HPV

- Double stranded DNA virus
- The HPV infect epithelial cells of the skin and mucous membranes
- Highest risk types to cause cancer: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59

HPV and Cancer

- 15% of cancers are caused by viruses
- HPV accounts for 600,000 cases yearly
  - Anal, Cervix, Oropharyngeal, Vulvovaginal, and penile
- HPV 16 and 18 are the most oncogenic types
HPV and Cervical Cancer

- Squamous cell carcinoma (69%)
  - HPV 16 (53%), HPV 18 (13%), HPV 58 (5%), HPV 45 (4%)

- Adenocarcinoma (25%)
  - HPV 16 (36%), HPV 18 (37%), HPV 45 (5%), HPV 31 (2%), HPV 33 (2%)

HPV

Natural History

- Even with prevalence rates noted, most HPV infection is cleared by immune system
- Studies show 1 year clearance rates of 40-70% with 2-5 year clearance rates of 70-100%
- Younger women clear quicker than older women
- Low risk HPV clears quicker than high risk
  - HPV 16, 31, 54, and 53 are associated with longest persistent infection
Transmission

- Sexual exposure is most common through skin and mucosal surfaces
- Genital–genital, oral–genital, anal–genital, or oral–anal contact
- Condoms may not be fully protective due to HPV found on areas of the vulva and scrotum

HPV causing cervical dysplasia

- Most affected area is transformation zone (squamo-columnar junction)
- CIN has nuclear atypia which happens when the HPV infects the cell and replicates
- Basaloid cells are a single layer in contact with the basement membrane. These cells can show crowding, abnormal mitosis, loss of polarity and the extent of abnormal basaloid cells will determine grade of CIN
  - CIN 1 = undifferentiated basaloid cells involve lower 1/3 of the epithelium
  - CIN 2 = lower 2/3 of epithelium
  - CIN 3 = >2/3 of the epithelium

Squamo-columnar junction

- Original
  - Junction in fetal life between stratified squamous epithelium of the vagina and columnar epithelium of the endocervical canal
- New
  - Increasing estrogen and acidity of the vagina causes damage to the columnar epithelium which becomes replaced by immature squamous metaplasia that matures to stratified squamous metaplastic epithelium
  - The original junctional zone is replace by a zone of squamous metaplasia and the upper margin of this zone is an area of morphologically squamous cells and colposcopy columnar cells
  - This is the new squamo-columnar junction
Transformation Zone

- Area between the original squamo-columnar junction and the new squamo-columnar junction
- Cervical neoplasia arises in this area

HPV and cervical cancer – HOW???

- 4 steps in the development of cancer
  - Infection of the metaplastic epithelium of the transformation zone with carcinogenic HPV
  - Viral persistence
  - Progression of infected epithelium to precancer (CIN)
  - Invasion
Screening for cervical cancer

- PAP (Papanicolaou) smear
  - Cervical and vaginal cytology
  - Identify cells from the transformation zone and ectocervix/endocervix junction
  - Easier to detect squamous lesions than adeno lesions
    - Due to adenocarcinoma forming skip lesions and being in endocervix
  - Since using PAP the incidence of cervical cancer decreased from 36.3 to 7.2 per 100,000
- Despite PAP smears the risk of cervical cancer in those properly screened are 20-39%
  - Due to poor cellularity, collection or transfer
  - Inflammation of the cervix, scant cellularity, blood obscuring
  - Rates of unsatisfactory PAP is 1-8%
- HPV testing overcomes these human error problems

PAP Smear

- Conventional screening
  - Cells sampled from cervix and vagina with a brush or spatula and directly placed on a slide and fixed
  - HPV collected separate

- Liquid based screening
  - Cells collected the same but placed in liquid transport media and spun/filtered in the lab
    - HPV can be run on this specimen
Screening Guidelines

- ACS, ASCCP and ASCP say to screen with cytology every 3 years starting at 21 y/o
- No HPV testing because HPV infection usually transient and increase risk of procedures / colposcopy
- At age 30 y/o co-testing with cytology and HPV testing
  - Screening every 5 years if both are negative
  - HPV more persistent in this age group and clinical significance is greater
  - If no HPV test then cytology every 3 years

Screening Guidelines

- HIV patients
  - Yearly screening, ability of HPV clearance is low
- Immunocompromised (systemic disease / transplants)
  - Yearly PAP and HPV from 21 y/o and up
- Prior hysterectomy for CIN 2/3
  - Screen for 20 years

HPV causes changes in guidelines

- Patients with negative PAP but HPV 16 or 18 + should have a colposcopy
- LSIL or ASCUS PAP with HPV negative can be monitored
- HPV is now used to triage how to treat abnormal cytology
Why do we screen?

+ To detect precancerous lesions and early stage disease
+ Decrease the mortality and incidence of cervical cancer
+ Studies show higher cure rates and decreased risk of invasive cervical cancer

PAP smears

+ ASCUS – atypical squamous cells of undetermined significance
  + 5-27% will have a CIN 2/3 lesion
  + 0.3% have cervical carcinoma
+ ASC-H – atypical squamous cells cannot exclude a high grade lesion
  + 40% have a CIN 2/3 lesion
+ LSIL – Low grade squamous intraepithelial lesion
  + 25% have a CIN 2/3 lesion
+ HSIL – High grade squamous intraepithelial lesion
  + Up to 66% have CIN 2/3 lesions
+ AGS – Atypical glandular cells
  + 9-38% have carcinoma in situ or invasive cancer

HPV Vaccine

+ 2 are FDA approved
+ Quadrivalent type (Gardasil)
  + Contains VLPs to HPV 6, 11, 16, 18
  + Injection given 0, 2 and 6 months
  + Age 9-16
+ Bivalent (Cervarix)
  + VLPs to 16 and 18
  + Injection given 0, 1, and 6 months
  + Age 15-25
HPV Vaccine

- The L1 capsid protein was the target for a vaccine
- The vaccine has recombinant L1 protein that forms virus-like particles that are combined with different adjuvants
- The adjuvants stimulate the immune system and increase response to vaccine
- Response produced is mostly humoral response with antibodies but it also can have a cell-mediated response

How well does vaccine work?

- Study of 20,000 HPV naïve women aged 16-26 showed the quadrivalent vaccine prevented 99% of HPV 16 or 18 preinvasive or invasive lesions
- Similar studies of the bivalent showed 100% of HPV 16 and 18 mediated CIN 3 lesions were prevented
- There was less effect on those already affected with HPV which lends idea that this is more of a prophylactic vaccine

CIN history

- Cervical intraepithelial neoplasia
- CIN 1
  - Few convert to higher grade lesions (4-10%)
  - Most persist or regress away
- CIN 2/3
  - More high risk
  - At least 30% become invasive cancer without treatment
Unsatisfactory Cytology

Cytology normal, EC cells absent / insufficient

PAP negative, HPV +
Colposcopy

- Initial exam of cervix should look for
  - Hyperkeratosis which is a white, thickened epithelial area of the cervix
  - Atypical vessels which can be seen by green filtered light
- 3-5% acetic acid then placed
  - Acetowhite epithelium
  - Atypical vessels termed mosaicism and punctation
- Lugols iodine (schillers test)
  - Normal tissue has glycogen and stains mahogany brown
  - Neoplastic tissue do not and stain mustard yellow
ECC / Cervical Biopsy

- Performed to exclude occult cancer in the canal
- Can omit when entire SCJ can be visualized
- Biopsy any and all abnormal cervical lesions

Colposcopy Grading

- Normal
- Low grade disease (CIN 1)
- High grade disease (CIN 2,3)
- Invasive Cancer

Management of AGC
Management of CIN 1

Management of Woman with No Lesion or Biopsy-confirmed Cervical Intraepithelial Neoplasia — Grade 1 (CIN1) Processed by "Lesser Abnormalities"*:

- HPV negative
- Cytology negative

Follow-up without treatment

- ASC-US or HPV positive
- CIN 2/3

Follow-up at 6 months

Management of Woman with No Lesion or Biopsy-confirmed Cervical Intraepithelial Neoplasia — Grade 1 (CIN1) Processed by ASC-H and HSIL Cytology:

- HPV negative
- Cytology negative

Follow-up at 6 months

- HPV positive
- Cytology positive

Referral to gynecologist

Management of Woman with No Lesion or Biopsy-confirmed Cervical Intraepithelial Neoplasia — Grade 1 (CIN1) Processed by "Greater Abnormalities", CIN 2/3:

- HPV negative
- No lesion

Follow-up for at least 2 years

- HPV positive
- "Greater Abnormalities"

Cervical biopsy

Management of Woman Aged 21-24 y/o with no CIN 1 but abnormal PAP:

- HPV negative
- No lesion

Follow-up for at least 2 years

- HPV positive
- "Greater Abnormalities"

Cervical biopsy

21-24 y/o with no CIN 1 but abnormal PAP
Management of CIN 2 or 3

Management of 21-24 y/o with CIN 2,3

AIS
Treatment of dysplasia

- Ablative
  - Cryosurgery
  - Electrocoagulation diathermy
  - CO₂ laser
- Excisional procedure
  - LEEP
  - Excisional cone (CKC)
  - Hysterectomy

Cryosurgery

- Cryonecrosis of the lesion through compressed nitrous oxide
- Crystallization of intracellular water results in cell death
- Must cover a 5 mm depth and a 7 mm lateral spread
- Probe must cover entire lesion and transformation zone
- Usually only for smaller lesions and ectocervical lesions
- Freeze-thaw-freeze technique where you freeze a second time in order to ensure proper treatment of the cervical lesion
- Watery, malodorous, blood tinged discharge for 2-3 weeks
Loop Electrosurgical Excision Procedure

+ Excisional procedure
+ Locate lesion and select correct loop
+ You want to have 2 mm lateral on both sides of the lesion and a depth of 5-7 mm
+ ECC or cowboy hat biopsy of cervical canal
+ Cauterize the cervical area or place monsels

CO₂ Laser

+ Using CO₂ laser to ablate a lesion and the transformation zone
+ Ablate to a depth of 7-10 mm
Cold Knife Conization

- Procedure
  - Locate lesion
  - Stitches at 3 and 9 o’clock for hemostasis and traction
  - 11 blade scalpel to excise lesion
  - ECC done
  - Cauterize cervix / stitches / monsel
- Higher cure rates for high grade CIN
- Especially important when you need to have clean margins (i.e. AIS)
ASCCP

+ Guidelines should be used to help you evaluate and treat patients
+ Remember guidelines are the minimum you need to do for your patient
+ When in doubt do a biopsy or colposcopy if the lesion looks more high grade to you