

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Proctitis: a glance beyond inflammatory bowel diseases

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1747984> since 2020-10-22T12:55:02Z

Published version:

DOI:10.23736/S1121-421X.20.02670-7

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

Proctitis: a glance beyond inflammatory bowel diseases

Journal: Minerva Gastroenterologica e Dietologica

Paper code: Minerva Gastroenterol Dietol-2670

Submission date: January 10, 2020

Article type: Review Article

Files:

1. Manuscript

Version: 1

Description: Manuscript

File format: application/vnd.openxmlformats-officedocument.wordprocessingml.document

2. Figures 1

Version: 1

Description: Anal cryptitis caused by *N. gonorrhoeae*.

File format: application/pdf

3. Figures 2

Version: 1

Description: Linfo granuloma Venereum

File format: application/pdf

4. Figures 3

Version: 1

Description: Anal fissure and condilomata in syphilis.

File format: application/pdf

5. Figures 4

Version: 1

Description: Syphilitic proctitis.

File format: application/pdf

PROCTITIS:

A GLANCE BEYOND INFLAMMATORY BOWEL DISEASES

Stefano Rizza¹, Massimiliano Mistrangelo², Davide Giuseppe Ribaldone¹, Mario Morino², Marco Astegiano³, Giorgio Maria Saracco^{1,3}, Rinaldo Pellicano³

¹ Department of Medical Sciences, Unit of Gastroenterology, University of Turin, Turin, Italy

² Department of Surgical Sciences, University of Turin, Turin, Italy

³ Unit of Gastroenterology, Molinette Hospital, Turin, Italy

Corresponding author: Rinaldo Pellicano, MD, Unit of Gastroenterology, Molinette-SGAS Hospital,
Via Cavour 31, 10126 Turin, Italy. E-mail: rinaldo_pellican@hotmail.com

Abstract

Proctitis is an inflammation involving the anus and the distal part of the rectum, frequently diagnosed in the context of inflammatory bowel diseases (IBD). Nevertheless, when the standard therapy for IBD is ineffective, it becomes necessary for the clinician to review alternative etiologies, beginning from the broad chapter of infectious causes up to rare causes such as radiation, ischemia, diversion and traumatism. While it is possible to find infectious proctitides caused by pathogens generally inducing extensive colitis, the growing incidence of both sexually transmitted infections and isolated proctitis reported in the recent years require a lot of attention. The risk appears to be higher in individuals participating in anal intercourse, especially men having sex with men (MSM) or subjects who use sex toys and participate to sex parties, dark rooms and so on. The commonest implicated pathogens are *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, Herpes Simplex virus and *Treponema pallidum*. Herpes and Chlamydia infections mainly occur in HIV-positive MSM patients. Since symptoms and signs are common independently from etiology, performing a differential diagnosis based on clinical manifestations is complicated. Therefore, the diagnosis is supported by the combination of clinical history and physical examination and, secondly, by endoscopic, serologic and microbiologic findings. Particular emphasis should be given to simultaneous infections by multiple organisms. The involvement of experts in infectious diseases and in sexual health is crucial for the diagnostic and therapeutic management. The available therapies, empirically initiated or specific, in many cases are able to guarantee a good prognosis and to prevent relapses.

1 Proctitis is an inflammation confined to the distal 12-15 cm of the rectum. The most common type is
2 part of chronic inflammatory bowel diseases (IBD), conditions of unknown etiology including
3 Crohn's disease and ulcerative colitis¹ and presenting with rectal bleeding, diarrhea, tenesmus,
4 discharge, cramps and pain on the left side of the abdomen during the bowel movement. Proctitis as
5 part of IBD has a good response to topical and oral therapy with 5-aminosalicylic acid (5-ASA) and/or
6 prednisone, but it may also have a more aggressive course, especially in the context of Crohn's disease
7 of the ano-rectal region, so that a therapy with biological drugs or immune-modulators could be
8 required.^{2,3}

9 Despite these well-known aspects of IBD, it is necessary to emphasize how proctitis could be
10 ascribed to other causes, infectious and not. It is not rare, for clinicians, to deal with clinical cases
11 having an initial diagnose of IBD but over time not responder to standard therapy and, therefore,
12 requiring a good attitude to take into consideration other etiologies.

13
14 Considering infectious etiologies, this review highlights on the main pathogens acting in the
15 rectum as a prevalent or exclusive site. Among non-infectious causes, those due to radiation
16 ischemic, diversion and traumatic proctitis will be discussed.
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55

Table 1. Etiology of proctitis.

INFECTIOUS	NON INFECTIOUS
<p>1. Sexually transmitted pathogens (isolated proctitis)</p> <ul style="list-style-type: none"> • Neisseria gonorrhoeae • Chlamydia trachomatis • Herpes Simplex virus • Treponema pallidum • Haemophilus ducreyi • Cytomegalovirus <p>2. Sexually and non sexually transmitted pathogens (extended colitis)</p> <ul style="list-style-type: none"> • Campylobacter jejuni, Shigella, Entamoeba histolytica, Giardia lamblia and others. 	<ul style="list-style-type: none"> • Inflammatory bowel diseases • Radiation therapy • Ischaemia • Surgical diversion • Trauma (anal intercourse, fisting, masturbation)

Clinical and endoscopic findings in patients with proctitis

Regardless of the specific etiology, the clinical pictures and endoscopic characteristics are often superimposable in patients with proctitis, so further investigation are needed to trace the exact cause, as it will be explained below. Peculiar symptoms include: diarrhea (mild or severe), urgency, tenesmus, cramping pain during bowel movements, mild/severe rectal bleeding, hematochezia, involuntary spasms, pruritus, anorectal discharge (pus), anal warts and the feeling of incomplete emptying of the bowel. Endoscopic findings associated with acute injury include edema, erythema, friability and mucosal ulceration, while, in the chronic cases, distinctive findings are nodules, inflammatory polyps, abscesses, fistulae and strictures

Table 2. Common clinical manifestations and endoscopic features in patients with proctitis.

Clinical manifestations	Endoscopic features	
Diarrhea	Acute injuries: Edema Erythema Friability Ulceration	
Stool urgency		
Tenesmus		
Cramping pain		
Rectal bleeding		
Hematochezia		
Involuntary spasms		Chronic injuries: Nodules Abscesses Fistulae Strictures Inflammatory polyps
Anorectal discharge		
Pruritus		
Anal warts		
Feeling of incomplete emptying		

INFECTIOUS PROCTITIS

Sexually transmitted pathogens

In several cases it is essential to take into consideration pathogens which are specifically responsible of isolated proctitis. In the last years, indeed, there has been a rising incidence, especially in men have sex with men (MSM), of sexually transmitted infections (STIs), which can have proctitis as the main manifestation. This often occurs in healthy patients presenting with rectal symptoms, so that gastroenterologists or other specialists dedicated to proctology are required to have an adequate knowledge of the potential etiological agents in order to guide the proper approach and a successful therapeutic intervention.

It is unavoidable to collect a detailed and careful clinical history regarding recent traveling history and also risk behaviors, such as anal intercourse and number of sexual partners. The most frequent agents of infectious proctitides are represented by *Neisseria gonorrhoeae* (*N. gonorrhoeae*), *Chlamydia trachomatis* (*C. trachomatis*), Herpes Simplex virus (HSV) and *Treponema pallidum* (*T. pallidum*). In about a half of cases the infectious cause is not identifiable.⁴ Furthermore, should be considered the possibility to find coinfections with two or more pathogens (10% of all cases). Once an infectious proctitis is diagnosed, all STI sample testing, including human immunodeficiency virus

(HIV), are mandatory. In case of suspicious of a STI, patients must be submitted to a STI Clinic to assess all possible sexually transmitted co-infections.

Neisseria Gonorrhoeae

N. gonorrhoeae represents the most frequent bacterial cause of infectious proctitis and the second most prevalent STIs in the United States; however, the actual number of cases is likely much higher due to asymptomatic infections or self administered therapy.^{5,6} *N. gonorrhoeae* is a Gram-negative bacterium, facultative intracellular, obligate aerobe and able to move with twitching motility. It typically appears in pairs, diplococci, and resembles the shape of coffee beans. The way of transmission is by direct contact of mucosal surfaces, and so gonorrhea is commonest in individuals participating in receptive anal intercourse, typically in MSM,⁷⁻⁹ while in females it can be transmitted to the anal canal via a genital infection due to the proximity of the vagina, even in the absence of receptive anal intercourse.

The most typical symptoms, not allowing alone to achieve a differential diagnosis from other infectious causing proctitis, occur after 5-7 days of incubation and include tenesmus, rectal bleeding, pruritus, lower abdominal pain, diarrhea and anorectal purulent discharge. In a small part of cases this infection can be asymptomatic.¹⁰

Due to the lack of sensitivity and specificity of the clinical diagnosis it is necessary to proceed to a microbiological diagnosis. The test of choice is NAAT (Nucleic Acid Amplification Testing, eg. polymerase chain reaction or PCR) which is the most sensitive. If this method is unavailable it is possible to evaluate the presence of Gram-negative diplococci in Gram stain of mucosal biopsies or purulent discharge, with a sensitivity of 90–95%,¹¹ or with culture executed on Thayer-Martin agar, which prevents the overgrowth of other endogenous flora. Appropriate material for culture should be obtained using a swab through the anal canal into the distal rectum or under direct vision via proctoscopy.¹⁰ Culture has the advantage to assess antibiotic susceptibilities but the results are not usually available until 48 hours: its sensitivity is 72-95%, declining in asymptomatic patients to 65-85%.¹² When no specific diagnostic test is available, the diagnosis of gonorrhea remains presumptive.

Rectal gonorrhea should be treated with ceftriaxone 250 mg intramuscularly (i.m.) in a single dose, alongside oral azithromycin 1 g once. Alternatives oral antibiotics can be cefixime 400 mg once daily or doxycycline 100 mg once daily for 7-10 days.¹³ Gonorrhea is becoming increasingly resistant to cephalosporins and so it is better to verify eradication by repeating testing at the end of treatment in order to prevent further resistance development. Co-treatment with azithromycin and ceftriaxone may

1 improve eradication of the bacterium and allows to slow down the development of further
 2 cephalosporin resistance. Differential diagnosis must be performed with other STI but also with
 3 criptitis and anal abscess.
 4
 5
 6
 7
 8

9 **Fig. 1. Anal cryptitis caused by *N. gonorrhoeae*.**

10
 11
 12
 13 ***Chlamydia trachomatis***

14
 15
 16 *C. trachomatis* belongs to a group of obligate intracellular parasites of eukaryotic cells which can
 17 replicate only within a host cell. It has a life cycle consisting of two morphologically distinct forms:
 18 firstly *C. trachomatis* attaches to a new host cell as a small spore-like form, called elementary
 19 body, which penetrates the host cell, surrounded by a host vacuole, called inclusion. Within the
 20 inclusion, *C. trachomatis* turns into a bigger and more metabolically active form called reticulate
 21 body, which penetrates the host cell, surrounded by a host vacuole, called inclusion. Within the
 22 inclusion, *C. trachomatis* turns into a bigger and more metabolically active form called reticulate
 23 body.¹⁴
 24
 25

26 *C. trachomatis* serotypes L1, L2 and L3 are the responsible pathogens for “linfogranuloma
 27 venereum (LGV)” and especially serotype L2 has been reported to be mostly implicated,^{15,16} while
 28 serovars A–K are responsible for the non-LGV infections.
 29
 30
 31
 32
 33
 34
 35

36 **1. Linfogranuloma Venereum**

37
 38
 39 LGV, also known as “Durand–Nicolas–Favre disease” and “lymphogranuloma inguinale” is
 40 an uncommon sexually transmitted disease (STD). The ways of transmission are vaginal, oral or anal
 41 sex. In the last 20 years the incidence of LGV has shown a remarkable increase in Europe and North
 42 America but it still remains more common in the tropical and subtropical regions around the world.¹⁷
 43 The highest incidence of LGV occurs in the sexually active population between 15 and 40 years. LGV
 44 probably affects both sexes equally, although it is more commonly reported in MSM,¹⁸ in whom
 45 emerges as a leading cause of proctitis and proctocolitis.¹⁹ It is important to emphasize that LGV
 46 patients are frequently HIV-positive MSM with proctitis (85%) and approximately 50% carry other
 47 STIs.²⁰
 48
 49
 50
 51
 52
 53

54 LGV has different stages of infection: a primary stage characterized by the appearance of painless
 55 genital ulcer or papules at the site of inoculation, which, if unnoticed, can evolve in a secondary stage,

1 with the development of unilateral or bilateral tender inguinal and/or femoral lymphadenopathy (also
2 called “buboes”). In the secondary stage, symptoms of infection are local, such as tenesmus, anal
3 pain, mucous and bloody rectal discharge, but also systemic like body aches, headache, and fever. In
4 a quarter of the cases patients manifest only rectal symptoms without the development of a
5 lymphadenopathy.²¹

9 Longstanding LGV can lead to a late stage of the disease with the development of fibrosis, strictures
10 and fistulae of the ano-genital area, findings which can mimic histological, endoscopic and
11 radiological views of IBD or anal cancer.²²

14 Currently, a definitive diagnosis of LGV is based on serological tests as complement fixation titers >
15 1:64 or micro-immunofluorescence titers > 1:256.^{19, 23} However, the interpretation of these tests have
16 not been yet standardized or validated for rectal infections so that, in most circumstances, the
17 diagnosis of LGV is based on epidemiological and clinical findings with the supports of methods of
18 identification of *C. trachomatis* in genital, rectal and lymph node specimens like culture (although it
19 is difficult and requires a special medium, cycloheximide-treated McCoy or HeLa cells, and yields
20 are still only 30-50%), NAAT or direct immunofluorescence of rectal swabs or lymph node aspirate.¹⁷
21 Since this has implications for the duration of treatment, genotyping might be required as an
22 additional test to distinguish LGV from non-LGV. HIV testing should be a consideration in patients
23 with a STD.

30 Treatment, based on the clinical experience of more than 50 years, considers, as first line, a course
31 of doxycycline 100 mg twice daily for 3 weeks.^{13, 24-26} This duration is mandatory because these
32 infections are more invasive and harder to eradicate than uncomplicated genito-urinary tract
33 infections, which generally require only 1 week of treatment. A valid alternative is represented by
34 oral erythromycin 500 mg four times daily for 3 weeks, although its use can be limited by
35 gastrointestinal intolerance. This option is recommended for pregnant women,²⁷ while doxycycline
36 and other tetracyclines should be avoided in pregnancy due to the risk of disruption of bone and teeth
37 development. Despite the lack of clinical evidence supporting the routine use of azithromycin, it could
38 also be effective as additional option for treating LGV, given its efficacy against other genital tract
39 and systemic non-LGV *Chlamydia* infections. Fluoroquinolone antibiotics with demonstrated anti-
40 *Chlamydia* activity, such as levofloxacin, ofloxacin, moxifloxacin, may also be useful for treating
41 LGV, but no comparative treatment trial has been published. Treatment of asymptomatic rectal
42 *Chlamydia* infections is still controversial.²⁸ Asymptomatic sexual partners should also be treated
43 with a course of doxycycline, 100 mg twice daily for 1 week.

Fig. 2. Linfoagranuloma Venereum.**1. Non-LGV Chlamydial proctitis**

C. trachomatis serovars A–K are responsible for the non-LGV infections. Transmission is similar to that of *N. gonorrhoeae* and the infection may occur after anal receptive intercourse. Symptoms usually appear 7–10 days after infection and, in over 50% of cases registered in MSM, they are limited to the anal area, without urethral infection. They consist of anal pain, diarrhea, tenesmus, blood and mucous discharge and, sometimes, generalized symptoms as fever. The infection can also be asymptomatic in up to 50-70 % of patients.²⁹

Sigmoidoscopy can show findings difficult to distinguish from IBD: friability and erythema of the mucosa with ulcerations and a “cobblestone” appearance for the infiltration of underlying lymphoid follicles. Histological examination can reveal granulomas, another non-specific finding generating confusion with IBD.

Microbiological diagnosis is based on culture or NAAT on rectal swabs. NAAT has been estimated to have a sensitivity of about 90% and a specificity of about 99% in cervical swab and by urine specimen³⁰ but recent evidences indicates that it may give reliable results on rectal specimens. Moreover, it could be useful to analyze with Aptima combo 2 (Hologic Gen-Probe) that is a transcription mediated assay with the advantage of detecting both *N. gonorrhoeae* and *C. trachomatis*.³¹

Treatment of proctitis takes into consideration doxycycline 100 mg twice daily for 1 week. Alternatively, with comparable efficacy, it is possible to use azithromycin 1 g as a single dose³² although up to 20% of failure has been observed and therefore it is recommended to repeat NAAT after 6 weeks from the end of treatment. It is advisable to start the same therapy in sexual partners and to consider the high risk of a co-infection with *N. gonorrhoeae* and, therefore, starting empiric treatment against the latter in patients with non-LGV *C. trachomatis* infection.

Herpes simplex virus

Herpes simplex virus (HSV) is one of the most known and widespread infections in humans, involving about 60-95% of the adult population worldwide, more than 400 million persons.^{33,34} It is the most common viral coinfection among HIV positive patients, with up to 95% of MSM.

1 HSV infection has been involved in several diseases.^{35,36} Therefore, its constant epidemiologic
2 monitoring is considered of high relevance for public health in order to decrease the risk of neonatal
3 HSV infection and associated diseases.³⁷ Seroprevalence for HSV-1 is present in 93% of the adult
4 population but seroprevalence of HSV-2 is lower, confined to 5.5% in adults³⁸ and frequently
5 associated with other STDs. In US, according to the US Centers for Disease Control and Prevention,
6 it has been reported a seroprevalence, in the years 2005-2008, of 16.2%.¹⁶

7
8
9
10
11 The two types of HSV, HSV-1 and HSV-2, are both DNA viruses transmitted by direct contact with
12 infected secretions. HSV-1 is generally associated to infections manifesting around labial, oral, and
13 ocular areas, while HSV-2 is associated to lesions around ano-genital area. However, it is frequent to
14 have overlap infections and recent studies demonstrated an increase in ano-genital manifestations due
15 to HSV-1, primarily in developed countries and probably secondary to a greater diffusion of oro-
16 genital sex practices, especially in MSM.^{39,40} HSV is second only to *N. gonorrhoeae* as a sexually
17 transmitted cause of infectious proctitis in MSM.^{41,42} Moreover, in a recent review, it was postulated
18 a leading role for HSV in causing proctitis in HIV-infected patients.⁴³

19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
Once the virus has entered the host, HSV creates a persistent and latent infection: in fact, it remains
in a dormant state inside the neuronal ganglia, near the spinal cord, and periodically reactivates,
travelling through the nerve fibers back to the skin, causing symptoms again. Recurrence has been
reported to occur in about 60% of those infected with HSV-1 and in 90% of those with HSV-2.¹¹

56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173
174
175
176
177
178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207
208
209
210
211
212
213
214
215
216
217
218
219
220
221
222
223
224
225
226
227
228
229
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
246
247
248
249
250
251
252
253
254
255
256
257
258
259
260
261
262
263
264
265
266
267
268
269
270
271
272
273
274
275
276
277
278
279
280
281
282
283
284
285
286
287
288
289
290
291
292
293
294
295
296
297
298
299
300
301
302
303
304
305
306
307
308
309
310
311
312
313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454
455
456
457
458
459
460
461
462
463
464
465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521
522
523
524
525
526
527
528
529
530
531
532
533
534
535
536
537
538
539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565
566
567
568
569
570
571
572
573
574
575
576
577
578
579
580
581
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599
600
601
602
603
604
605
606
607
608
609
610
611
612
613
614
615
616
617
618
619
620
621
622
623
624
625
626
627
628
629
630
631
632
633
634
635
636
637
638
639
640
641
642
643
644
645
646
647
648
649
650
651
652
653
654
655
656
657
658
659
660
661
662
663
664
665
666
667
668
669
670
671
672
673
674
675
676
677
678
679
680
681
682
683
684
685
686
687
688
689
690
691
692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726
727
728
729
730
731
732
733
734
735
736
737
738
739
740
741
742
743
744
745
746
747
748
749
750
751
752
753
754
755
756
757
758
759
760
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777
778
779
780
781
782
783
784
785
786
787
788
789
790
791
792
793
794
795
796
797
798
799
800
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
825
826
827
828
829
830
831
832
833
834
835
836
837
838
839
840
841
842
843
844
845
846
847
848
849
850
851
852
853
854
855
856
857
858
859
860
861
862
863
864
865
866
867
868
869
870
871
872
873
874
875
876
877
878
879
880
881
882
883
884
885
886
887
888
889
890
891
892
893
894
895
896
897
898
899
900
901
902
903
904
905
906
907
908
909
910
911
912
913
914
915
916
917
918
919
920
921
922
923
924
925
926
927
928
929
930
931
932
933
934
935
936
937
938
939
940
941
942
943
944
945
946
947
948
949
950
951
952
953
954
955
956
957
958
959
960
961
962
963
964
965
966
967
968
969
970
971
972
973
974
975
976
977
978
979
980
981
982
983
984
985
986
987
988
989
990
991
992
993
994
995
996
997
998
999
1000
1001
1002
1003
1004
1005
1006
1007
1008
1009
1010
1011
1012
1013
1014
1015
1016
1017
1018
1019
1020
1021
1022
1023
1024
1025
1026
1027
1028
1029
1030
1031
1032
1033
1034
1035
1036
1037
1038
1039
1040
1041
1042
1043
1044
1045
1046
1047
1048
1049
1050
1051
1052
1053
1054
1055
1056
1057
1058
1059
1060
1061
1062
1063
1064
1065
1066
1067
1068
1069
1070
1071
1072
1073
1074
1075
1076
1077
1078
1079
1080
1081
1082
1083
1084
1085
1086
1087
1088
1089
1090
1091
1092
1093
1094
1095
1096
1097
1098
1099
1100
1101
1102
1103
1104
1105
1106
1107
1108
1109
1110
1111
1112
1113
1114
1115
1116
1117
1118
1119
1120
1121
1122
1123
1124
1125
1126
1127
1128
1129
1130
1131
1132
1133
1134
1135
1136
1137
1138
1139
1140
1141
1142
1143
1144
1145
1146
1147
1148
1149
1150
1151
1152
1153
1154
1155
1156
1157
1158
1159
1160
1161
1162
1163
1164
1165
1166
1167
1168
1169
1170
1171
1172
1173
1174
1175
1176
1177
1178
1179
1180
1181
1182
1183
1184
1185
1186
1187
1188
1189
1190
1191
1192
1193
1194
1195
1196
1197
1198
1199
1200
1201
1202
1203
1204
1205
1206
1207
1208
1209
1210
1211
1212
1213
1214
1215
1216
1217
1218
1219
1220
1221
1222
1223
1224
1225
1226
1227
1228
1229
1230
1231
1232
1233
1234
1235
1236
1237
1238
1239
1240
1241
1242
1243
1244
1245
1246
1247
1248
1249
1250
1251
1252
1253
1254
1255
1256
1257
1258
1259
1260
1261
1262
1263
1264
1265
1266
1267
1268
1269
1270
1271
1272
1273
1274
1275
1276
1277
1278
1279
1280
1281
1282
1283
1284
1285
1286
1287
1288
1289
1290
1291
1292
1293
1294
1295
1296
1297
1298
1299
1300
1301
1302
1303
1304
1305
1306
1307
1308
1309
1310
1311
1312
1313
1314
1315
1316
1317
1318
1319
1320
1321
1322
1323
1324
1325
1326
1327
1328
1329
1330
1331
1332
1333
1334
1335
1336
1337
1338
1339
1340
1341
1342
1343
1344
1345
1346
1347
1348
1349
1350
1351
1352
1353
1354
1355
1356
1357
1358
1359
1360
1361
1362
1363
1364
1365
1366
1367
1368
1369
1370
1371
1372
1373
1374
1375
1376
1377
1378
1379
1380
1381
1382
1383
1384
1385
1386
1387
1388
1389
1390
1391
1392
1393
1394
1395
1396
1397
1398
1399
1400
1401
1402
1403
1404
1405
1406
1407
1408
1409
1410
1411
1412
1413
1414
1415
1416
1417
1418
1419
1420
1421
1422
1423
1424
1425
1426
1427
1428
1429
1430
1431
1432
1433
1434
1435
1436
1437
1438
1439
1440
1441
1442
1443
1444
1445
1446
1447
1448
1449
1450
1451
1452
1453
1454
1455
1456
1457
1458
1459
1460
1461
1462
1463
1464
1465
1466
1467
1468
1469
1470
1471
1472
1473
1474
1475
1476
1477
1478
1479
1480
1481
1482
1483
1484
1485
1486
1487
1488
1489
1490
1491
1492
1493
1494
1495
1496
1497
1498
1499
1500
1501
1502
1503
1504
1505
1506
1507
1508
1509
1510
1511
1512
1513
1514
1515
1516
1517
1518
1519
1520
1521
1522
1523
1524
1525
1526
1527
1528
1529
1530
1531
1532
1533
1534
1535
1536
1537
1538
1539
1540
1541
1542
1543
1544
1545
1546
1547
1548
1549
1550
1551
1552
1553
1554
1555
1556
1557
1558
1559
1560
1561
1562
1563
1564
1565
1566
1567
1568
1569
1570
1571
1572
1573
1574
1575
1576
1577
1578
1579
1580
1581
1582
1583
1584
1585
1586
1587
1588
1589
1590
1591
1592
1593
1594
1595
1596
1597
1598
1599
1600
1601
1602
1603
1604
1605
1606
1607
1608
1609
1610
1611
1612
1613
1614
1615
1616
1617
1618
1619
1620
1621
1622
1623
1624
1625
1626
1627
1628
1629
1630
1631
1632
1633
1634
1635
1636
1637
1638
1639
1640
1641
1642
1643
1644
1645
1646
1647
1648
1649
1650
1651
1652
1653
1654
1655
1656
1657
1658
1659
1660
1661
1662
1663
1664
1665
1666
1667
1668
1669
1670
1671
1672
1673
1674
1675
1676
1677
1678
1679
1680
1681
1682
1683
1684
1685
1686
1687
1688
1689
1690
1691
1692
1693
1694
1695
1696
1697
1698
1699
1700
1701
1702
1703
1704
1705
1706
1707
1708
1709
1710
1711
1712
1713
1714
1715
1716
1717
1718
1719
1720
1721
1722
1723
1724
1725
1726
1727
1728
1729
1730
1731
1732
1733
1734
1735
1736
1737
1738
1739
1740
1741
1742
1743
1744
1745
1746
1747
1748
1749
1750
1751
1752
1753
1754
1755
1756
1757
1758
1759
1760
1761
1762
1763
1764
1765
1766
1767
1768
1769
1770
1771
1772
1773
1774
1775
1776
1777
1778
1779
1780
1781
1782
1783
1784
1785
1786
1787
1788
1789
1790
1791
1792
1793
1794
1795
1796
1797
1798
1799
1800
1801
1802
1803
1804
1805
1806
1807
1808
1809
1810
1811
1812
1813
1814
1815
1816
1817
1818
1819
1820
1821
1822
1823
1824
1825
1826
1827
1828
1829
1830
1831
1832
1833
1834
1835
1836
1837
1838
1839
1840
1841
1842
1843
1844
1845
1846
1847
1848
1849
1850
1851
1852
1853
1854
1855
1856
1857
1858
1859
1860
1861
1862
1863
1864
1865
1866
1867
1868
1869
1870
1871
1872
1873
1874
1875
1876
1877
1878
1879
1880
1881
1882
1883
1884
1885
1886
1887
1888
1889
1890
1891
1892
1893
1894
1895
1896
1897
1898
1899
1900
1901
1902
1903
1904
1905
1906
1907
1908
1909
1910
1911
1912
1913
1914
1915
1916
1917
1918
1919
1920
1921
1922
1923
1924
1925
1926
1927
1928
1929
1930
1931
1932
1933
1934
1935
1936
1937
1938
1939
1940
1941
1942
1943
1944
1945
1946
1947
1948
1949
1950
1951
1952
1953
1954
1955
1956
1957
1958
1959
1960
1961
1962
1963
1964
1965
1966
1967
1968
1969
1970
1971
1972
1973
1974
1975
1976
1977
1978
1979
1980
1981
1982
1983
1984
1985
1986
1987
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
2022
2023
2024
2025
2026
2027
2028
2029
2030
2031
2032
2033
2034
2035
2036
2037
2038
2039
2040
2041
2042
2043
2044
2045
2046
2047
2048
2049
2050
2051
2052
2053
2054
2055
2056
2057
2058
2059
2060
2061
2062
2063
2064
2065
2066
2067
2068
2069
2070
2071
2072
2073
2074
2075
2076
2077
2078
2079
2080
2081
2082
2083
2084
2085
2086
2087
2088
2089
2090
2091
2092
2093
2094
2095
2096
2097
2098
2099
2100
2101
2102
2103
2104
2105
2106
2107
2108
2109
2110
2111
2112
2113
2114
2115
2116
2117
2118
2119
2120
2121
2122
2123
2124
2125
2126
2127
2128
2129
2130
2131
2132
2133
2134
2135
2136
2137
2138
2139
2140
2141
2142
2143
2144
2145

1 because these findings are reported in only about 30% of the patients affected at the time of the
 2 diagnosis.⁴⁰

3
 4 Currently, PCR assays for HSV-DNA, viral cultures and direct fluorescent antibody (DFA) are
 5 commonly used for the diagnosis, with immunohistochemistry demonstrating to be one of the best
 6 tool among them. In fact, DFA is highly sensitive and specific and permits to distinguish between
 7 numerous viruses using specific monoclonal antibodies.⁴⁴ In alternative, it is possible to use serology,
 8 with assays based on the HSV-specific glycoprotein G1 (HSV-1) and glycoprotein G2 (HSV-2) and
 9 can reliably distinguish HSV-1 from HSV-2.⁴⁶ An historical test is the Tzanck smear of samples
 10 obtained by scraping of an ulcer base: it would permit diagnosis revealing multinucleated giant cells
 11 or intranuclear inclusion bodies. However, this test has a limited sensitivity and specificity and has
 12 been largely replaced by DFA. Treatment for the first clinical episode is based on a cycle of 7–10
 13 days with one of the following oral antiviral therapies: acyclovir 400 mg 3 times daily, acyclovir 200
 14 mg 5 times daily, valacyclovir 500 mg twice daily, famciclovir 250 mg 3 times daily.⁴⁷ Pain control
 15 with local anesthetics and warm soaks could be useful as a supportive care. In immunosuppressed
 16 individuals or in case of frequent/severe recurrences it should be considered a long-term daily
 17 suppressive antiviral therapy to reduce the risk of further episodes of HSV proctitis.
 18
 19
 20
 21
 22
 23
 24
 25
 26
 27
 28
 29

30 ***Treponema pallidum***

31
 32 Belonging to the spirochete group, *T. pallidum* is a pathogen causing an infectious disease called
 33 “syphilis”. Approximately 17.7 million individuals, 15–49 years of age, globally have contracted
 34 syphilis in 2012, with an estimated 5.6 million new cases every year.^{48,49} The estimated prevalence
 35 and incidence of syphilis varies by country, with the highest prevalence in Africa. In general, the
 36 incidence of syphilis both in men and women has risen in recent years, especially in MSM, and
 37 syphilis remains a continuing public health challenge globally.⁵⁰

38
 39 *T. pallidum* is an obligate human pathogen very invasive and immunoevasive,^{51,52} able to induce
 40 local inflammatory response by replicating within the tissue and so causing clinical manifestations.
 41 Transmission occurs during sexual contact with an actively infected partner and it has been reported
 42 that exudate containing as few as 10 organisms can transmit the infection and induce the disease.⁵³

43
 44 The typical course of the disease is divided into primary, secondary, latent and tertiary stage over a
 45 period of ≥ 10 years. Primary syphilis presents on average within 3 weeks of exposure (or better within
 46 30–90 days), with a painless solitary ulcer (chancre), indurated and with discharge serous fluid, and a
 47 regional lymphadenopathy that may involve genitalia, rectum or mouth. Symptoms like bleeding,
 48
 49
 50
 51
 52
 53
 54
 55

1 significant pain and itching can occur.¹⁶ A painless anal fissure is typical of anal infection. This could
2 develop a proctitis. If unidentified, primary disease can evolve to secondary syphilis in 4–10 weeks
3 (but up to 2 years) later, in which bacteremia leads to multisystem disease that may include a lot of
4 clinical manifestations: maculopapular or pustular rash, peripheral neuropathy, hepatitis, periostitis,
5 glomerulonephritis, meningitis, anterior uveitis and interstitial keratitis. The typical rash may form
6 flat, broad, whitish, wart-like lesions on mucous membranes, covered in a greyish exudate, known as
7 condylomata lata, papules commonly perianal or genital in anatomical origin. Condylomata lata are
8 highly infectious. Tertiary syphilis may occur approximately 3-15 years after the initial infection, in
9 one third of people who did not receive treatment, and may be distinguished into three different forms:
10 gummatous syphilis (gummae are granulomatous nodules or ulcers of the gastrointestinal tract or
11 buttocks), late neurosyphilis (dementia, paresis, seizures), and cardiovascular syphilis (aortitis or
12 aneurisms).⁵⁴ Up to 2 years after acquisition, early infection without any manifestations of the first
13 two stages is defined as “early latent syphilis”. Primary, secondary and early latent stages of syphilis
14 are infectious, whereas the later stages of tertiary syphilis are largely non-infectious. Therefore, the
15 biggest efforts should focus on diagnosing and treating primary, secondary and early latent syphilis
16 so as to avoid later complications.

17 A diagnosis of syphilis cannot be made by culture but by using dark ground microscopy and PCR
18 of affected tissues as ulcer exudate, condylomata lata exudate or rectal biopsies. Blood tests are
19 divided into non-treponemal and treponemal tests.⁵⁵ Non-treponemal serologic tests are most
20 commonly used to establish a diagnosis: venereal disease research laboratory (VDRL) and rapid
21 plasma reagin (RPR) tests are used to diagnose an initial infection and to monitor response to therapy.
22 False positives on the non-treponemal tests can occur with some viral infections, such
23 as varicella and measles, but also with lymphoma, tuberculosis, malaria, pregnancy and some other
24 conditions. Therefore, treponemal tests, such as treponemal pallidum particle agglutination (TPHA)
25 or fluorescent treponemal antibody absorption (FTA-Abs) test, should be performed because are
26 confirmatory and are required to identify false-positive VDRL or RPR tests. Antibodies may be
27 undetectable within serum before 12 weeks from infection and so repeat blood sample 3 months after
28 the last sexual risk may be necessary. As 40–60% of contactable sexual partners may be infected,
29 contact tracing and screening are required.

30 Treatment of primary and secondary syphilis consists, as first line, of a single i.m. penicillin G
31 benzathine 2.4 million units. This is a form of penicillin slowly hydrolysed to benzylpenicillin and it
32 permits to improve bioavailability and better monitor. Alternatively, i.m. procaine penicillin 600.000
33 units daily for 10–14 days can be given. In case of penicillin allergy, an alternative therapy is a 2-
34 week regimen with doxycycline 100 mg twice daily. Recurrent syphilis infections are not rare and the
35

1 risk to develop it is substantially increased in case of HIV co-infection: 6.7% of MSM with an initial
 2 diagnosis of rectal syphilis experienced a recurrence within one year.⁵⁶
 3
 4
 5

6 **Fig. 3. Anal fissure and condilomata in syphilis.**
 7

8
 9 **Fig. 4. Syphilitic proctitis.**
 10

11
 12 ***Haemophilus ducreyi***
 13

14
 15 *Haemophilus ducreyi* (*H. ducreyi*) is a Gram-negative bacterium known as the causative agent of
 16 an ulcerating sexually transmitted disease called “chancroid”. Although this infection is rare and its
 17 incidence seems to be in decline, the true incidence of chancroid remains uncertain and
 18 underdiagnosed because few laboratories are able to correctly approach a microbiologic diagnosis.⁵⁷
 19 *H. ducreyi* is transmitted by sexual contact through breaks in the skin during intercourse. Hours to
 20 days after exposure, infection manifests as tender papules with erythema that eventually goes into a
 21 pustule then an ulceration. The ulcers are typically painful and frequently multiple, but these features
 22 are not helpful to distinguish them from ulcers caused by other STDs. The most common site is the
 23 genitals, but perianal and anorectal region can be involved with abscesses and ulceration. In 50% of
 24 chancroid infections in men it is reported a painful unilateral inguinal adenopathy, which is rare in
 25 women.⁵⁸
 26
 27
 28
 29
 30
 31
 32

33 Diagnosis is based on culture on selective medium but PCR testing is more sensitive than culture
 34 for detecting *H. ducreyi*, although it is not widely available. Gram’s stain of material from the base
 35 of suspicious ulcers shows Gram-negative rods in small groups, with a sensitivity of 40-60%.^{58,59}
 36 Treatment is with one of the following alternatives: oral azithromycin 1 g in single dose, ceftriaxone
 37 250 mg, i.m., in single dose,⁵⁰ oral ciprofloxacin 100 mg twice daily for 3 days or oral erythromycin
 38 base 500 mg twice daily for 3 days.
 39
 40
 41
 42
 43
 44
 45

46 **Cytomegalovirus**
 47

48
 49 Although most of the current guidelines on diagnosis and treatment of STIs do not consider
 50 extensively this etiology and although it is mostly considered in the context of proctocolitis, in HIV-
 51 immunocompromised patients, some cases of Cytomegalovirus (CMV) isolated proctitis have been
 52 reported. CMV infection in MSM is characterized by prolonged excretion of CMV in semen, and is
 53
 54
 55

1 associated with unprotected anal intercourse: the triad of mononucleosis like illness with rectal
2 bleeding shortly after unprotected anal intercourse are considered as pathognomonic characteristics
3 for sexually transmitted CMV proctitis. Peculiar findings on sigmoidoscopy are rectal mucositis and
4 ulceration. CMV serology and biopsy (including CMV histochemistry) confirm the diagnosis.
5 Suggestive histopathological findings include: enlarged cells with intracytoplasmic and intranuclear
6 inclusion bodies.⁶¹ The role of antiviral therapy in primary CMV proctitis has not yet been defined as
7 very often it spontaneously regresses. However, in patients at risk such as HIV-infected or
8 immunocompromised, the therapy is necessary and is based on the use of ganciclovir and
9 valganciclovir. CMV should be considered in any case of unexplained proctitis.

18 Sexually and non-sexually transmitted pathogens

21 *Campylobacter jejuni*

25 Considered as one of the most common causes of human gastroenteritis in the world,
26 *Campylobacter jejuni* is a Gram-negative bacterium, appearing as curved or comma-shaped rods, able
27 to move via flagella and typically surviving in environments with a low amount of oxygen. Food
28 poisoning caused by its infection can be severely debilitating. In 2017, it has been described an
29 increased incidence of culture-confirmed *Campylobacter* infections, till to 19.2 per 100,000 persons,
30 the highest of all pathogens studied.⁶² Although in healthy patients the ingestion of contaminated food
31 (raw or under-cooked poultry, raw dairy products) or water is the main way of transmission, some
32 alternatives could exist. In fact, sexual transmission by practices promoting fecal-oral contact has
33 been reported: *Campylobacter species* have been isolated from stool and rectal cultures obtained from
34 homosexual individuals presenting with proctocolitis.^{58,62} The infection is characterized by an
35 inflammatory, sometimes bloody diarrhea or dysentery, associated to cramps, fever, myalgias, chills
36 and abdominal pain, which appear 1-3 days after the infection.⁶³ The clinical manifestations can be
37 confused with appendicitis or IBD. In HIV-positive patients it is frequent to observe a more severe
38 course with bacteremia, due to its capability to spread in the blood, or with extraintestinal
39 manifestations such as cellulitis and pneumonia.⁶⁴

49 Usually, endoscopy offers non-specific findings of proctocolitis and is not useful for differential
50 diagnosis. Stool culture is the most reliable tool for the diagnosis.

52 Treatment is necessary, especially in immunocompromised patients, and is based on azithromycin
53 500 mg daily for 3 days or erythromycin 500 mg four times a day for 7 days. In immunocompetent
54
55

1 individuals, the infection is self-limiting and, in most cases, symptomatic treatment by liquid and
2 electrolyte replacement is sufficient.
3
4

5 ***Shigella***

6
7
8

9 In the genus *Shigella* are included Gram-negative pathogenic enterobacteria known to be the cause
10 of bacillary dysentery (shigellosis). Shigellosis is due to the capacity to invade and colonize the
11 colonic mucosa, particularly the rectosigmoid portion of the colon, leading to its disruption. The most
12 frequent species are *Shigella Flexneri* (*S. Flexneri*) e *Shigella Sonnei* (*S. sonnei*). The transmission
13 of *Shigella* can occur via contaminated food and water and via direct person-to-person spread, but in
14 1974 its sexual transmission was first reported.⁶⁵ Patients with shigellosis typically present with high
15 fever, abdominal cramps, vomiting and bloody, mucoid or watery diarrhea. *S. sonnei* is usually
16 associated to a mild course, in general watery diarrhea, *S. flexneri* commonly causes bloody
17 diarrhea.⁶⁶
18
19
20
21
22

23 Sigmoidoscopy shows a proctitis but inflammation may be extended proximally to the rectum.
24 Diagnosis relies on the presence of erythrocytes, polymorphonuclear neutrophils (PMNs), and mucus
25 in patient stools, which are considered as diagnostic elements. Nowadays, in most laboratories,
26 automated PCR on stool is a commonly used test. In an immunocompetent host, the course of disease
27 is generally self-limited, lasting no more than one week when left untreated.
28
29
30
31

32 Treatment consists of supportive care and symptomatic drugs (antimotility agents are
33 contraindicated). Antibiotics can be used in immunocompromised patients and should be selected on
34 the basis of regional antibiotic susceptibility profiles due to the high rate of antibiotic resistance.
35
36
37

38 ***Entamoeba histolytica***

39
40

41 *Entamoeba histolytica* (*E. histolytica*) is a protozoan that causes non-febrile intestinal infection,
42 called amebiasis. Although it can occur worldwide, the prevalence is disproportionately higher in low
43 and middle-income countries because of poor socioeconomic conditions and sanitation levels, while
44 in developed countries, amebiasis is generally seen in migrants or travelers coming from endemic
45 areas (Mexico, Latin America and Asia) after a long stay (it is not a common cause of travelers'
46 diarrhea). With over 100.000 deaths per year, it is the third most deadly parasitic infection.⁶⁷ The most
47 known way of transmission is the fecal-oral route but it can also be transmitted sexually, both in
48 homosexual and heterosexual individuals.⁶⁸ Risk factors for contracting this infection have been
49 mostly identified in MSM, in case of HIV coinfection or oro-anal sexual practices.⁶⁹ In 90% of cases,
50
51
52
53
54
55

1 *E. histolytica* infection is asymptomatic, but there are several factors which may determine the
2 outcome such as genetic susceptibility, young age, corticosteroid or immunosuppressive treatments,
3 malnutrition, malignancy and alcoholism.⁷⁰ Amebiasis generally presents a subacute onset, symptoms
4 appear after 1-3 weeks from ingestion of cysts, when trophozoites damage the mucosa causing an
5 inflammatory infiltrate and proctocolitis. Diarrhea can range from mild to severe, with bloody stool,
6 abdominal pain and weight loss, configuring a dysentery syndrome. In some case the course can be
7 deleterious with a fulminant amebic colitis: bowel necrosis leads to perforation and peritonitis,
8 conditions associated to a mortality rate higher than 40%.⁷¹

9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
Diagnosis is well established by the combination of antigen testing (using monoclonal antibodies to bind specific epitopes in stool and serum) or serology together with identification of trophozoites or cysts on microscopic examination of stool specimens. Antibodies are detectable within 5-7 days of acute infection and may be result positive for years. Also molecular methods may be helpful and PCR techniques can detect *E. histolytica* in stool specimens. Endoscopy shows ulcers, erosions, exudates, edematous cecal mucosa or the common findings which are “flask-like” ulcerations or erosions typically present in the cecum, followed by the rectum and the other segments of the colon.⁷² However, in the acute phase, colonoscopy should be avoided because of the risk of perforation due to the instillation of air necessary to expand and visualize the colon.

Treatment is based on nitroimidazole drugs as metronidazole 500 to 750 mg by mouth three times daily for 7-10 days or tinidazole 2 g once a day for 3-5 days.⁷³ After a 10-day course of a nitroimidazole, paromycin (or, in second line, diiodohydroxyquin and diloxanide furoate) should be administered to assure that the luminal parasites are deleted and to prevent relapse.⁷⁴ Promising results are coming from the investigation of vaccines in rodent and non-human primate models.

Giardia Lamblia

Giardia Lamblia (*G. Lamblia*) is a flagellated protozoan parasite, etiological agent of giardiasis. More than 200 million cases of giardiasis are annually diagnosed worldwide, with a higher prevalence in developing countries. This parasite is transmitted via fecal-oral route (water is a major source of transmission) through direct or indirect ingestion of infectious cysts but, sexual transmission has been reported in MSM.⁷⁵ Parasites penetrates the human organism adhering and replicating on the brush border of the duodenum and jejunum and feeding on the mucous secretions of the intestine. Clinical manifestations of infection have a wide spectrum, from the absence of symptoms to diarrhea, malaise, steatorrhea, abdominal cramps, bloating, flatulence, and nausea. Although rare, in some cases proctitis may be clinically relevant.

Direct stool microscopy may reveal trophozoites, especially in liquid feces, while oocysts may be seen in either liquid or solid feces. Limitations of stool microscopy include intermittent excretion of *Giardia* cysts (necessitating up to three stool exams). Antigen detection assays and nucleic acid detection assays have been also developed for detecting *Giardia*. In some cases, duodenal biopsy or aspirate may be required to confirm the diagnosis. First line for treatment of giardiasis is based on metronidazole 400 mg three times daily for 5-10 days. Other effective treatments include tinidazole and nitazoxanide. Alternatives to these medications include paromomycin, mebendazole, albendazole and furazolidone.⁷⁶

NON INFECTIOUS PROCTITIS

Radiation therapy

Radiation-associated proctitis is a complication after exposure to x-rays or other ionizing radiation used in the context of radiation therapy for pelvic tumors such as prostate, cervix, uterus, testicles, bladder, rectum, anal or for lymphoproliferative malignancies. Due to its topographic and fixed position in the pelvis, the rectum is highly exposed to damage from radiation therapy. This inflammation can be distinguished in two types, acute or chronic. Acute form, manifesting with the typical proctitis symptoms and endoscopic features, usually occurs within the first 3 months of radiation therapy and is often self-limiting. Chronic proctitis, generally occurs in patients who had suffered from severe acute proctitis, with the median interval of onset ranging between 8 and 13 months.⁷⁷ Sometimes it appears as chronic from the beginning, after 3 months of therapy completion. Among the risk factors for its development are included: diabetes mellitus, IBD, smoking, peripheral vascular disease, chemotherapy administration.⁷⁸ Typical manifestations are rectal bleeding, tenesmus and symptoms of intestinal obstruction.

Mucosal friability, strictures, fistulas, spontaneous hemorrhage, teleangectasias and ulcerations are distinctive endoscopic features that explain the most reported symptoms. Biopsies, directed at the lateral and posterior walls to avoid the irradiated areas because of the risk of fistula formation, may be helpful in the differential diagnosis and show the presence of eosinophilic crypt abscesses, endothelial arteriole swelling and loss of mucosal cells in the acute form^{79,80} whereas arteriolar endarteritis, fibrosis of the lamina propria, crypt distortion, and Paneth cell metaplasia characterize the chronic form.

In absence of large clinical trials, the experiences on treatment are very limited. Three main therapeutic strategies can be considered: medical, endoscopic and surgical. The first line is the

1 medical therapy which includes: enemas containing drugs with antiinflammatory and antioxidant
2 action and beneficial properties for epithelial microvascular injury (5-aminosalicylic acid, sucralfate,
3 short-chain fatty acid, pentoxifylline),^{81,82} oral antibiotics (metronidazole), topical applications and
4 oxygen therapy. Endoscopic therapy includes dilation, laser, argon plasma coagulation (APC),
5 cryotherapy, radiofrequency ablation, and mesenchymal stem cell therapy.⁸³

6
7
8
9
10 In a recent review focused on agents studied for the prevention and treatment of gastrointestinal
11 mucositis (GIM), the evidence continues to support use of probiotics containing *Lactobacillus spp.*
12 for prevention of chemoradiotherapy and radiotherapy-induced diarrhea in patients with pelvic
13 malignancy, and hyperbaric oxygen therapy to treat radiation-induced proctitis. Additional well-
14 designed research is encouraged to enable a decision regarding palifermin, glutamine, sodium
15 butyrate, and dietary interventions, for the prevention or treatment of GIM.⁸⁴

16
17
18
19
20 Formaldehyde administration should be attempted before surgical therapy. When surgical therapy is
21 required, a descending or transverse colostomy must be carried out. Advanced methods such as
22 intraperitoneal injections of formalin or novel methods of cold therapy and radiofrequency ablation
23 (RFA) provide a wider remedial field.

24
25
26
27 Surgical therapy contemplates diversion of the fecal stream via a colostomy or an ileostomy, local
28 repair with reconstruction and mobilization of an advanced flap in cases of fistulas and, for more
29 severe or refractory cases, proctectomy.^{85,86}

30
31
32
33 Since aggressive treatments like coloanal anastomosis and colorectal surgery are correlated with
34 remarkable mortality and morbidity, they must be considered as the final course of remedial treatment.

35
36
37 Radiation injury can be limited through two main strategies: reducing the dose delivered to adjacent
38 structures using, for example, intensity-modulated, volumetric-modulated and 3-dimensional
39 conformal radiation therapy⁸⁷ or brachytherapy; reducing the radiosensitivity of the organs at risk,
40 using some medications such as amifostine, a prodrug that scavenges oxygen free radicals, used
41 intravenously in some randomized trials.⁸⁸

42 43 44 45 46 47 **Surgical diversion**

48
49
50 First described as a new entity in 1981 by Glotzer et al.,⁸⁸ diversion proctitis is an inflammatory
51 disease involving the excluded rectum, which is diverted from the fecal stream by surgical
52 interventions, and is part of the broader spectrum defined as radiation colitis. Its incidence as well as
53 its pathogenesis are still unknown. Different pathogenetic mechanisms have been proposed but data
54
55

1 supporting them are very limited. Among the hypothesized models are included: bacterial
2 overgrowth, presence of harmful bacteria, toxins or disturbance in the symbiotic relationship between
3 luminal bacteria and the mucosal layer and nutritional deficiency.⁹⁰ Usually, the onset is between 3
4 and 36 months after fecal diversion.
5

6
7 Endoscopic features are various: erythema, mucous plugs, granularity, friability, blurring of
8 vascular pattern, aphthous ulcers, spontaneous bleeding, nodularity, edema, inflammatory polyps, and
9 strictures. No pathognomonic signs have been identified up to now and biopsies can reveal lymphoid
10 follicular hyperplasia, which is one of the commonest finding, crypt distortion, regenerative
11 hyperplasia, Paneth cell metaplasia, thickening of muscularis mucosa, diffuse active mucosal
12 inflammation with crypt abscess, ulceration, vacuolar and epithelial degeneration. In most cases,
13 inflammatory changes and symptoms related are resolved after re-establishment of gastrointestinal
14 continuity.⁹⁰
15
16
17
18
19

20 21 22 **Ischemic damage**

23
24
25 Ischemic involvement of the rectum takes place in 5% of the cases of ischemic colitis. Indeed, in
26 75% damage is located in colon and, frequently, in the splenic flexure, because the rectum has a wide
27 arterial supply network from the inferior mesenteric, internal iliac, internal pudendal arteries and the
28 marginal artery.⁹² Elderly patients with significant atherosclerotic disease compromising blood flow
29 and cardiac risk factors are the subjects most frequently exposed to developing ischemic proctitis.⁹³
30 Conditions at risk include those implying the possibility to develop a sudden acute compromise in
31 blood flow: previous vascular intervention, aorto-iliac surgery, radiotherapy and hypotensive shock.⁹⁴
32 Spontaneous ischemic proctitis is a very rare event, limited to less than 2% of all cases of ischemic
33 colitis. Severity can be various: in transient ischemia damages are generally reversible and limited to
34 the superficial mucosal layers, consisting of edema and hemorrhage, but, in prolonged ischemia,
35 mucosal necrosis with ulceration and/or perforation may lead to fatal consequences.
36
37
38
39
40
41
42

43 Clinical presentation is not different from the other etiologies and is often misleading. In support to
44 the diagnosis computed tomography (CT) scan can give a contribution of suspicion, but colonoscopy,
45 performed within 48 h from the beginning of the symptoms, remains the more reliable tool, allowing,
46 also, to do biopsies which are generally useful in confirming diagnosis.⁹⁵
47
48
49

50 In the early stages of treatment, the most important aspect is monitoring vital parameters and
51 restoration of the patient's blood volume in order to maintain or improve the cardiac output. When
52 ischemia is transient this management is generally enough to induce recovery and avoid worsening.
53 Careful clinical observation is of paramount importance to catch early signs of sepsis or perforation.
54
55

1 Broad-spectrum antibiotics can be necessary in this context. The most severe cases, inducing
2 perforation, may require surgical interventions: abdominal perineal resection or, when the lower
3 rectum is spared, a low anterior resection, represents the commonest adopted technique.⁹⁶
4
5
6
7

8 **Traumatisms**

9
10 Chronic traumatism linked to prolonged and repetitive practice of masturbation with anal objects
11 can lead to the appearance of ano-rectal lesions similar to those described for other forms of proctitis.
12 In addition to the essential anamnestic information, some features help to depose mainly for a
13 traumatic form: tears, abrasions, hematoma, discoloration with tenderness, fissures. Similar speech
14 can be made for injuries observed after anal intercourse, fisting, which could also cause rectal
15 perforation or a lesion of anal sphincters, and sexual abuse.⁹⁷
16
17
18
19
20
21

22 **Conclusions**

23
24
25 Nowadays, it is increasingly more common in a gastroenterological setting, to come across of cases
26 of proctitis whose nature is not ascribable to IBD. The clinical and endoscopic characteristics, on
27 their own, configure clinical pictures that are difficult to distinguish from one another. When it is
28 necessary to exclude all other forms of proctitis for which the anamnestic data plays a fundamental
29 role, specifically referring to radiation, diversion, ischemic and traumatic form, the clinician is faced
30 with the great chapter of the proctitis of infectious origin. As a matter of fact, in the last years, it has
31 been registered a growing incidence of infectious proctitides, particularly in MSM, within the broader
32 context of STIs. Although the clinical presentation may be undistinguishable from an ulcerative colitis
33 or a Crohn's disease involving ano-rectal region, the response to standard treatments adopted for IBD
34 is inadequate. In order to avoid this kind of mistakes, clinicians are required to proceed in a reasoned
35 manner, that is to say starting with the collection of an in-depth medical history aimed at assessing
36 life-style, recent traveling and sexual habits, including anal intercourse. In addition, it is essential to
37 perform a focused physical examination which can help to highlight salient traits attributable to a
38 particular etiology. Based on these findings, it is possible to start an empirical treatment with
39 antibiotics or antivirals. Further diagnostic tools may contribute to the diagnosis such as culture, PCR,
40 serology and endoscopy. Once an infectious cause has been identified it should be provided
41 information to patients about transmission risks to partners and it should be emphasized the
42 importance that also partners undergo to investigations, due to the high risk of contagion. It is
43 advisable for gastroenterologists to refer to an expert in sexual health and associated infections, in
44 order to improve the management of these patients. As very frequent, co-infection with other sexually
45
46
47
48
49
50
51
52
53
54
55

1 transmitted pathogens should be investigated and a complete screening including HIV, first of all, but
2 also hepatitis B (HBV) and hepatitis C (HCV)⁹⁸ viruses should be taken into consideration. With a
3
4 timely and appropriate treatment, the long-term prognosis of infectious proctitis is auspicious.
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55

PEER REVIEW COPY
Minerva Gastroenterologica e Dietologica

References

- [1] Ribaldone DG, Pellicano R, Actis GC. Inflammation: a highly conserved, Janus-like phenomenon—a gastroenterologist's perspective. *J Mol Med (Berl)* 2018;96:861–71.
- [2] Ribaldone DG, Adriani A, Caviglia GP, Nicolò A, Agnesod D, Simiele M, et al. Correlation between Thiopurine S-Methyltransferase Genotype and Adverse Events in Inflammatory Bowel Disease Patients. *Medicina (Kaunas)*. 2019;55(8).
- [3] Macaluso FS, Orlando A. Anti-TNF Combination Therapy in Inflammatory Bowel Disease: de novo or selective? *Minerva Gastroenterol Dietol*. 2019 Oct 9. doi: 10.23736/S1121-421X.19.02617-5. [Epub ahead of print].
- [4] Klausner JD, Kohn R, Kent C. Etiology of clinical proctitis among men who have sex with men. *Clin Infect Dis* 2004;38:300–302.
- [5] Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance, 2016*. Atlanta, GA: US Department of Health and Human Services; 2017.
- [6] Satterwhite CL, Torrone E, Meites E, Dunne EF, Mahajan R, Ocfemia MC, et al. Sexually transmitted infections among US women and men: prevalence and incidence estimates, 2008. *Sex Transm Dis* 2013;40(3):187-93.
- [7] Fox KK, del Rio C, Holmes KK, Hook EW, Judson FN, Knapp JS, et al. Gonorrhea in the HIV era: a reversal in trends among men who have sex with men. *Am J Public Health* 2001;91(6):959.
- [8] Stall RD, Hays RB, Waldo CR, Ekstrand M, McFarland W. The Gay '90s: a review of research in the 1990s on sexual behavior and HIV risk among men who have sex with men. *AIDS* 2000;14 Suppl 3:S101.
- [9] Lutz AR. Screening for Asymptomatic Extragenital Gonorrhea and Chlamydia in Men Who Have Sex with Men: Significance, Recommendations, and Options for Overcoming Barriers to Testing. *LGBT Health* 2015; 2(1):27-34.
- [10] de Vries HJ, Zingoni A, White JA, Ross JD, Kreuter A. 2013 European Guideline on the management of proctitis, proctocolitis and enteritis caused by sexually transmissible pathogens. *Int J STD AIDS* 2014; 25(7):465.
- [11] Lamb C, Lamb EI, Mansfield JC, Sankar KN. Sexually transmitted infections manifesting as proctitis. *Front Gastroenterol*. 2013; 4(1):32–40.
- [12] Goldenberg SD, Finn J, Sedudzi E, White JA, Tong CY, et al. Performance of the GeneXpert CT/NG assay compared to that of the Aptima AC2 assay for detection of rectal Chlamydia trachomatis and Neisseria gonorrhoeae by use of residual Aptima Samples. *J Clin Microbiol*. 2012; 50(12):3867-9.

- 1 [13] Workowski KA, Bolan GA. Centers for Disease Control and Prevention. Sexually transmitted
2 diseases treatment guidelines, 2015. *MMWR Recomm Rep.* 2015; 64:1-137.
- 3
4 [14] Nunes A, Gomes JP. Evolution, Phylogeny, and molecular epidemiology
5 of Chlamydia". *Infection, Genetics and Evolution* 2014; 23: 49–64.
- 6
7 [15] Mabey D, Peeling RW. Lymphogranuloma venereum. *Sex Transm Infect* 2002;78(2):90–92.
- 8
9 [16] Hoentjen F, Rubin DT. Infectious proctitis: when to suspect it is not inflammatory bowel disease.
10 *Dig Dis Sci.* 2012;57(2):269-73.
- 11
12 [17] Rawla P, Limaïem F. Lymphogranuloma Venereum. StatPearls [Internet]. Treasure Island (FL):
13 StatPearls Publishing; 2019-.2019 Jun 26.
- 14
15 [18] Schachter J. Chlamydial infections. *West. J. Med.* 1990 Nov;153(5):523-34.
- 16
17 [19] Stoner BP, Cohen SE. Lymphogranuloma Venereum 2015: Clinical Presentation, Diagnosis, and
18 Treatment. *Clin Infect Dis.* 2015 Dec 15;61 Suppl 8:S865-73.
- 19
20 [20] Martin-Iguacel R, Llibre JM, Nielsen H, Heras E, Matas L, Lugo R, et al. Lymphogranuloma
21 venereum proctocolitis: a silent endemic disease in men who have sex with men in industrialised
22 countries. *Eur J Clin Microbiol Infect Dis.* 2010;29:917–925.
- 23
24 [21] Ward H, Martin I, Macdonald N, Alexander S, Simms I, Fenton K, et al. Lymphogranuloma
25 venereum in the United Kingdom. *Clin Infect Dis.* 2007;44:26–32.
- 26
27 [22] Mistrangelo M, Dal Conte I, Gregori G, Castellano I, Famiglietti F, De Vries HJ. Rectal
28 lymphogranuloma venereum. *Colorectal Dis.* 2012 Nov;14(11):e792-3).
- 29
30 [23] Dal Conte I, Mistrangelo M, Gregori G, Pasqualini C. Lymphogranuloma venereum in North-
31 West Italy, 2009-2014. *Sex Transm Infect.* 2015 Nov;91(7):472.
- 32
33 [24] McLean CA, Stoner BP, Workowski KA. Treatment of lymphogranuloma venereum. *Clin Infect*
34 *Dis* 2007; 44(suppl 3):S147–52.
- 35
36 [25] de Vries HJC, Morre SA, White JA, Moi H. European guideline for the management of
37 lymphogranuloma venereum, 2010. *Int J STD AIDS* 2010; 21:533–6.
- 38
39 [26] Devi B, Kumar Y, Shrivastav B, Sharma GN, Gupta G, Dua K. Current updates in biological and
40 pharmacological activities of doxycycline Panminerva Med 2018;60:36-9.
- 41
42 [27] Arnold CA, Limketkai BN, Illei PB, Montgomery E, Voltaggio L. Syphilitic and
43 lymphogranuloma venereum (LGV) proctocolitis: clues to a frequently missed diagnosis. *Am J Surg*
44 *Pathol* 2013; 37(1):38–46.
- 45
46 [28] Steedman NM, McMillan A. Treatment of asymptomatic rectal Chlamydia trachomatis: is single-
47 dose azithromycin effective? *Int J STD AIDS* 2009; 20:16–8.
- 48
49 [29] Miller WC, Zenilman JM. Epidemiology of chlamydial infection, gonorrhea, and trichomoniasis
50 in the United States-2005. *Infect Dis Clin North Am.* 2005;19(2):281–296.
- 51
52
53
54
55

- 1 [30] Haugland S, Thune T, Fosse B, Wentzel-Larsen T, Hjelmevoll SO, Myrmel H. "Comparing urine
2 samples and cervical swabs for Chlamydia testing in a female population by means of Strand
3 Displacement Assay (SDA)". *BMC Women's Health* 2010;10 (1): 9.
- 4 [31] Cheng A, Kirby JE. Evaluation of the Hologic Gen-Probe PANTHER, APTIMA Combo 2 Assay
5 in a Tertiary Care Teaching Hospital. *Am J Clin Pathol.* 2014;141(3):397-403.
- 6 [32] Lau CY, Qureshi AK. Azithromycin versus doxycycline for genital chlamydial infections: a
7 meta-analysis of randomized clinical trials. *Sex Transm Dis.* 2002;29(9):497–502.
- 8 [33] Marchi S, Trombetta CM, Gasparini R, Temperton N, Montomoli E. Epidemiology of herpes
9 simplex virus type 1 and 2 in Italy: a seroprevalence study from 2000 to 2014. *J Prev Med Hyg.* 2017;
10 58(1):E27-E33.
- 11 [34] Looker KJ, Magaret AS, Turner KME, Vickerman P, Gottlieb SL, Newman LM. Global estimates
12 of prevalent and incident herpes simplex virus type 2 infections in 2012. *PLoS One.* 2015;1:e114989.
- 13 [35] Imperatrice B, Giudici G, Marzano A. Human herpes viruses as cause of liver injury and acute
14 liver failure. *Minerva Gastroenterol Dietol.* 2019 May 30. doi: 10.23736/S1121-421X.19.02596-0.
15 [Epub ahead of print]
- 16 [36] Pellicano R, Fagoonee S. Herpes zoster in patients with peptic ulcer disease: a plausible
17 association? *Int J Epidemiol* 2015;44:361.
- 18 [37] Woestenberg PJ, Tjhie JH, de Melker HE, van der Klis FR, van Bergen JE, van der Sande MA,
19 et al. Herpes simplex virus type 1 and type 2 in the Netherlands: seroprevalence, risk factors and
20 changes during a 12-year period. *BMC Infect Dis* 2016;16:364.
- 21 [38] Suligoj B, Cusan M, Santopadre P, Palu G, Catania S, Girelli G, et al. HSV-2 specific
22 seroprevalence among various populations in Rome, Italy. *The Italian Herpes Management Forum.*
23 *Sex Transm Infect* 2000;76:213-4.
- 24 [39] Ayoade F, Gonzales Zamora JA, Tjendra Y. Herpes Simplex Virus Proctitis Masquerading as
25 Rectal Cancer. *Diseases* 2019;7(2). pii: E36.
- 26 [40] Jin, F, Prestage, GP, Mao L, Kippax SC, Pell CM, Donovan B, et al. Transmission of herpes
27 simplex virus types 1 and 2 in a prospective cohort of HIV-negative gay men: the health in men study.
28 *J. Infect. Dis.* 2006, 194, 561–570.
- 29 [41] Sandgren KE, Price NB, Bishop WP, McCarthy PJ. Herpes Simplex Proctitis Mimicking
30 Inflammatory Bowel Disease in a Teenaged Male. *Case Rep Pediatr.* 2017;2017:3547230.
- 31 [42] Cone MM, Whitlow CB. "Sexually transmitted and anorectal infectious diseases," *Gastroenterol*
32 *Clin North Am.* 2013;42(4):877-92.
- 33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55

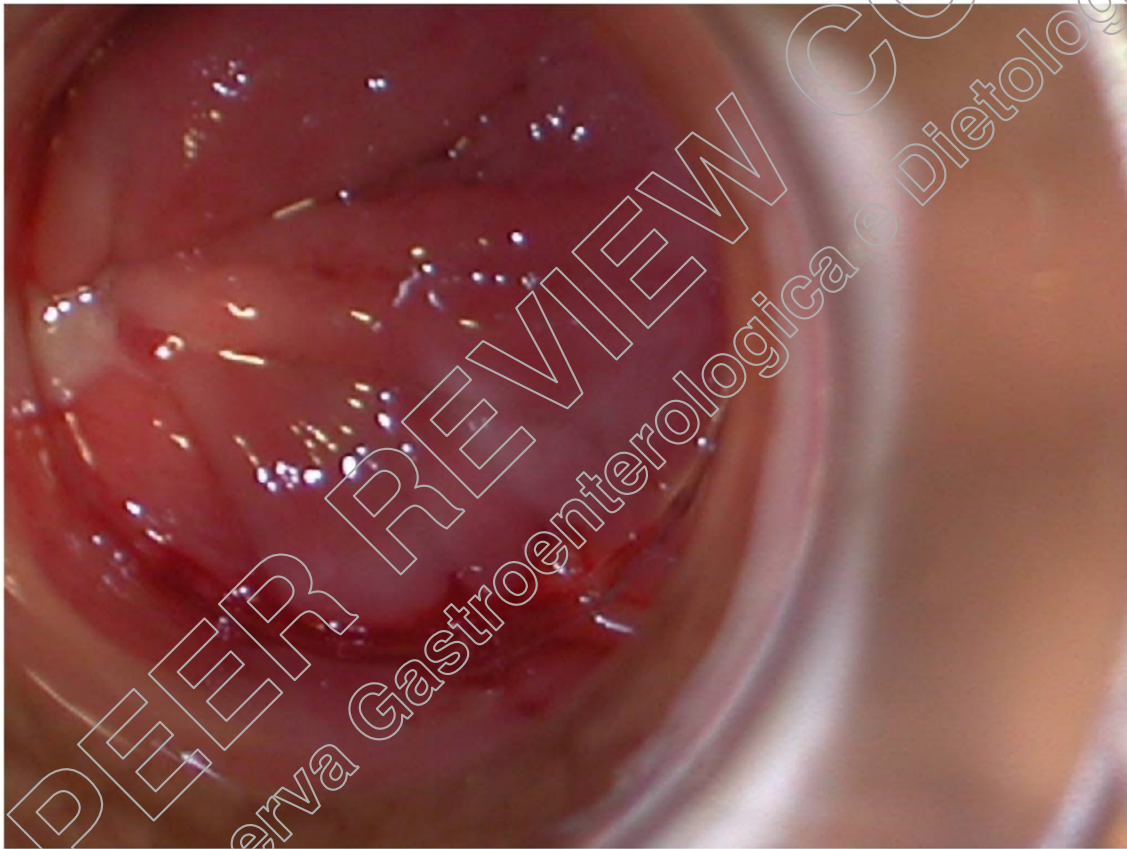
- 1 [43] Bissessor M, Fairley CK, Read T, Denham I, Bradshaw C, Chen M. The etiology of infectious
2 proctitis in men who have sex with men differs according to HIV status. *Sex Transm Dis.*
3 2013;40(10):768-70.
4
5 [44] Brugha R, Keersmaekers K, Renton A, Meheus A. Genital herpes infection: a review. *Int J*
6 *Epidemiol* 1997;26:698-709.
7
8 [45] Goodell SE, Quinn TC, Mkrtychian E, Schuffler MD, Holmes KK, Corey L. Herpes simplex
9 virus proctitis in homosexual men. Clinical, sigmoidoscopic, and histopathological features. *N. Engl.*
10 *J. Med.* 1983, 308, 868–871.
11
12 [46] Ashley RL, Militoni J, Lee F, Nahmias A, Corey L. "Comparison of Western blot (immunoblot)
13 and glycoprotein G-specific immunodot enzyme assay for detecting antibodies to herpes simplex
14 virus types 1 and 2 in human sera". *J Clin Microbiol.* 1988;26(4):662-7.
15
16 [47] Patel R, Kennedy OJ, Clarke E, Geretti A, Nilsen A, Lautenschlager S, et al. 2017 European
17 guidelines for the management of genital herpes. *Int J STD AIDS.* 2017;28(14):1366-1379.
18
19 [48] Stone RB, Chung Y, Ansa BE. Syphilis Trends in the Central Savannah River Area (CSRA) of
20 Georgia and South Carolina, USA. *J Clin Med.* 2018 Jul 31;7(8).
21
22 [49] Newman L, Rowley J, Vander Hoorn S, Wijesooriya NS, Unemo M, Low N, et al. Global
23 estimates of the prevalence and incidence of four curable sexually transmitted infections in 2012
24 based on systematic review and global reporting. *PLoS One.* 2015;10(12):e0143304.
25
26 [50] Hook EW, Peeling RW. Syphilis control – a continuing challenge. *N Engl J Med.* 2004
27 8;351(2):122-4.
28
29 [51] Stamm LV, Hodinka RL, Wyrick PB, Bassford PJ Jr. Changes in the cell surface properties of
30 *Treponema pallidum* that occur during in vitro incubation of freshly extracted organisms. *Infect*
31 *Immun.* 1987;55(9):2255-61.
32
33 [52] Salazar JC1, Rathi A, Michael NL, Radolf JD, Jagodzinski LL. Assessment of the kinetics of
34 *Treponema pallidum* dissemination into blood and tissues in experimental syphilis by real-time
35 quantitative PCR. *Infect Immun.* 2007;75(6):2954-8.
36
37 [53] Radolf, JD, Hazlett KRO, Lukehart SA. in *Pathogenic Treponemes: Cellular and Molecular*
38 *Biology* (eds Radolf, J. D. & Lukehart, S. A.) 197–236 (Horizon Scientific Press, 2006).
39
40 [54] Kent ME, Romanelli F. Reexamining syphilis: an update on epidemiology, clinical
41 manifestations, and management. *Ann Pharmacother.* 2008;42(2):226-36.
42
43 [55] Eccleston K, Collins L, Higgins SP. Primary syphilis. *Int J STD AIDS.* 2008;19(3):145-51.
44
45 [56] Phipps W, Kent CK, Kohn R, Klausner JD. Risk factors for repeat syphilis in men who have sex
46 with men, San Francisco. *Sex Transm Dis.* 2009;36:331–335.
47
48
49
50
51
52
53
54
55

- 1 [57] Lewis DA. Epidemiology, clinical features, diagnosis and treatment of *Haemophilus ducreyi* - a
2 disappearing pathogen? *Expert Rev Anti Infect Ther.* 2014;12(6):687-96.
- 3 [58] Whitlow CB. Bacterial sexually transmitted diseases. *Clin Colon Rectal Surg.* 2004;17(4):209-
4 14.
- 5 [59] Morse SA. Chancroid and *Haemophilus ducreyi*. *Clin Microbiol Rev.* 1989;2(2):137-57.
- 6 [60] Martin DH, Sargent SJ, Wendel GD Jr, McCormack WM, Spier NA, Johnson RB. Comparison
7 of azithromycin and ceftriaxone for the treatment of chancroid. *Clin Infect Dis.* 1995;21(2):409.
- 8 [61] Studemeister A. Cytomegalovirus Proctitis: A Rare and Disregarded Sexually Transmitted
9 Disease. *Sex Transm Dis.* 2011;38(9):876-8.
- 10 [62] Marder Mph EP, Griffin PM, Cieslak PR, Dunn J, Hurd S, Jervis R, et al. Preliminary Incidence
11 and Trends of Infections with Pathogens Transmitted Commonly Through Food - Foodborne Diseases
12 Active Surveillance Network, 10 U.S. Sites, 2006-2017. *MMWR Morb Mortal Wkly Rep.*
13 2018;67(11):324-328.
- 14 [63] Sorvillo FJ, Lieb LE, Waterman SH. Incidence of campylobacteriosis among patients with AIDS
15 in Los Angeles County. *J Acquir Immune Defic Syndr* 1991;4:598-602.
- 16 [64] Tee W, Mijch A. *Campylobacter jejuni* bacteremia in human immunodeficiency virus (HIV)-
17 infected and non-HIV infected patients: comparison of clinical features and review. *Clin Infect Dis*
18 1998;26:91-96.
- 19 [65] Dritz SK, Back AF. Letter: *Shigella* enteritis venereally transmitted. *N Engl J Med*
20 1974;291:1194.
- 21 [66] Khan WA, Griffiths JK, Bennish ME. Gastrointestinal and extra-intestinal manifestations of
22 childhood shigellosis in a region where all four species of *Shigella* are endemic. *PLoS One.* 2013
23 May 17;8(5):e64097.
- 24 [67] Billet AC, Salmon Rousseau A, Piroth L, Martins C. An underestimated sexually transmitted
25 infection: amoebiasis. *BMJ Case Rep.* 2019 May 10;12(5).
- 26 [68] Allason-Jones E, Mindel A, Sargeant P, Williams P. *Entamoeba histolytica* as a commensal
27 intestinal parasite in homosexual men. *N Engl J Med* 1986;315:353-6.
- 28 [69] Salit IE, Khairnar K, Gough K, Pillai DR. A possible cluster of sexually transmitted *Entamoeba*
29 *histolytica*: genetic analysis of a highly virulent strain. *Clin Infect Dis* 2009;49:346-53.
- 30 [70] Ximénez C, Morán P, Rojas L, Valadez A, Gómez A. Reassessment of the epidemiology of
31 amebiasis: state of the art. *Infect Genet Evol.* 2009;9(6):1023-32.
- 32 [71] Verstockt B, Vermeire S, Van Assche G, Ferrante M. When IBD is not IBD. *Scand J*
33 *Gastroenterol.* 2018 Sep;53(9):1085-1088.
- 34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55

- [72] Kantor M, Abrantes A, Estevez A, Schiller A, Torrent J, Gascon J, et al. Entamoeba Histolytica: Updates in Clinical Manifestation, Pathogenesis, and Vaccine Development. *Can J Gastroenterol Hepatol*. 2018 Dec 2;2018:4601420.
- [73] Gonzales MLM, Dans LF, Sio-Aguilar J. Antiamoebic drugs for treating amoebic colitis. *Cochrane Database Syst Rev*. 2019;1:CD006085.
- [74] Gardiner BJ, Woolley I, Simpson I. Caught in the act... a case of fulminant amoebic colitis. *Journal of Medical Microbiology Case Reports*. 2. 10.1099/jmmcr.0.000081.
- [75] Escobedo AA, Almirall P, Alfonso M, Cimerman S, Chacín-Bonilla L. Sexual transmission of giardiasis: A neglected route of spread? *Acta Trop*. 2014;132:106-11.
- [76] Dunn N, Juergens AL. Giardiasis. *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing; 2019-.2019 Jan 6.
- [77] Linard C, Busson E, Holler V, Strup-Perrot C, Lacave-Lapalun JV, Lhomme BL, et al. Repeated autologous bone marrow-derived mesenchymal stem cell injections improve radiation-induced proctitis in pigs. *Stem Cells Transl Med*. 2013;2:916–927.
- [78] Barnett GC, De Meerleer G, Gulliford SL, Sydes MR, Elliott RM, Dearnaley DP. The impact of clinical factors on the development of late radiation toxicity: results from the Medical Research Council RT01 trial (ISRCTN47772397). *Clin Oncol (R Coll Radiol)*. 2011;23:613–624.
- [79] Tabaja L, Sidani SM. Management of Radiation Proctitis. *Dig Dis Sci*. 2018;63(9):2180-2188.
- [80] Hong JJ, Park W, Ehrenpreis ED. Review article: current therapeutic options for radiation proctopathy. *Aliment Pharmacol Ther*. 2001;15:1253–1262.
- [81] Baum CA, Biddle WL, Miner PB Jr. Failure of 5-aminosalicylic acid enemas to improve chronic radiation proctitis. *Dig Dis Sci*. 1989;34:758–760.
- [82] Shadad AK, Sullivan FJ, Martin JD, Egan LJ. Gastrointestinal radiation injury: symptoms, risk factors and mechanisms. *World J Gastroenterol*. 2013;19:185–198.
- [83] Kochhar R, Sriram P, Sharma SC, Goel RC, Patel F. Natural history of late radiation proctosigmoiditis treated with topical sucralfate suspension. *Dig Dis Sci*. 1999;44:973–978.
- [84] Bowen JM, Gibson RJ, Collier JK, Blijlevens N, Bossi P, Al-Dasooqi N, et al. Mucositis Study Group of the Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO). Systematic review of agents for the management of cancer treatment-related gastrointestinal mucositis and clinical practice guidelines. *Support Care Cancer*. 2019 Oct;27(10):4011-4022).
- [85] Lucarotti ME, Mountford RA, Bartolo D. Surgical management of intestinal radiation injury. *Dis Colon Rectum*. 1991; 34:865–869.

- 1 [86] Turina M, Mulhall AM, Mahid SS, Yashar C, Galandiuk S. Frequency and surgical management
2 of chronic complications related to pelvic radiation. *Arch Surg.* 2008;143:46–52.
3
- 4 [87] Otto K. Volumetric modulated arc therapy: IMRT in a single gantry arc. *Med Phys.* 2008;35:310–
5 317.
6
- 7 [88] Athanassiou H, Antonadou D, Coliarakis N, Kouveli A, Synodinou M, Paraskevaïdis M, et al.
8 Protective effect of amifostine during fractionated radiotherapy in patients with pelvic carcinomas:
9 results of a randomized trial. *Int J Radiat Oncol Biol Phys.* 2003;56:1154–1160.
10
- 11 [89] Glotzer DJ, Glick ME, Goldman H. Proctitis and colitis following diversion of the fecal stream.
12 *Gastroenterology.* 1981;80(3):438-41.
13
- 14 [90] Wu XR, Liu XL, Katz S, Shen B. Pathogenesis, diagnosis, and management of ulcerative
15 proctitis, chronic radiation proctopathy, and diversion proctitis. *Inflamm Bowel Dis.* 2015;21(3):703-
16 15.
17
- 18 [91] Kabir SI, Kabir SA, Richards R, Ahmed J, MacFie J. Pathophysiology, clinical presentation and
19 management of diversion colitis: a review of current literature. *Int J Surg.* 2014;12(10):1088-92.
20
- 21 [92] Azimuddin K, Raphaeli T. Acute ischemic gangrene of the rectum: Report of 3 cases and r view
22 of literature. *Int J Surg Case Rep.* 2013;4(12):1120-3.
23
- 24 [93] Durazzo M, Campion D, Fagoonee S, Pellicano R. Gastrointestinal tract disorders in the elderly.
25 *Minerva Med.* 2017 Dec;108(6):575-591.
26
- 27 [94] Silva M, Peixoto A, Albuquerque A, Rodrigues S, Gaspar R, Morais R, et al. Clinical features
28 and outcome of acute ischemic proctocolitis. *Gastroenterol Hepatol.* 2017;40(1):28-31.
29
- 30 [95] Yip VS, Downey M, Teo NB, Anderson JR. Management of ischemic proctitis with severe rectal
31 haemorrhage: a case report. *World J Gastroenterol.* 2006 Jun 21;12(23):3776-8.
32
- 33 [96] Brandt LJ, Feuerstadt P, Longstreth GF, Boley SJ; American College of Gastroenterology. ACG
34 clinical guideline: epidemiology, risk factors, patterns of presentation, diagnosis, and management of
35 colon ischemia (CI). *Am J Gastroenterol.* 2015 Jan;110(1):18-44.
36
- 37 [97] White C. Genital injuries in adults. *Best practice & research..Best Pract Res Clin Obstet*
38 *Gynaecol.* 2013 Feb;27(1):113-30.
39
- 40 [98] Cuomo G, Puzzolante C, Lazzaretti C, Guaraldi G, Borghi V, Mussini C. Treatment rate for HCV
41 in the direct-acting antivirals era in HIV co-infected patients: data from an Italian cohort. *Minerva*
42 *Med.* 2018 Jun;109(3):203-210.
43
44
45
46
47
48
49
50
51
52
53
54
55

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55



PEER REVIEW COPY
Minerva Gastroenterologica e Dietologica



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55