Genital Ulcer Diseases: Diagnosis and Management

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Outline

- Overview of GUD etiology and evaluation
- GUD case studies
  - Infectious
  - Non-infectious

Genital Ulcer Disease (GUD) and HIV

- The genital ulcer serves as portal of entry and exit for HIV
- Independent risk factor for HIV seroconversion
- Presence of GUD associated with RR of HIV infection from 1.5 -7

Differential Diagnosis of Genital Ulcer Disease

Infectious	Non-infectious
• Herpes Simplex Virus (HSV) • Syphilis • Chancroid • Lymphogranuloma venereum (LGV) • Donavanosis Granuloma Inguinale) • HIV	• Behcet's disease • Squamous cell carcinoma • Trauma • Drug-induced • Other

Table 1. Results of the multiplex polymerase chain reaction (M-PCR) assay, by city.

City	No. tested by M-PCR	*Haemophilus ducreyi* No. (%)	*Treponema pallidum* No. (%)	HSV No. (%)	*T. pallidum*/HSV No. (%)	Negative No. (%)
Birmingham	50	0	13 (26)	25 (50)	0	12 (24)
Chicago	49[a]	6 (12)	4 (8)	24 (49)	1 (2)	14 (29)
Cincinnati	52	0	1 (2)	41 (79)	0	10 (19)
Dallas	52	0	6 (12)	35 (67)	2 (4)	9 (17)
Houston	51	0	1 (2)	38 (75)	1 (2)	11 (22)
Los Angeles	54	0	0	41 (76)	0	13 (24)
Memphis	50	10 (20)[b]	15 (30)	14 (28)	6 (12)	5 (10)
New York	55	0	1 (2)	36 (65)	1 (2)	17 (31)
Philadelphia	50	0	3 (6)	38 (76)	1 (2)	8 (16)
St. Louis	53	0	7 (13)	28 (53)	1 (2)	17 (32)
Total	516	16 (3)[b]	51 (10)	320 (62)	13 (3)	116 (22)

[a] 50 patients were enrolled; 1 specimen was unsatisfactory and was not tested.
[b] Includes 1 participant with both *H. ducreyi*/herpes simplex virus (HSV) detected and 2 with both *H. ducreyi*/*T. pallidum* detected.

Mertz KJ, Trees D, Levine WC, et al. Etiology of genital ulcers and prevalence of human immunodeficiency virus coinfection in 10 US Cities. J Infect Dis. 1993;178:1795-8.

Changes in the etiology of sexually transmitted diseases in Botswana between 1993 and 2002: implications for the clinical management of genital ulcer disease.

Paz-Bailey G, Rahman M, Chen C, et al. *Clin Infect Dis*. 2005;41:1304-1312

	1993	2002
Men and women with genital ulcer disease[a]		
HIV	40/108 (37.0)	72/98 (73.5)
Syphilis (RPR and TPHA)	56/108 (51.9)	7/137 (5.1)
Haemophilus ducreyi	27/108 (25.0)	1/137 (0.7)
Treponema pallidum	1/108 (0.9)	2/137 (1.5)
Herpes simplex virus	25/108 (23.1)	80/137 (58.4)
Lymphogranuloma venereum	2/108 (1.9)	NT/137
No organism identified	58/108 (53.7)	54/137 (39.4)

Genital Ulcer Disease Evaluation…

- Herpes simplex virus test
  - Culture, DFA, PCR or serology
- Darkfield
- RPR
- Consider other…
  - Chancroid
  - Donovanosis
  - Trauma, medication side effect, Gram stain of lesion if chancroid a possibility (also culture/PCR)

Case Study 1

A 29 year old man presented with a genital ulcer of 15 days duration. He had unprotected sex with a commercial sex worker during a business trip to Nairobi, Kenya about 2 weeks ago.

A dark-field examination, Tzanck smear, RPR were negative. A viral culture was subsequently reported as negative for herpes simplex virus.

Initial treatment was with 2,400,000 units of intramuscular benzathine penicillin G and 250 mg of intramuscular ceftriaxone.

Upon reexamination 10 days following treatment, the ulcer had improved.

Chancroid – Epidemiology

- Annual incidence 7 million
- Endemic in Africa, Asia, Latin America
- In US, steady decline since peak of 4986 cases (1987)
- M:F > 6:1

Chancroid – Clinical Manifestations

- Gram negative anaerobic bacteria, *H. ducreyi*
- Likely innoculated through microabrasions
- Incubation 4-7 days
- Tender erythematous papule develops, followed by pustule which rupture in 2-3 days
- Painful ragged ulcer, undermined edges, dirty base
- 40% with unilateral inguinal lymphadenitis

Chancroid – Diagnosis

Test	Se/Sp
Culture	80%/100%
PCR	> 95%
Serology (EIA)	48-97%/71-97%
Antigen Detection	89-100%/74-81%

2006 STD Treatment Guidelines: Chancroid

Azithromycin 1 g orally in a single dose

OR

Ceftriaxone 250 mg intramuscularly (IM) in a single dose

OR

Ciprofloxacin 500 mg orally twice a day for 3 days

OR

Erythromycin base 500 mg orally three times a day for 7 days

LGV – Epidemiology

- *C. trachomatis* serovars L_1, L_2 or L_3
- Africa, Asia, South America, Caribbean
- Emerging (versus newly recognized) in Europe and North America
- M:F ratio 5:1

Natural History of LGV

- Clinical manifestations (days postexposure)
  - 3-12 NGU, vesicle, papule, or ulcer
  - 14-168 constitutional symptoms, regional LAD
- Complications
  - Suppurative lymphadenitis
  - Fistulae, rectal strictures, chronic ulcerations, elephantiasis of external genitalia

LGV Among Men Who Have Sex with Men Netherlands, 2003-2004

MMWR October 29, 2004

- 92 cases, all white
- 77% HIV positive
- Only one patient with classic presentation, remainder with GI symptoms (proctitis)
- Temporally associated with seroconversion to HIV in 2 and Hepatitis C in 5

LGV - Diagnosis

- Frei skin test
- Complement fixation (titers >/=1:64) or microimmunoflourescence (titers >/= 1:256)
- Culture (recovery rate 24-30%)
- Histopathology
- Nucleic Acid Amplification Tests

2006 CDC STD Treatment Guidelines
Lymphogranuloma Venereum

Recommended:

- Doxycycline 100 mg twice daily for 21 days

Alternative:

- Erythromycin base 500 mg four times a day for 21 days

Case Study 2

- 36yo Latino male with painless, progressive lesions x 1 year. No sexual contact in 6 months.
- What is the differential diagnosis?

Squamous Cell Carcinoma

- Males
  - <1% of all malignancies in males
  - Almost all cases in uncircumcised males
  - Average age 55-65
- Females
  - Vulvar lesions similar to penile
  - Onset after age 60
- May be confused with GI

Donovanosis - Epidemiology

- Gram negative bacterium, *Calymmatobacterium* (now *Klebsiella*) *granulomatis*
- Main Foci
  - Papua New Guinea (46% of all GUD in women)
  - South Africa
  - Northeast Brazil
  - French Guyana
  - Australia (aborigines)
- Peaks between ages 20-40
- M:F ratio 6:1

Diagnostic Techniques in Donovanosis

- Smear
  - Giemsa stain
  - Wright stain
  - Leishman stain
- Histology
  - H&E
  - Silver stains*
  - Giemsa*
  - Thionine azure II basic fuchsin
- Serology, culture and PCR not routinely available

Donovanosis - Treatment

- Azithromycin 500mg qd or 1g qwk*
- Ceftriaxone 1g IM/IV qd
- Co-trimoxazole 800/160mg BID*
- Doxycycline 100mg BID*
- Erythromycin 500mg QID*
- Norfloxacin 400mg or Ciprofloxacin 750mg* BID
- Gentamicin 1mg/kg IM/IV q8

*CDC 2006 guidelines

**Rx at least 3 wks and/or until lesions heal

Case Study 4

A 25 year old man in previously good health presents to the emergency room with a 2 day history of malaise, anorexia, fever, and chills. Five days ago the noticed a painless ulcer on the glans penis. He has a history of injection drug use and has recently had sexual encounters in exchange for illicit drugs. He is steadily employed as a truck driver.

On physical examination he is a well-nourished man but lethargic and lying prostrate. He is febrile, tachycardic and slightly tachypneic. Examination findings include thrush, bilateral cervical lymphadenopathy and bilateral inguinal adenopathy. He is uncircumcised, and on retraction of the foreskin a round, 2-cm diameter, indurated, painless ulcer slightly elevated with smooth margins is present on the distal shaft.

What is the most likely etiology of the ulcer?

Differential Features of Sexually Transmitted Genital Ulcers

	Lesions	Tenderness	Edge	Base	Adenopathy
Syphilis	Usually single	None or mild	Indurated	Clean	Indolent
Chancroid	Usually multiple	Marked	Soft	Dirty	Tender, fluctuant
Herpes	Multiple	Marked	Soft	Clean	Tender
Donovanosis	Multiple	None	Serpiginous, may be white	Beefy red, granulation tissue	Erosive lesions overlying nodes
LGV	Single	None	Soft	Eroded papule	Prominent, tender

Why is he systemically ill?

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HIV Ab negative

HIV Viral load >2 million

Non-Infectious Genital Ulcers

Factitial Ulceration

- Usually erosions or ulcers
- Linear or geometric borders
- Clinical history may be difficult to elicit
  - genital self-mutilation (65-87% schizophrenic)
  - unconventional sexual practices

Erythema Multiforme

- "Target" or "iris" type lesions
- Mucosal surface involvement frequent
- Spectrum of severity
  - Stevens-Johnson syndrome
  - Toxic epidermal necrolysis
- Etiology
  - HSV*, EBV, MTb, fungal infection, lymphoma
  - Drugs (sulfa, dilantin, nevirapine)

Fixed Drug Eruption

- Tetracyclines
- Sulfonamides
- Barbiturates
- Phenolphthalein
- NSAIDS, Flagyl, Tylenol, Oral contraceptives, penicillins and salicylates also implicated.

Questions?