

## **Perinatal Infections: Update on Group B Streptococci and Herpes Virus**

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77 Slides

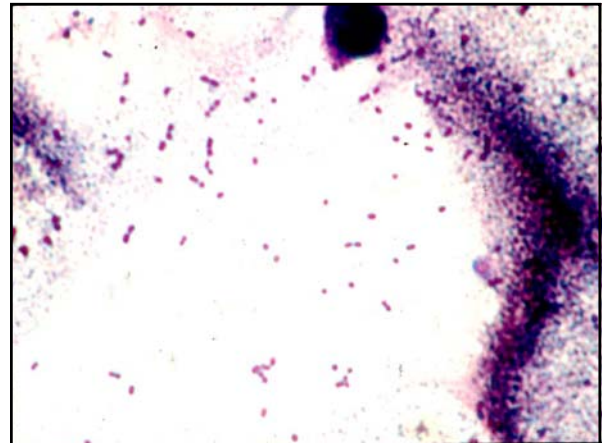
## **Learning Objectives**

Following this activity, in the learner's practice she/he will:

1. Know how and when to screen for Group B Streptococci (GBS) among pregnant women;
2. Know which antibiotics to use for GBS prophylaxis among women who can not receive penicillin;
3. Know the strategy to prevent GBS neonatal sepsis in colonized women having elective cesarean delivery

## **Learning Objectives (Cont'd)**

4. Know how to differentiate the following genital herpes syndromes: primary first episode, non-primary first episode, and recurrent;
5. Be able to apply at least one strategy during prenatal care to prevent neonatal herpes infection.

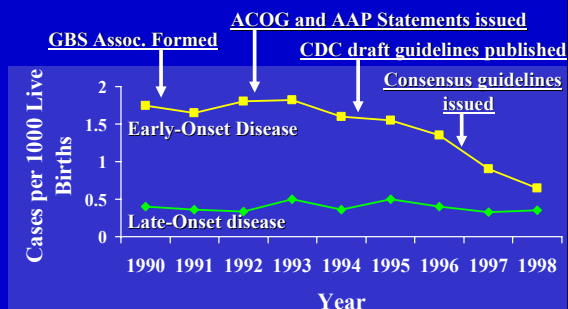


## **Prevention Strategies: 1996**

- Screen-based
- Risk-based

CDC. MMWR 1996; 45; 1-24

## Impact of 1996 Guidelines on Early- and Late-Onset GBS Disease



Based upon 3 CDC Surveillance areas. Schrag et al. NEJM 2000;342:15-20



## 2002 GBS Prevention Guidelines

- Recommend screen based approach only.
- Change alternative antibiotics for penicillin allergic patients.
- More specific recommendations for clinical scenarios.

## Comparison of Strategies to Prevent GBS Disease in Neonates

Routine screening prevents more cases of early onset disease than risk based approach by:

- \* higher degree of coverage of at risk population (including GBS positive without risk factors)
- \* better compliance

Schrag S, et al., NEJM 2002; 347: 233-39.

## 2002 GBS Screen Based Approach

1. All pregnant women should be screened at 35-37 weeks' gestation for vaginorectal GBS colonization. At time of labor or ROM, intrapartum chemoprophylaxis (IPC) should be given to pregnant women identified as GBS carriers. (A-II)

## 2002 GBS Screen Based Approach

1. (cont'd) GBS colonization in a previous pregnancy does not obviate need for screening in subsequent pregnancies; colonization in a previous pregnancy not an indication for IPC in subsequent deliveries. (A-II)

## 2002 GBS Screen Based Approach

### 2. GBS bacteriuria

- Give IPC to women with GBS in urine in any concentration. (B-II)
- Prenatal screen @ 35-37 weeks not necessary.
- Treat bacteriuria by standards of care.

## 2002 GBS Screen Based Approach

3. Women with previous birth of infant with GBS disease should receive IPC; prenatal screening not necessary for these women. (B-II)

## 2002 GBS Screen Based Approach

### 4. If result of GBS culture not known at time of labor, give IPC if:

- < 37 weeks' gestation or
- ROM  $\geq$  18 hours or
- T  $\geq$  100.4F ( $\geq$  38.0C) (A-II)

## 2002 GBS Screen Based Approach

### 5. Onset of Labor or ROM <37 weeks with "significant risk for imminent preterm delivery."

+ GBS this pregnancy: PCN x  $\geq$  48h; IPC at delivery.

- GBS this pregnancy: No IPC.

No GBS culture at admission: Culture & initiate PCN IV. If culture -, stop PCN.

## 2002 GBS Screen Based Guidelines

### 6. Specimen Collection

- Distal vagina and anorectum
- Collected by patient or provider (B-II)
- No speculum
- Transport medium acceptable
- Label "GBS culture"



## 2002 GBS Screen Based Approach

### 6. Laboratory Processing

- Inoculate into selective broth medium. (eg LIM or Trans-Vag) (A-II)
- Methods provided for susceptibility to clinda/erythro for GBS from penicillin allergic women.
- Labs “should report results to site of delivery and provider.”

## 2002 GBS Screen Based Approach

### 7. Inform patients of results and recommended intervention.

In absence of GBS bacteriuria, do not treat GBS genital colonization before intrapartum period. (D-I)

## 2002 GBS Screen Based Approach

### 8. For cesarean delivery before ROM and before labor: no GBS IPC.

## 2002 GBS Screen Based Guidelines

### 9. Penicillin G: Drug of choice.

Ampicillin: Alternative.

For penicillin allergy:  
Clindamycin/erythromycin  
no longer drugs of choice.

## Resistance of GBS to “Alternate” Antibiotics

<u>Antibiotics</u>	<u>Resistance</u>
Erythromycin	7 - 41 %
Clindamycin	3 - 24 %

Pearlman O/G 1998; Fernandez AAC 1998; Morales AJOG 1999; ABC/EIP (Lynfield); Gagnon, IDSOG, 2008

## 2002 GBS Screen Based Guidelines

### 10. Patients with PCN allergy, not at high risk for anaphylaxis:

Cefazolin, 2gm IV then 1gm every 8 hours until delivery. (B-III)

## 2002 GBS Screen Based Guidelines

### 10. Patients with PCN allergy at high risk for anaphylaxis:

GBS susceptible:

**Clinda, 900 mg IV q 8h**

**OR Erythro, 500 mg IV q 6h**

GBS resistant to Clinda or Erythro  
or unknown susceptibility:

**Vancomycin, 1 gm IV q 12h (C-III)**

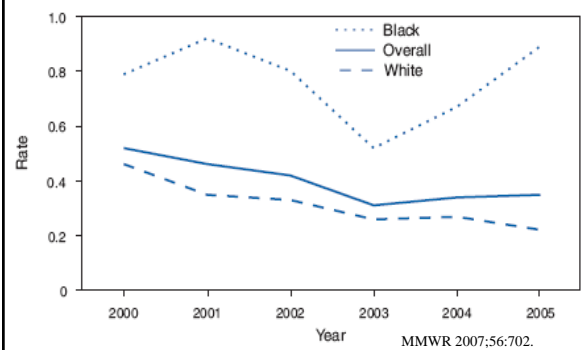
## 2002 GBS Guidelines- CDC

**Summary:** If GBS isolate is resistant to EITHER erythromycin OR clindamycin and patient has high risk allergy to penicillin, then use vancomycin.

## GBS: What's happened since 2002

- Decreasing incidence of neonatal sepsis (GBS)
- Better compliance
- Inducible resistance to clindamycin
- Rapid testing

FIGURE 1. Rate\* of early-onset† invasive group B streptococcal disease, by race and year — Active Bacterial Core surveillance system, United States, 2000–2005§



## GBS Resistance to Macrolide Antibiotics

GBS isolates resistant to erythromycin may:

- be susceptible to clindamycin
  - have constitutive resistance to clindamycin
- OR

- have inducible resistance to clindamycin

Most isolates with inducible resistance to clindamycin are NOT identified as clindamycin resistant by usual testing (minimal inhibitory concentrations, MICs)

Schoening et al. Clin Microbial Infect 2005;11:579-82

## GBS Resistance to Macrolide Antibiotics

- Testing for induction of clindamycin resistance for erythromycin-resistant isolates of *S. aureus* using the "D test" has been reported by CDC.
- Some clinical labs including University of Colorado Hospital have applied D test to GBS, but current CDC guidelines do not recommend this to select antibiotics in penicillin-allergic women.

Steward CD et al. J Clin Micro 2005;43:1716-21



### Inducible Resistance to Clindamycin Among GBS Isolates

Antibiotic	Susceptibility by Traditional Testing
Erythromycin	19 of 32 (59%)
Clindamycin	21 of 32 (66%)
<u>Inducible Resistance</u>	
Clindamycin	3 of 21 (14%)

Gagnon, A et al. IDSOG, 2008

### Rapid GBS Screening Using Real Time PCR

- Compared real time PCR (Xpert GBS assay) to rectovaginal cultures with selective media.
- Turn around 75-90 minutes

Edwards, R., et al. O&G 2008; 111:1335-41

### “Rapid Detection” of GBS Using Real Time PCR

Sensitivity	173/190	(91.1%)
Specificity	570/594	(96.0%)
PPV	173/197	(87.8%)
NPV	570/587	(97.19%)
GBS Prevalence by Culture	190/784	(24.2%)

Edwards, R., et al. O&G 2008; 111:1335-41

### Considerations: PCR for Rapid Detection of GBS in Labor

- How long will actual time be from collection to result (transport time, actual turn-around time on 24/7 basis)?
- Will results be timely enough to get adequate prophylaxis (>4 hours) to high percentage of woman?
- For women who can not take penicillin, how will susceptibility to erythromycin and clindamycin be determined?

### Membrane Sweeping in GBS Colonized Women

	<u>Chorioamnionitis (*p)</u>	
	“No Sweep” (N = 35)	“Sweep” (N = 41)
GBS Positive	0%	7%

Gagnon, A et al. IDSOG, 2008

\*p = 0.24

## Genital Herpes Infection: Prevalence and Natural History

## How Common is HSV Infection?

- Genital herpes – a recurrent, sometimes life-long infection.
- HSV-1 and HSV-2 types.
- At least 50 million persons in the U.S. have genital herpes.

2006 STD Guidelines, MMWR 2006; 55:16-20

## How Common is Genital HSV Infection?

- Overall, 5-10% of population has a history of symptomatic genital HSV-2 infection.
- However, another 20-30% have type specific HSV-2 antibodies (G-2 protein) and have never had a symptomatic genital infection.

## Genital Herpes Syndromes

- **Primary infection** – Isolation of HSV-1 or HSV-2 in absence of HSV antibodies in serum.
- **Recurrent infection** – Reactivation of latent virus, isolation of HSV-1 or HSV-2 in presence of homologous antibodies in serum.
- **Non-primary first episode** – Isolation of HSV-2 in the presence of HSV-1 antibodies in serum.

Brown ZA, et al. Obstet Gynecol 2005.

## Genital Herpes Infection: Diagnosis

## Diagnosis of HSV Infection

- Clinical diagnosis is insensitive and nonspecific.
- Up to 50% of first episodes are caused by HSV-1\*, but most recurrences are by HSV-2.
- Among college-age population, up to 80% are due to HSV-1.\*
- Virologic and type-specific serologic tests should be available.

2006 STD Guidelines. MMWR 2006 \*Brown ZA. O&G 2005

## Laboratory Diagnosis of Herpes Virus

- Culture – preferred in persons with ulcers, but sensitivity declines rapidly; isolates should be typed.
- Polymerase chain reaction (PCR) – “more sensitive,” but not FDA cleared for genital specimens.

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## FDA Approved Type-Specific Assays for HSV\*

- Biokit™ HSV-2 Rapid Test
- SureVue HSV-2
- HerpeSelect™ -1 and -2 ELISA IgG
- HerpeSelect™ -1 and -2 Immunoblot IgG
- HSV-2 ELISA
- Sensitivity for HSV-2: 80-98%
- Specificity for HSV-2: >96%

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\*Based upon glycoprotein G antibodies

## How to Use HSV Type Specific Antibodies

- Recurrent genital symptoms or atypical symptoms with negative culture.
- A clinical diagnosis of genital herpes without laboratory confirmation.
- Screening for HSV-1 and HSV-2 in general population is not indicated.

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## Genital Herpes Infection: Treatment

### First Clinical Episode of Genital Herpes

#### Recommended Regimens

Acyclovir 400 mg PO tid x 7-10 d  
OR  
Acyclovir 200 mg PO 5x/d x 7-10 d  
OR  
Famciclovir 250 mg PO tid x 7-10 d  
OR  
Valacyclovir 1 g PO bid x 7-10 d

Note: Treatment may be extended if healing is incomplete after 10 days of therapy.

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### Episodic Therapy for Recurrent Genital Herpes

- Initiate within 1 day of lesion onset or during prodrome.
- Provide supply of meds or Rx to self-initiate treatment.

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## Episodic Therapy for Recurrent Genital Herpes

### Recommended Regimens

Acyclovir 400 mg PO tid x 5 d  
**OR**  
 Acyclovir 800 mg PO bid x 5 d  
**OR**  
 Acyclovir 800 mg PO tid x 2 d  
**OR**  
 Famciclovir 125 mg PO bid x 5 d  
**OR**  
 Famciclovir 1000 mg PO bid x 1 d

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## Episodic Therapy for Recurrent Genital Herpes

### Recommended Regimens, Cont'd

Valacyclovir 500 mg PO bid x 3 d  
**OR**  
 Valacyclovir 1.0 g PO qd x 5 d

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## Suppressive Therapy for Recurrent Genital Herpes

### Recommended Regimens

Acyclovir 400 mg PO bid **OR**  
 Famciclovir 250 mg PO bid **OR**  
 Valacyclovir 500 mg PO qd\* **OR**  
 Valacyclovir 1.0 gram PO qd

\*May be less effective in those with  $\geq 10$  episodes/year

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## Genital Herpes Infection: Prevention of Adult Infection

### Once Daily Valacyclovir (VAL) to Reduce Risk of Transmission of Genital Herpes

- 1484 immunocompetent, monogamous couples, discordant for HSV-2.
- Partner with HSV-2 randomized to either 500 mg VAL qd or placebo for 8 months.
- All counseled re: safer sex and offered condoms.

Corey, L. et al., NEJM 2004; 350:11-19

### Daily VAL to Reduce HSV- 2 Transmission

	VAL (N=743)	PLAC (N=741)	P
	N (%)		
Symptomatic Acquisition	4 (0.5)	16 (2.2)	0.008
Overall Acquisition	14 (1.9)	27 (3.6)	0.04

Corey, L. et al., NEJM 2004; 350:11-19

### Daily VAL to Reduce HSV-2 Transmission, Cont'd

	VAL (N=743)	PLAC (N=741) N (%)	P
Acquisition HSV-1/2	4 (1.9)	31 (4.2)	0.01
HSV DNA detected (dys)	(2.9)	(10.8)	<0.001

Corey, L. et al., NEJM 2004; 350:11-19

### Prevention Against HSV-2 Infection in Susceptible Women

- 528 monogamous couples discordant for HSV-2 infection.
- Acquisition in women about 1/1000 acts of intercourse (9.7% of women, 1.9% of men).

Wald A, et al. JAMA 2001; 285: 3100-3106

### Prevention Against HSV-2 Infection in Susceptible Women

- Condom use >25% of acts protective (Adj HR. 0.085, 95 CI 0.01 – 0.67) for women, but not for men.
- Changes in behavior (decreased acts when partner has lesion) reduced HSV=2 infection over time.

Wald A, et al. JAMA 2001; 285: 3100-3106

### Genital Herpes Infections: Pregnancy

### Recommended HSV Treatment: Pregnancy\*

Indication	Acyclovir	Valacyclovir
Primary or 1 <sup>st</sup> episode.	400mg PO TID x 7-14 days	1 gm PO BID x 7-14 days
Symptomatic recurrence	400mg PO TID x 5 days	500mg PO BID x 5 days
Suppressive	400mg PO TID from 36 weeks	500mg PO BID from 36 weeks

Brown ZA et al. Obstet &Gynecol 2005

\*No recommended dose of famciclovir in pregnancy



## Acquisition of Herpes Simplex Virus During Pregnancy: Methods

- Serum samples at first prenatal visit, 14-18 and 24-28 weeks and at delivery.
- Type specific antibodies by Western blot to HSV-1 and 2.
- Genital cultures for HSV on admission.

Brown ZA, et al. NEJM 1997;337:509-15

## Effect of Maternal HSV Seroconversion on Neonate

- Comparing neonates of 94 mothers with seroconversion to those of 6009 without, no differences observed in BW, GA, IUGR, stillbirth, or neonatal death.

Brown, et al. NEJM 1997

## Effect of Maternal HSV Seroconversion on Neonate (Cont'd)

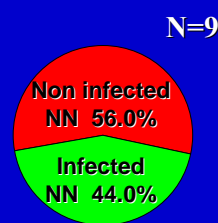
Chance of woman with seroconversion in pregnancy infecting her newborn

Observed = 0/94

95% upper CI = 3.2%

Brown, et al. NEJM 1997

## Recent Acquisition of Genital HSV\* and NN Infection



Of 4 Infected Neonates

- 2 born to 2 mothers with primary HSV-1
- 2 Born to 7 mothers with non primary first episode of HSV-2
- 1 died (non primary maternal infection)
- 1 developmentally disabled (primary maternal infection)

Brown, et al. NEJM 1997

\*Mothers had positive culture in labor, but without homologous antibody.

## Revised Summary of HSV Infections in Pregnancy

Characteristics	Primary	Recurrent	Non Primary First Episode
Maternal Symptoms	Asymptomatic to Severe	Same	Same
Fetal-Neonatal Infection risks	Transplental and Neonatal	Neonatal	Mainly Neonatal
Estimated Neonatal risk	Up to 30-50%*	3%	Up to 30-50%*

\*Depending upon presence or absence of maternal antibody

## Genital Herpes Infection: Prevention of Perinatal Infection

### Acyclovir Prophylaxis to Prevent Herpes Simplex Virus Recurrence at Delivery: Systematic Review

- Selected 5 trials with 799 patients
- Included patients with first episode, recurrent or all herpes simplex virus infections
- Included acyclovir from 200 mg QID to 400 mg QID, all beginning at 36 weeks

Sheffield, JS, et. al. (UT-D)  
Obstet Gynecol 2003; 102: 1396-1403

### Acyclovir Prophylaxis to Prevent Herpes Simplex Virus Recurrence at Delivery: Systematic Review

#### Effect of Acyclovir Prophylaxis

	<u>ACV</u>	<u>Placebo</u>	<u>OR</u> (95% CI)
Clinical recurrences at delivery, %	4	15	0.25 (0.15, 0.40)
Cesarean delivery for HSV, %	4	14.6	0.30 (0.13, 0.67)

Sheffield, JS, et. al.  
Obstet Gynecol 2003; 102: 1396-1403

### Acyclovir Prophylaxis to Prevent Herpes Simplex Virus Recurrence at Delivery: Systematic Review

#### Effect of Acyclovir Prophylaxis, Cont'd

	<u>ACV</u>	<u>Placebo</u>	<u>OR</u> (95% CI)
Total Cesarean Rate, %	16.7	25.8	0.61 (0.43, 0.86)
Asymptomatic HSV Shedding, %	0	3	0.09 (0.02, 0.39)

Sheffield, JS, et. al.  
Obstet Gynecol 2003; 102: 1396-1403

### Acyclovir Prophylaxis to Prevent Herpes Simplex Virus Recurrence at Delivery: Systematic Review

#### Summary

1. Among women with genital herpes, prophylactic acyclovir is an effective therapy to decrease herpes simplex virus recurrences at delivery, HSV detectable by culture, and cesarean delivery for recurrences.
2. Odds ratios for preventing clinical recurrences were similar in those studies of first episode versus those including women with recurrences (0.21 vs. 0.25, respectively).

Sheffield, JS, et. al.  
Obstet Gynecol 2003; 102: 1396-1403

### Acyclovir Prophylaxis to Prevent Herpes Simplex Virus Recurrence at Delivery: Systematic Review

#### Summary

3. Odds ratios for HSV detected at delivery were similar for those studies of 800 mg/day vs. 1200 mg/day (0.09 vs. 0.13, respectively).

Sheffield, JS, et. al.  
Obstet Gynecol 2003; 102: 1396-1403

### Counseling Pregnant Women About Herpes

- Women without known genital HSV – avoid intercourse in third trimester with partners known, or suspected of, having genital HSV.
- Pregnant women without known orolabial herpes – avoid cunnilingus in third trimester with partners with orolabial herpes.

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### **Counseling Pregnant Women about Herpes, Cont'd**

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- All pregnant women should be asked if they have a history of HSV.
- Some specialists believe that type-specific serologic tests are useful to identify pregnant women at risk for HSV infection and to guide counseling regarding risk for acquiring genital HSV during pregnancy.
- Such testing should be offered to women without genital herpes if their sex partner has HSV infection.

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### **Counseling Pregnant Women about Herpes, Cont'd**

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- Effectiveness of antiviral therapy to decrease the risk of HSV transmission to pregnant women has not been established.
- In labor, all women should be questioned carefully about symptoms of genital herpes and should be examined carefully for herpetic lesions.

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### **Counseling Pregnant Women about Herpes, Cont'd**

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- The majority of specialists recommend that women with recurrent genital herpetic lesions at the outset of labor be delivered by cesarean section, but this does not completely eliminate risk of NN HSV.
- The safety of systemic Acyclovir, Valacyclovir, and Famciclovir in pregnancy 'has not been definitively established' but data 'provide some reassurance' for acyclovir.

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### **Neonatal HSV Persists**

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- Estimated 1500 cases/year in United States
  - Mainly from asymptomatic mothers.
- Potential strategies
  - Seroscreening of pregnant women
  - HSV vaccine
  - PCR screening of newborns