Task Category (HSTC) Definitions: Cognitive-Simple: Tasks requiring simple cognitive involvement (low levels of attention, following simple checklists, and not requiring extensive decision making) in conjunction with inputs from other systems. Cognitive-Complex: Tasks requiring complex cognitive involvement (requiring constant attention, frequent interpretation of outside stimuli to inform real-time situations) in conjunction with inputs from other systems. Communication: Tasks requiring primarily communication, via hearing and speaking. Interpersonal Skills: Tasks requiring interpersonal, social interaction between crew including complex technical tasks that require extended crew interaction. Vision: Tasks in which visual information is required. Hearing: Tasks in which primarily auditory information is required, excluding communication, e.g. hearing alarms, medical auscultation, OOHAs. Cardiopulmonary: Tasks requiring greater-than-baseline cardiopulmonary effort, e.g. physically strenuous activities. Dentition: Tasks requiring use of teeth for mastication. GI (Gastrointestinal): Tasks requiring use of the alimentary system, e.g. solids/liquids consumption and solids excretion. GU (Genitourinary): Tasks requiring use of the male/female genitourinary systems. Hand (Dominant): Tasks performed using primarily the hand, requiring use of the dominant hand (piloting, medical procedures, dental procedures). Hand (Any): Tasks performed using primarily the hand(s), with no preference for dominance, with equivalent bilateral effectiveness. Upper Extremity: Tasks requiring specific use of the upper extremities, excluding hands. Lower Extremity: Tasks requiring specific use of the lower extremities (excluding ambulation and standing in the presence of gravity), e.g. using exercise equipment. Ambulation and Standing (g): Tasks requiring use of both lower extremities to accomplish ambulation or standing in the presence of gravity. Translation and Stabilization (microgravity): Tasks requiring use of either the upper or lower extremities to accomplish translational movement and stabilization (securing oneself to remain stationary) in the setting of microgravity. Don/Doff Equipment: Tasks requiring the donning of personal equipment (including pressure suit, exercise harness, EVA equipment, etc). Pressure Ops: EVA/contingency tasks performed while pressurized in a suit.

Criteria for Assignment of Conditions to HSTCs (any of the following):

- 1) Is affected crew member physically incapable of performing the human system task category, without impairment, with the condition?
- 2) Would the treatment (e.g. medications) impair the crewmember's ability to perform the human system task category? (Does not apply to UTx)
- 3) Does the condition have a high likelihood of causing a significant aeromedical contraindication with an associated human system task category?
- 4) Would performing tasks in an associated task category worsen the condition? (If so, it is affected).
- 5) Does pain associated with the condition impair any further human system categories?

TASK IMPAIRMENT COMMENTS

CP2: none. CP3: none.

EVIDENCE COLLECTION PROCESS

Mesh terms that most closely resembled the best-case and worst-case scenarios, and associated Conditions Included but Not Explicitly Stated (CNES), were utilized to build incidence, duration, RTDC, and LOCL searches by best- and worst-case.

Incidence:

Databases searched for spaceflight and analog incidence data included: PubMed, Google Scholar, NASA Technical Reports Server (NTRS) public search, Defense Technical Information Center (DTIC), and Barratt MR, Baker E, Pool SL. Principles of Clinical Medicine for Space Flight. New York, NY: Springer; 2019. 2nd Edition. Databases searched for terrestrial incidence included: DynaMed, PubMed, and Google Scholar.

Duration, RTDC, LOCL:

Databases searched for duration, RTDC, and LOCL included: Dynamed, Cochrane, PubMed, and Google Scholar. Note, that if duration, RTDC, or LOCL data was found in a DynaMed search, the other search engines were not included. Relevant articles were selected and reviewed. If applicable, the article was included in the CLIFF.

LEVEL OF CONFIDENCE (LOC) SCORING

Articles obtained to update the evidence behind this CLIFF were scored by ExMC editors, based on their applicability to the Exploration Spaceflight environment using the following grading scale:

- 4 – Confident
- 3 – Somewhat confident
- 2 – Neutral
- 1 – Somewhat unconfident
- 0 – Not confident

The following considerations factor into the grading scale above:

- How closely does the paper describe the medical condition as defined by the IMPACT 1.0 Condition List (relevance)?
- How closely does the population included resemble the astronaut population?
- Quality of the paper (number of subjects, methods, etc.)
- How much does the editor trust the source of the evidence?
- How closely does the editor think that the data represents the exploration spaceflight environment?
- Other considerations, at the discretion of the editor, supported in the comments for LOE scoring.

REFERENCES

Reference

Nice S, Hilton, SM. Sex Differences in Health Care Requirements Aboard U.S. Navy Ships. 1989.

Hanna JH. An analysis of gynecological problems presenting to an evacuation hospital during Operation Desert Storm. *Mil Med.* 1992 May;157(5):222-4. PMID: 1630650.

Foxman B, Barlow R, D'Arcy H, Gillespie B, Sobel JD. Candida vaginitis: self-reported incidence and associated costs. *Sex Transm Dis.* 2000 Apr;27(4):230-5. doi: 10.1097/00007435-200004000-00009. PMID: 10782746.

Grigoriou, O., Baka, S., Makrakis, E., Hassiakos, D., Kapparos, G., & Kouskouni, E. (2006). Prevalence of clinical vaginal candidiasis in a university hospital and possible risk factors. *Eur J Obstet Gynecol Reprod Biol*, 126(1), 121-125.

Tibaldi, C., Cappello, N., Latino, M. A., Masuelli, G., Marini, S., & Benedetto, C. (2009). Vaginal and endocervical microorganisms in symptomatic and asymptomatic non-pregnant females: risk factors and rates of occurrence. *Clin Microbiol Infect*, 15(7), 670-679. doi:10.1111/j.1469-0691.2009.02842.

Crucian BE. Et al. Immune system dysregulation during spaceflight: potential countermeasures for deep space exploration missions. *Front Immunol.* 2018; 9:1437

Bruna Gonçalves et al. Vulvovaginal candidiasis: Epidemiology, microbiology and risk factors. *Crit Rev Microbiol* 2016 Nov;42(6):905-27.

Centers for Disease Control and Prevention. 2015 Sexually Transmitted Diseases Treatment Guidelines. Vulvovaginal Candidiasis. www.cdc.gov/stf/ta2015/candidiasis.htm

Vaginitis in Nonpregnant Patients: ACOG Practice Bulletin, Number 215. *Obstet Gynecol.* 2020 Jan;135(1):e1-e17. doi: 10.1097/AOG.0000000000003604. PMID: 31856123.

Denison HJ, Worswick J, Bond CM, Grimshaw JM, Mayhew A, Gnani Ramadoss S, Robertson C, Schaafsma ME, Watson MC. Oral versus intra-vaginal imidazole and triazole anti-fungal treatment of uncomplicated vulvovaginal candidiasis (thrush). *Cochrane Database Syst Rev.* 2020 Aug 24;8:CD002845. doi: 10.1002/14651858.CD002845.pub3. PMID: 32845024.

Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, Reboli AC, Schuster MG, Vazquez JA, Walsh TJ, Zaoutis TE, Sobel JD. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2016 Feb 15;62(4):e1-50. doi: 10.1093/cid/civ933. Epub 2015 Dec 16. PMID: 26679628; PMCID: PMC4725385.

Sobel JD, Kapernick PS, Zervos M, Reed BD, Hooton T, Soper D, Nyirjesy P, Heine MW, Willems J, Panzer H, Wittes H. Treatment of complicated Candida vaginitis: comparison of single and sequential doses of fluconazole. *Am J Obstet Gynecol.* 2001 Aug;185(2):363-9. doi: 10.1067/mob.2001.115116. PMID: 11518893.

Stein GE, Mummaw N. Placebo-controlled trial of itraconazole for treatment of acute vaginal candidiasis. *Antimicrob Agents Chemother.* 1993 Jan;37(1):89-92. doi: 10.1128/aac.37.1.89. PMID: 8381643; PMCID: PMC187610.

Bro F. Single-dose 500-mg clotrimazole vaginal tablets compared with placebo in the treatment of Candida vaginitis. *J Fam Pract.* 1990 Aug;31(2):148-52. PMID: 2199599.

Brand SR, Degenhardt TP, Person K, Sobel JD, Nyirjesy P, Schotzinger RJ, Tavakkol A. A phase 2, randomized, double-blind, placebo-controlled, dose-ranging study to evaluate the efficacy and safety of orally administered VT-1161 in the treatment of recurrent vulvovaginal candidiasis. *Am J Obstet Gynecol.* 2018 Jun;218(6):624.e1-624.e9. doi: 10.1016/j.ajog.2018.03.001. Epub 2018 Mar 11. PMID: 29534874.

Aballéa S, Guelfucci F, Wagner J, Khemiri A, Dietz JP, Sobel J, Toumi M. Subjective health status and health-related quality of life among women with Recurrent Vulvovaginal Candidosis (RVVC) in Europe and the USA. *Health Qual Life Outcomes.* 2013 Oct 11;11:169. doi: 10.1186/1477-7525-11-169. PMID: 24119427; PMCID: PMC3815627.

Sobel JD, Wiesenfeld HC, Martens M, Danna P, Hooton TM, Rompalo A, Sperling M, Livengood C 3rd, Horowitz B, Von Thron J, Edwards L, Panzer H, Chu TC. Maintenance fluconazole therapy for recurrent vulvovaginal candidiasis. *N Engl J Med.* 2004 Aug 26;351(9):876-83. doi: 10.1056/NEJMoa033114. PMID: 15329425.

ACRONYMS

ACRONYM	PHRASE
AAOMS	American Association of Oral and Maxillofacial Surgeons
AMA	American Medical Association
ARCL	All Remaining Conditions List
ARS	Acute Radiation Sickness

BHP	Behavioral Health and Performance
CAC	Coronary Artery Calcium
CHS	Crew Health and Safety
CL	Condition List
ClIFF	Clinical Finding Form
CMO	Crew Medical Officer
COMFORT	Clinical Outcome Metrics for Optimization of Robust Training
CP1	Clinical Phase 1
CP2	Clinical Phase 2
CP3	Clinical Phase 3
CRL	Clinical Resource Level
CRT	Capability Resource Table
CST	Clinical Science Team
DCS	Decompression Syndrome
DRM	Design Reference Mission
ED	Emergency Medicine Doctor
EL	Evidence Library
EMCL	Exploration Medical Condition List
EMT	Emergency Medical Technician
EVA	Extravehicular Activity
EXMC	Exploration Medical Capability
HRP	Human Research Program
ICD	International Classification of Disease
ICL 1.0	IMPACT 1.0 Medical Conditions List
ICU	Intensive Care Unit
IMCL	iMED Condition List
iMED	Integrated Medical Evidence Database
IMM	Integrated Medical Model
IMPACT-MD	Impact Medical Database
IP	Incidence Proportion
IR	Incidence Rate
ISS	International Space Station
IV	Intravenous
JSC	Johnson Space Center
LEO	Low-Earth orbit
LEVA	Lunar Extravehicular Activity
LOCL	Loss of Crew Life
LOM	Loss of Mission
LSAH	Lifetime Surveillance of Astronaut Health
LSO	Lunar Surface Operations
MCL	Master Condition List
MEVA	Medical Extravehicular Activity
NASA	National Aeronautics and Space Administration

N/A	Not Applicable
NP	Nurse Practitioner
OBGYN	Obstetrics and Gynecology
OR	Occurrence Rate
PA	Physician Assistant
PDQ	Pain Disability Questionnaire
PFCL	Proposed Future Conditions List
PPE	Personal Protective Equipment
PTRS	Project Technical Requirements Specification
PRL	Pharmaceutical Resource Level
QTL	Quality Time Lost
RCL	Removed Conditions List
REP	Rochester Epidemiology Study
RTDC	Removal to Definitive Care
SANS	Spaceflight-Associated Neuro-ocular Syndrome
SAS	Space Adaptation Syndrome
SEVA	Spaceflight Extravehicular Activity
SME	Subject Matter Expert
SoP	Standard Operating Procedure
SPE	Solar Particle Event
TBD	To Be Determined
TI	Task Impairment