

PAP SMEAR ACCURACY

The cervicovaginal (“Pap”) smear is one of the most successful tests ever created for the detection and prevention of cancer. Like any laboratory test, the Pap smear is not perfect. Because the Pap smear is a **screening** test, much attention has been given to the rate of false negatives associated with the test. That is, how often does the Pap smear fail to detect disease that is present in the screened population? This focus on false negatives led to CLIA 88, The Bethesda System, and a host of new technologies including liquid-based, monolayer preparations for cervical/vaginal screening. Interestingly, large studies of patients with cervical cancer consistently find that the most common cause of “Pap smear failure” is, in fact, **failure to have a Pap smear performed!** The next most common cause is patients with an abnormal Pap smear who are lost to follow-up. The third largest category of Pap smear failures involves problems with specimen collection. Any attempt at cleansing of the cervix before obtaining the sample increases the rate of false negatives. This includes the patient that douches before seeing her physician as well as the physician who swabs the cervix to clean it before obtaining the sample. Studies consistently show that endocervical brushes collect better samples than brooms and that cotton swabs and wooden spatulas provide inferior samples.¹ Improperly prepared slides, which are too thick or air-dried, may result in false negative samples. (The circumvention of these slide preparation errors is one of the advantages of liquid-based preparations.) The final (but statistically the smallest) contributor to false negative Pap Smears involves the screening of the slide. Excessive blood or inflammation impair cytologic screening and may obscure abnormal cells. Errors of omission in the screening of the slide as well as errors in the interpretation of properly screened slides fall into this category as well. It is this source of error which has enjoyed the most intense scrutiny in the lay press and by government agencies. It is generally agreed that Pap Smear screening is associated with an irreducible error rate of 5 -20%.² A major problem in determining Pap Smear error rates is that the “gold standard” used to determine accuracy is histologic examination of cervical biopsy specimens. Cervical biopsy interpretation also suffers from significant false negative and false positive rates and lack of consensus among pathologists.

A recent JAMA article discussed the issue of interpretative variability for all types of cervical specimens including traditional Pap smears, monolayer Pap smears, cervical biopsies and LEEP cone specimens.³ In this study there was significant variability in the interpretation of these specimens by different pathologists. For the histologic specimens, the lack of agreement was worse in cases of low-grade dysplasia where agreement was achieved in only 44% of cases for either cervical biopsies or LEEP cone specimens. The histologic agreement was much better for high-grade dysplasia cases at approximately 80%. As one might expect, for liquid-based Pap specimens, the worst agreement rate (43%) was reached in cases of ASCUS (Atypical Squamous Cells of Uncertain Significance). However, the lack of agreement for cases of high grade dysplasia was also high at 47% of cases, with most of the discrepant cases subsequently classified either as cases of ASCUS or low grade dysplasia. In cases of low-grade dysplasia, the cytology (Pap smear) diagnosis was more reproducible than the histologic diagnosis from either cervical biopsy or LEEP cones. Most cases with a Pap smear diagnosis of low-grade dysplasia, in which the subsequent histologic specimen was negative for dysplasia, tested positive for Human Papilloma Virus (HPV) DNA on follow-up. This suggests a significant false negative rate for cervical biopsy specimens. One major problem mentioned by the authors as contributing to the lack of concordance is the recent practice whereby Pap smears are often interpreted in large commercial laboratories while cervical biopsies and LEEP specimens are often read by local pathologists who do not have the opportunity to review the abnormal Pap smear and compare any findings with those seen on the biopsy specimen. This

practice has significantly decreased the opportunity for cytohistologic correlation and thus improvement in interpretative reproducibility.

The Pap smear also has a false positive rate. This can be subdivided into “true” false positives and “false” false positives. “True” false positive Pap smears are those in which there are misinterpretation of reactive changes, squamous metaplasia or other findings on the smear. “False” false positives are more common and are usually due to sampling errors on the part of the cervical biopsy (i.e. false negative cervical biopsy). The false negative rate of the cervical biopsy following a positive Pap smear has been shown to be as high as 45% in the recent JAMA article as well as in other studies.^{3,4} The spontaneous regression rate of cytologically diagnosed dysplasia may be as high as 60%.⁵ It has also been suggested that the trauma of taking the Pap smear can lead to sloughing of the dysplastic epithelium in some cases. What should be emphasized is that a significant number of patients thought to have false positive Pap smears will eventually be diagnosed with dysplasia. Because of this, diligent follow-up of patients with noncorrelating cervical studies is recommended since they represent a population at high risk for the subsequent detection of premalignant lesions.

At the Rex Healthcare Department of Pathology we have correlated cervical cytology with biopsy findings since 1988. This data includes analysis of over 2200 cases. The overall Pap smear to cervical biopsy correlation rate is 76% and has exceeded 80% for the past few years. The concordance rate for the diagnosis of high-grade squamous intraepithelial lesion (moderate to severe dysplasia, carcinoma-in-situ) is greater than 90% while that for low-grade lesions is between 75-80%. Approximately two-thirds of our ASCUS Pap smear cases have dysplasia confirmed on the subsequent biopsy. Many of the non-correlating cases represent cervical biopsy sampling errors as confirmed by follow-up cone specimens. We have witnessed an increase in non-correlating cases secondary to prominent thermal artifact in LEEP cone specimens which can obscure the epithelium and preclude a definitive diagnosis. There are also “true” false positive Pap smear cases in which reactive change or metaplasia is “overdiagnosed” as dysplasia. Our overall concordance rate is quite good. We attribute this to our practice of receiving both the Pap specimens and the biopsy specimens on our patients, allowing us to correlate the findings in individual cases and to learn from our mistakes.

Keith V. Nance, MD

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2. Austin RM: Can Regulatory Proficiency Testing by the Cytobureauacrcy Decrease Both False Negatives and Cervical Cancer Deaths? Diagn Cytopathol 11: 109-112, 1994.
3. Stoler MH and Schiffman M: Interobserver Reproducibility of Cervical Cytologic and Histologic Interpretations. JAMA 285(11): 1500-1505, 2001.
4. Anderson MB and Jones BA: False Positive Cervicovaginal Cytology. Acta Cytol 41: 1697-1700, 1997.
5. Nasiell K, et al: Behavior of Mild Cervical Dysplasia during Long Term Follow-up. Obstet Gynecol 67: 665-669, 1986.

Met. CA - ? Primary

A recurring challenge in the practice of medicine is the management of patients who present with carcinoma metastatic to liver, lung, lymph node, or elsewhere – in the absence of an obvious primary source. At times, the morphologic appearance of the neoplasm is sufficiently characteristic to suggest the primary source. More often, the light optic appearance is either nonspecific (“non-small cell carcinoma”) or represents a pattern of adenocarcinoma which can be observed in tumors originating in several different organs. In this setting, immunohistochemical stains applied to the biopsy tissue or cell block may help discriminate the possible sources of the metastatic carcinoma, and assist in the appropriate selection of further imaging studies or diagnostic procedures. We have found the stains below useful in certain circumstances in assisting oncologists and others in managing patients who present with metastatic disease of unknown primary site. Differential staining patterns with antibodies to cytokeratin 7 (CK7) and cytokeratin 20 (CK20) are particularly useful (although the tables below represent a simplification, as not all tumors follow the algorithms.)¹ It is also important

to remember that the stains themselves have issues of sensitivity and specificity. Therefore stain results must be interpreted in the appropriate morphologic and clinical context. (Something that may be easier said than done.)

Rough CK7/20 Groups¹

CK7+/20+
Transitional (urothelial) Ca
Ovary Mucinous Ca
Pancreas/Bile Duct Ca (CK20+/-)

CK7+/20-
Lung AdenoCa
Ovary (Non-mucinous) Ca
Endometrium Ca
Breast Ca
Mesothelioma

CK7-/20+
Colorectal Ca
Merkel Cell Ca (CK7+/-)

CK7-/20-
Hepatocellular Ca
Lung Oat Cell Ca
Renal Cell Ca (CK7+/-)
Prostate Ca (both +/-)
Lung Squamous Ca

CA 125: Ovary, Gastrointestinal tract, ? Breast
Calretenin: Mesothelioma
Calcitonin: Medullary Ca of thyroid
Carcinoembryonic Antigen (CEA): AdenoCa (cf. mesothelioma)
Chromogranin/Synaptophysin: Oat cell Ca, carcinoid tumor, neuroendocrine Ca
Estrogen receptor/Progesterone receptor: Breast, Ovary, and Endometrium
Gross Cystic Disease Fluid Protein (GCDFP 15): Breast (very poor sensitivity!!!)
Leukocyte Common Antigen cocktail: Lymphoma
Placental Alkaline Phosphatase (PLAP): Germ cell tumors and some carcinomas
Prostate Specific Antigen/Prostatic Acid Phosphatase cocktail: Prostate
S-100/HMB-45: Melanoma
Thyroglobulin: Thyroid (follicular or papillary)

John D. Benson, MD

1. Rouse RV, Longacre TA. Immunohistologic Approaches to the Diagnosis of Neoplasms. American Society of Clinical Pathologists National Meeting. October, 1998.
2. Tot T. Adenocarcinomas Metastatic to the Liver. *Cancer* 85:171-7, 1999.
3. Carter TR. Personal communication.

**1999 ANTI-
BIOGRAM
DATA**

The Microbiology department is proud to publish the antibiogram data for 1999. Although there is a large quantity of data on the antibiogram, we hope that it is displayed in a form that is both readable and understandable. The organisms that have been published represent at least 20 specimens of an organism type. Cost data is being given as increments of \$25 per day on an intravenous basis. I would also like to thank at this time a group of individuals that were instrumental in accumulating, collating and displaying the data. These individuals include Dr. Kleeman from Clinical Microbiology, who is now retired; Duwayne Engman, Laboratory IT department, Joanne Kuszaj from the Intensive Care Unit, and Pat Brown from Cardiovascular Services. Our hope is that the 2000 antibiogram data will be published in the 3rd quarter of 2001.

John P. Sorge, MD

1999 Antibigram Data
(Percent Susceptible)

ORGANISM NAME	AMIKACIN	AMPICILLIN (OR AMOXICILLIN)	AMPICILLIN/SULBACTAM (4)	AZTREONAM	CARBENICILLIN (0) (NON-FORMULATED)	CEFZOLIN	CEFOPERAZONE (NON-FORMULATED)	CEFOTAXIME (1)	CEFOXITIN	CEFTAZIDIME	CEFTRIAXONE (1)	CEFUROXIME (2)	CEPHALOTHIN (3)(NON-FORMULATED)	CHLORAMPHENICOL	CIPROFLOXACIN (6)	CLINDAMYCIN	ERYTHROMYCIN (5)	GENTAMICIN	IMIPENEM (OR MEROPENEM)	LEVOFLOXACIN (6)	NITROFURANTOIN * (0)	NORFLOXACIN (0)(FOR LEVOFLOXACIN (6))	OFLOXACIN (6)(FOR LEVOFLOXACIN (6))	OXACILLIN	PENICILLIN	PIPERACILLIN	TETRACYCLINE (7)(FOR DOXYCYCLINE (7))	TICARCILLIN/CLAVULANIC ACID (4)	TICARCILLIN (NON-FORMULARY)	TOBRAMYCIN	TRIMETHOPRIM/SULFAMETHOXAZOLE	VANCOMYCIN				
CIT. FREUNDII COMPLEX	++	RR	RR	RR	RR	R	RR	RR	R	RR	RR	RR	RR	+				++	++	++	++	RR	RR			R	R	R	RR	++	+					
CITROBACTER DIVERSUS	++	RR	++	RR	R	++	++	RR	++	++	++	R	++	++				++	++	++	++	++	++			R	++	R	RR	++	++					
ENTEROBACTER AEROGENES	++	RR	RR	R	RR	RR	RR	RR	RR	R	RR	RR	RR	+				++	++		RR	+	+			RR	+	RR	RR	+	++					
ENTEROBACTER CLOACAE	++	RR	R	RR	RR	R	R	RR	R	R	RR	RR	RR	++				++	++		RR	++	++			R	R	R	R	++	+					
ENTEROCOCCUS FAECALIS (9)		++												RR							++	RR			++		RR							++		
ENTEROCOCCUS FAECIUM (9)		RR												R							+	RR			RR		RR								RR	
ESCHERICHIA COLI (8)	++	RR	RR	+	RR	RR	+	++	+	++	++	+	R	++				++	++		++	++	+			RR	R	R	RR	++	R					
KLEBSIELLA OXYTOCA (8)	++	RR	RR	++	RR	R	++	++	++	++	++	++	RR	+				++	++		+	R	++			++	+	++	RR	++	++					
KLEBSIELLA PNEUMONIA (8)	++	RR	R	++	RR	+	+	++	+	++	++	+	R	+				++	++		RR	+	+			+	R	+	RR	++	R					
MORGANELLA MORGANII	++	RR	RR	+	++	RR	R	++	++	++	++	RR	RR	R				++	R		RR	R	+			++	RR	++	++	++	++	R				
PROTEUS MIRABILIS	++	+	++	++	++	R	++	++	++	++	++	++	+	++				++	++		RR	++	+			R	RR	++	R	++	+					
PROVIDENCIA STUARTI	++	RR	RR	++	RR	RR	++	++	++	++	++	RR	RR	RR				RR	++		RR	RR	RR			R	RR	R	R	RR	RR					
PSEUDOMONAS AERUGINOSA	++	RR	RR	R		RR	R	RR	RR	++	RR	RR	RR	RR				R	+				RR	RR			++	RR	R	R	++					
SERRATIA MARCESCENS	++	RR	RR	R	RR		+	++	RR	++	++	RR	RR	R				R	++				RR	RR			RR	RR	RR	RR	R	+				
STAPH. AUREUS *															RR	RR									RR	RR		+					R	++		
STAPH. EPIDERMIDIS															R	RR									RR	RR		RR					RR	++		
STREP. PNEUMONIAE *** and **												RR			++	RR**				++**				RR	***										++	
INTRAVENOUS MAXIMUM DOSE (usual dose)	500mg IV q8h	2G IV q4h (1g IV q6h)	3G IV q6h (1.5G IV q6h)	2G IV q6h (1G IV q8h)	2G IV q8h (1G IV q8h)	2G IV q6h (1G IV q8h)	2G IV q6h (1G IV q8h)	2G IV q6h (1G IV q8h)	2G IV q8h (1G IV q8h)	2G IV q12h (1G IV q24h)	1.5G IV q8h (750mg IV q8h)			1g IV q6h	400mg IV q12h (200mg IV q12h)	900mg IV q8h (600mg IV q 8h)	1G IV q6h (500mg IV q6h)	120mg IV q8h	1G IV q6h (500mg IV q6h)	500mg IV q24h (250mg IV q 24h)				see LEVOFLOXACIN	2G IV q4h (1g IV q6h)	4mu IV q4h (2mu IV q4h)	4G IV q4h (3G IV q6h)	100mg IV q12h	3.1Gq6h				120mg IV q8h	varies	1G IV q12h	
COST (\$ = \$25) per day	Ⓛ	Ⓛ	2Ⓛ	5Ⓛ	Ⓛ	Ⓛ	Ⓛ	4Ⓛ	2Ⓛ	5Ⓛ	Ⓛ	Ⓛ	Ⓛ	2Ⓛ	Ⓛ	Ⓛ	Ⓛ	Ⓛ	17Ⓛ	Ⓛ			Ⓛ	Ⓛ	Ⓛ	Ⓛ	Ⓛ	Ⓛ	Ⓛ	Ⓛ	Ⓛ	Ⓛ	Ⓛ	Ⓛ	Ⓛ	
((+)=or<95% susceptible; (+)= or<90% susceptible; (R) >10% resistant; (RR) > 25% resistant																																				
Includes all isolates from inpatients, outpatients and office patients. Organisms, even multiple isolates on the same patient are counted (ie multiple cultures)																																				
*Oxacillin used to test Staph for Methicillin resistance **Clindamycin, erythromycin and levofloxacin should not be used totreat meningitis caused by S. pneumonia																																				
***For Streptococcus pneumonia and penicillin, R= 44%, I = 24%, S=32% (0) For use in treating urinary track infection only																																				
Groups of comparable agents that need not be duplicated in testing because interpretive results are usually similar and clinical efficacy comparable (drugs in bold are tested at Rex)																																				
(1) cefotaxime , ceftizoxime, ceftriaxone , cefixime (2) cefamandole, cefuroxime																																				
(3) cephalothin , cephapirin, cephradine, cephalixin, cefaclor, cefadroxil-some organisms may be susceptible to cefazolin , cefuroxime , cefidoxime, cefprozil and loracarbef (from urine) when resistant to cephaloth																																				
(4) amoxicillin/clavulanic acid, ampicillin/sulbactam , piperacillin/tazobactam, ticarcillin/clavulanic acid																																				
(5) azithromycin, clarithromycin, dirithromycin, erythromycin (6) ciprofloxacin , levofloxacin , ofloxacin																																				
(7) tetracycline , doxycycline, minocycline-some organisms may be more susceptible to minocycline and doxycycline than to tetracycline																																				
(8) Strains of Klebsiella and E.Coli that produce ESBLs may be clinically resistant to therapy with penicillins, cephalosporins or aztreonam despite apparent in vitro susceptibility to some of these agents																																				

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