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1605 Three Unexpected Diagnosis of Syphilis in Lymph Nodes, Oral Mucosa and Liver

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Background: Syphilis is a chronic infectious disease that is currently reemerging in Brazil, where 227,663 cases of acquired syphilis have been notified at the Brazilian Notifiable Grievance Information System (Sinan), from 2010 to June of 2016. It usually appears to pathologists in skin or genital specimens, but the infection may affect other sites that are not usually studied by histology.

Design: We present three cases of non-cutaneous syphilis lacking clinical suspicion of the disease, from a Brazilian university hospital. Case 1: a 26-year-old male with submental lymphadenomegaly measuring 3,0 cm. The biopsy of the lymph node showed follicular lymphoid hyperplasia with plasmocitosis. The patient was submitted to the Rapid Plasma Reagin test (RPR test), reactive at 1:32. Case 2: a 48-year-old female exhibiting a crusty, bleeding to the touch, growth of 2,5 cm on her lower lip. The biopsy showed chronic lymphoplasmacytic inflammation with histiocytic granulomas, combined with vascular proliferation. Her RPR test was reactive at 1:64. Case 3: a 63-year-old female with weight loss and hepatosplenomegaly. Liver biopsy showed chronic granulomatous inflammatory process with a central necrosis. Her RPR was reactive at 1:32. All three patients were submitted to the Fluorescente Treponemal Antibody Absorption test (FTA-ABS test), which resulted reactive.

Results: The three patients had a positive serology for syphilis. In case 1, the histological findings of lymphoid hyperplasia and plasmocitosis were compatible with secondary syphilis. In case 2 and 3, the histological findings of granulomatous and fibrous lesions with a central necrosis were compatible with lesions of tertiary syphilis, also known as gumma.

Conclusions: Pathological diagnosis of syphilis may be challenging without sufficient clinical information or suspicion, and may happen in association with another diagnose. In the light of the reemergence of the disease, it's important for a pathologist to be able to identify these nonspecific features and relate them to a possible syphilis infection.

1606 Association Between Histologic Findings in Lungs and Age in a Large Series of Autopsies in Fatal Dengue

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Background: Dengue is one of the most important arboviruses in the World in terms of morbidity and mortality. Currently, Brazil is responsible for 85% of the dengue cases in the South American continent (PAHO, 2016). There are few reports of the lung pathology in fatal Dengue according to age. In this work, we aim to identify the microscopic findings in the lung parenchyma of the studied cases, and establish patterns of pulmonary involvement according to the age groups in dengue.

Design: The autopsy findings of 126 patients from Ceará- Brazil, with confirmed dengue infection were evaluated. Viral isolation, detection of NS-1 viral antigen by ELISA, detection of anti-DENV IgM by ELISA or RT-PCR confirmed dengue virus infection. The following patterns were investigated: alveolar hemorrhage and edema; only alveolar edema; pneumonitis; bonchopneumonia; diffuse alveolar damage (DAD): acute pulmonary injury, exudative DAD, fibroproliferative DAD, and acute fibrinous and organizing pneumonia; and a pattern of previous lung disease. The patterns were defined through the predominant morphological findings greater than 50% of the sample. The age ranges were distributed: 0 to 15, 16 to 29, 30 to 59, and ≥ 60 years.

Results: The usual pattern was edema associated with hemorrhage (33.3%) or isolated edema (13.4%), followed by chronic interstitial pneumonitis (24.6%). The presence of the secondary infection with bronchopneumonia was of the order of 18.9%. Acute pulmonary injury fulfilling diffuse alveolar damage criterion was present in 13.3% of the cases. Histopathologic changes in a chronic lung disease prior to DENV infection were observed in three cases (2.38%). It was observed that in the age group of the child (0 to 15 years), pneumonitis was in a greater number of cases (64.5%), while bronchopneumonia and diffuse alveolar damage generally had a higher incidence in the range of 15 to 29 years (21% and 31.4%, respectively). Hemorrhage and edema were present in all age groups, but less frequently in children (9.6% bleeding and 3.2% edema).

Conclusions: The distribution of histopathological patterns according to the age groups shows frequency variation in the groups. The children present more pneumonitis than the other age groups, bronchopneumonia and diffuse alveolar damage generally had a higher incidence in the range of 15 to 29 years and the older group have more alveolar hemorrhage and edema.

1607 NGS-Based Pathogen Identification

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Disclosures:
Robert Schlaberg: *Consultant*, IDbyDNA; *Stock*, IDbyDNA

Background: Diagnosis of an infectious disease poses many challenges due to overlapping clinical symptoms seen across a wide range of pathogens. Current approaches rely on culture-based and pathogen-specific tests that have limited yield in many infectious syndromes. Diagnostic options are especially limited for formalin-fixed paraffin-embedded (FFPE) tissue that are widely used and often the only available specimens. We have previously described the use of hypothesis-free pathogen detection using metagenomic RNA sequencing (RNA-seq). Here we extend the utility of this approach to identify pathogens from archived FFPE blocks.

Design: 3 distinct cases were retrospectively selected to identify clinical scenarios where the patients had a known infection that was confirmed by culture or PCR. The cases were chosen to investigate bacterial, fungal, and viral pathogens and were selected from surgical pathology and/or autopsy cases. RNA was extracted from FFPE blocks. Total RNA was extracted, ribosomal RNA depleted, and cDNA libraries were sequenced using the Illumina NextSeq500 platform. Data analysis was performed using Taxonomer and Geneious software.

Results: Case 1 (bacterial) was selected based on a positive uterine culture for *Clostridium sordellii* from a 23-year-old female who developed severe sepsis and uterine necrosis two weeks after the placement of a progestin-releasing intrauterine device. Case 2 (fungal) was selected based on a positive lung culture for *Aspergillus fumigatus* from a 55-year-old female with a history of squamous cell carcinoma of the lung, status post chemotherapy and radiation, who developed a persistent pulmonary aspergilloma. Case 3 (viral) was selected based on a positive cytomegalovirus (CMV) quantitative blood PCR from a 68-year-old female with a history of autoimmune hepatitis who developed multisystem organ failure and disseminated CMV infection. RNA-seq and Taxonomer detected each of these pathogens in the respective samples. Taxonomer results were confirmed using Geneious by mapping reads against the reference sequence of *C. sordellii, A. fumigatus*, and Human herpes virus-5/CMV, respectively. Pathogen detection was consistent with culture or PCR results.

Conclusions: This study demonstrates proof-of-concept for hypothesis-free pathogen detection by RNA-seq using FFPE blocks. The potential utility of this methodology for cases with unknown pathogenic infections is very powerful and is an ongoing part of our efforts.

1608 Prevalence of Bacterial Contamination Among Excised Lymph Nodes and Implications for Molecular Testing

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Background: Lymph node excision specimens are routinely triaged for a multitude of special studies (e.g. flow cytometry, cytogenetics, molecular diagnostics, and microbial culture). The requirement for extensive hands-on processing predisposes these tissues to contamination by environmental microbes. The potential for such contamination has been under-emphasized in the era of molecular microbiology, enhancing the risk of falsely positive test interpretations. Here, we combine over 12 years of lymph node pathology and culture data to determine the frequency of microbial contamination among surgically excised lymph nodes and to identify the most common contaminating organisms.

Design: Using institutional databases, we analyzed 201 excisional lymph node biopsies, procured between 2005 and 2017, for which up-front tissue allocation included microbiological culture studies. We correlated positive culture results with histologic findings, including inflammatory tissue patterns and the results of microbiological stains (e.g. Gram, silver stain, AFB, etc.). Cases with positive culture results but discordant histology were flagged for further analysis.

Results: Nearly 30% (60/201) of all evaluated lymph node excisions

were associated with a positive culture result. Among those, the overwhelming majority (95%, 57/60) were not associated with infectious histologic findings (e.g. normal/benign appearing or overt involvement by lymphoma or metastatic carcinoma) and were considered contamination events. Coagulase-negative *Staphylococcus* (58%, 33/57) and *Propionibacterium acnes* (32%, 18/57) were, by far, the most frequently encountered contaminants. Others included potentially pathogenic *Citrobacter*, *Pseudomonas*, *Corynebacterium*, *Bacillus* and *Candida species*. All sites of tissue allocation (e.g. operating room, frozen section suite, pathology cutting room) were implicated, and no correlations between specific organisms and processing sites were apparent. Rates of contamination remained similar over the study period.

Conclusions: Culture-based techniques initiated at excision are increasingly being replaced by molecular testing of processed specimens. Our results indicate surprisingly high microbial contamination rates among a large collection of excised lymph nodes. Given that sequence-based studies may generate similarly high false-positive rates when used in the absence of concordant histopathological findings, more judicious application of these methods may be warranted.

1609 The Significance of Hyalinized Histoplasmomas in Surgical Specimens

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Background: *Histoplasma capsulatum,* the cause of the most common endemic mycosis in the United States, induces a granulomatous inflammatory response which resolves as a hyalinized nodule with a necrotic center. These old, hyalinized histoplasmomas are often found incidentally in surgical specimens, but their significance is unknown. We sought to clarify their significance by reviewing these specimens, assessing their location and reason for removal, and reviewing informative laboratory data to support or refute the presence of locally active or disseminated histoplasmosis.

Design: All surgical specimens at our institution with histopathologic evidence of *H. capsulatum* and hyalinized granulomas between January 1st 2006 and December 31st 2016 were included. We reviewed the reason for the surgery, as well as the location of the histoplasmoma. We reviewed the electronic medical record for data concerning fungal serologies, urine and blood antigens, and fungal cultures. These studies were assessed both near the time of the surgery (i.e. within 30 days) and long term (i.e. >30 days).

Results: 62 patients were included in the study. The primary surgical specimen was resected for cancer in 25/62 (40%) patients and 9/62 (15%) of the specimens were lymph nodes removed for suspicion/staging of cancer. 11/62 (18%) of the specimens were explants from heart or lung transplants. The remaining excisions, which did not contain cancer, included lung 12/62 (19%), and a variety of non-pulmonary sites 5/62 (8%). In 57/62 (92%) of the patients, the granulomas were located in lymph nodes, lung parenchyma, or both, with the remaining 5 (8%) in the spleen (2), liver, colon, or mediastinum. At least one diagnostic test for *H. capsulatum* was ordered on 25/62 (40%) of the patients within 30 days of the surgery. 1/19 (5%) cultures 4/12 (33%) serologies, 0/9 urine antigens, and 0/2 serum antigens were positive. Two additional seroconversions occurred at a date > 30 days after surgery. Subsequent active histoplasmosis did not occur in any of these patients.

Conclusions: Most hyalinized histoplasmomas were incidental findings and most clinicians did not pursue further diagnostic studies. The only corroborative laboratory findings included one positive culture and six positive serologic studies. These findings suggest that patients with old, hyalinized histoplasmomas have resolved or largely resolved the infection and likely do not need further laboratory studies or treatment.

1610 HPV Infection in Ocular Surface Squamous Neoplasia in HIV Seropositive Patients: Retrospective analysis of 49 Cases

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Background: Ocular surface squamous neoplasia (OSSN) encompasses conjunctival intraepithelial neoplasia (CIN) and squamous cell carcinoma (SCC) of the conjunctiva and cornea. Human papillomavirus (HPV) infection is a key risk factor for squamous neoplasia in other sites, including the cervix and head and neck. Epidemiologic studies have demonstrated significantly increased prevalence of OSSN in populations with high rates of HIV infection. However, the role of HPV infection and OSSN in this HIV+ population is unclear. Our hypothesis is that OSSN in HIV seropositive (HSP) patients is driven by HPV, as evidenced by immunohistochemical p16 expression. In this study, we retrospectively examined a large cohort of OSSN cases from HIV+ patients in Zimbabwe for HPV expression by p16 immunohistochemistry and by HPV16/18 PCR analysis.

Design: OSSN biopsies and resections were identified from 49 patients from Zimbabwe (28 female; 21 male). Ages ranged from 18-67 years old. Formalin fixed, paraffin-embedded tissue blocks from biopsies and resections were cut and stained with hematoxylin and eosin (H&E) and p16 immunohistochemistry. OSSN diagnoses were assigned by review of H&E slides, and p16 was classified as positive when the neoplastic cells showed diffusely strong nuclear and cytoplasmic staining. In parallel, nucleic acid material was extracted from these specimens, and HPV16/18 expression was assayed by quantitative RT-PCR.

Results: Nineteen patients (39%) were assigned the diagnosis of CIN and 30 (61%) were diagnosed with SCC. Forty-three (88%) patients were HIV-positive and 6 (12%) were HIV-negative. p16 immunoreactivity was detected in a minority of cases: 7 (37%) of CIN and 6 (20%) of SCC. For diagnoses of CIN, 5 (71%) of these p16 positive cases were in HIV-positive patients, and for SCC, all 6 (100%) of the p16 positive cases were in HIV-positive patients. All 49 cases were negative for HPV 16 and HPV 18 infection by PCR.

Conclusions: We found no association between HPV 16 or HPV 18 seropositivity and OSSN in our patient cohort. Furthermore, we found no statistically significant difference in p16 immunoreactivity in OSSN samples between HIV-positive and negative patients. Our study suggests that the increased incidence of OSSN in HIV+ patients in our cohort is not directly linked to HPV infection.

1611 Correlation of Fine Needle Aspirate (FNA) Cytology and Microbial Culture Results

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Background: FNA is an important tool for diagnosis of infectious disease, allowing for cytologic evaluation and ancillary studies. Rapid on-site evaluation (ROSE) allows for the opportunity to assess specimens for morphologic evidence of infection, such as inflammation or necrosis. This study aims to determine the correlation of FNA cytologic findings with culture results.

Design: We performed a search of cytology cases with corresponding culture results from 3/2014 to 4/2017. Cases were evaluated for predominant inflammatory pattern, necrosis, and culture results. Lymphocytes associated with lymphoid tissue or lymphoproliferative disorders were not considered inflammation. In cases with discordant cytology and culture results, the medical record was reviewed for immune status and clinical diagnosis. Positive cultures were considered contaminants if there were rare colonies, multiple organisms, or common contaminant organisms present, and if clinical suspicion for infection was low.

Results: 232 FNAs with corresponding culture results were identified. Cultures were positive in 64/232 cases. 48/64 cases were positive for bacteria, 12/64 for mycobacteria, and 4/64 for fungi. Inflammation and/or necrosis was identified in 59/64 (92%) of culture positive cases. In 5 culture positive cases with no inflammation or necrosis, patients were immunocompromised (CD4 <100) or cultures were considered contaminants. 5/36 cases with malignant diagnoses also had positive cultures, 2 of which were considered contaminants. Of the remaining 3 malignant cases, 2 showed necrosis and none showed inflammation. Two of these patients were severely immunosuppressed. Excluding cases from immunocompromised patients or with culture contaminants, we found a 100% negative predictive value for positive cultures when no cytologic signs of infection were seen. (Table 1).

Cases with positive bacterial cultures commonly showed neutrophilic inflammation (33/48). Cases with positive mycobacterial and fungal cultures mostly showed necrosis (8/12 and 3/4, respectively).

Specimen sites included lymph node (100), lung (48), soft tissue (34), breast (31), salivary gland (7), liver (5), thyroid (3), kidney (1), spleen (1), adrenal gland (1), and stomach (1).

Table 1. Comparison of cytologic findings with microbial culture results

	Cultures		
Cytology[a]	Positive	Negative	Total
Positive	57	99	156
Negative	0	69	69
Total	57[b]	168	225
[a] Positive cytologic findings include the presence of inflammation and/or necrosis			
[b] Cases with contaminant present in culture or severe immunocompromise (n=7) were excluded from analysis			

Conclusions: FNA with ROSE is a useful tool to triage and diagnose infectious disease when paired with ancillary testing. These findings suggest that submitting aspirate material with no significant inflammation or necrosis for microbial culture can be avoided in immunocompetent patients.

1612 Antimicrobial Resistance among Gram-Negative Bacilli causing Healthcare Associated Meningitis: A Single Tertiary Care Center Study

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Background: Healthcare-associated (HA) bacterial meningitis has very high mortality rates and rapid initiation of effective antimicrobial therapy is essential for its successful management. The frequent use of broad-spectrum antibiotics in the hospital setting contributes towards the emergence of multidrug-resistant strains; as a result, selection of appropriate antimicrobial agent(s) remains a significant challenge. In this study, we sought to analyze the antimicrobial resistance patterns in the gram-negative bacilli (GNB) causing HA meningitis.

Design: The laboratory record based cerebrospinal fluid culture reports of the patients diagnosed with GNB caused HA meningitis from 2009 to 2016 were collected. Data on demographic characteristics, infecting organism, and antimicrobial resistance were analyzed. Multidrug resistance was checked for the common bacterial isolates.

Results: A total of 788 culture positive cases of HA bacterial meningitis caused by GNB were recorded during this period (mean age±SD = 33.9±21.4, female = 40.5%). Overall, 55.8% cases were from the surgical wards, 21.5% from the medical wards, and 22.7% from the intensive care units. Acinetobacter species (36.7%), Klebsiella species (19.2%), Escherichia coli (17.1%), and Pseudomonas species (17.0%) were the most common isolates (**Figure 1**). **Table 2** shows the percentage resistance of these organisms to various antimicrobial agents. All organisms showed relatively high sensitivity to Cefoperazone-Sulbactam; Klebsiella species had high sensitivity to Tigecycline, Escherichia coli to Imipenem, and Pseudomonas species to Piperacillin-Tazobactam. Multidrug resistance rates were highest in the Acinetobacter species followed by Klebsiella species, Pseudomonas species and Escherichia coli (**Figure 2**).

Table 1. Antimicrobial resistance pattern (percentage resistance) of gram-negative bacilli causing healthcare-associated meningitis

	Acineto-bacter spp	Klebsiella spp	Escherichia coli	Pseudomo-nas spp	Others*
Amoxicil-lin-Sulbactam	63.31	81.43	73.13	76.00	72.73
Piperacil-lin-Tazobac-tam	66.19	61.38	36.36	23.26	52.70
Cefopera-zone-Sulbac-tam	7.09	54.68	21.71	32.00	38.89
Cefoxitin	92.96	80.00	89.47	73.68	80.00
Ceftazidime	95.24	93.48	82.17	66.92	83.58
Imipenem	80.94	45.64	23.13	47.29	43.66
Meropenem	85.36	55.86	33.59	58.73	46.05
Chloram-phenicol	79.28	43.20	41.03	70.48	50.00
Amikacin	82.80	79.02	79.53	50.76	67.57
Netilmicin	72.73	83.22	37.10	54.62	70.27
Ciprofloxacin	81.75	82.50	72.03	59.02	71.43
Tigecycline	25.00	4.55	50.00	85.71	0.00

All values are represented as percentage.

* Citrobacter spp, Enterobacter spp, Proteus Mirabilis and Providencia spp.

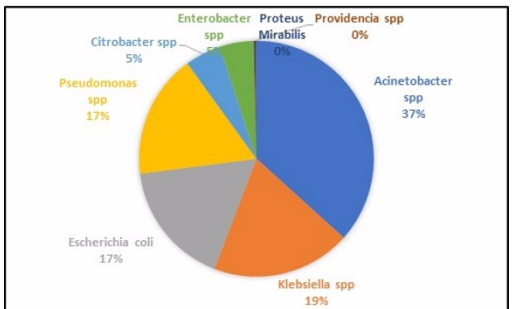

Figure 1: Gram-negative bacilli causing healthcare-associated meningitis

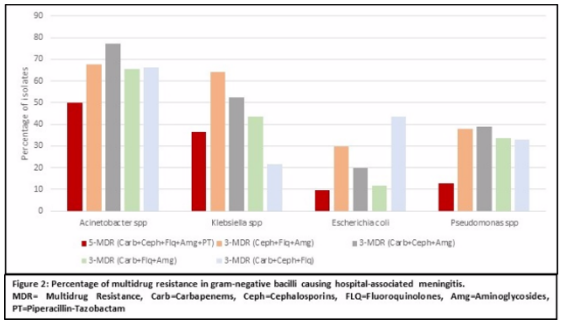

Figure 2: Percentage of multidrug resistance in gram-negative bacilli causing hospital-associated meningitis. MDR= Multidrug Resistance, Carb=Carbapenems, Ceph=Cephalosporins, FLQ=Fluoroquinolones, Amg=Aminoglycosides, PT=Piperacillin-Tazobactam

Conclusions: Resistance to the first line antibiotics and the prevalence of multidrug-resistant GNB remains high in the hospital setting. This study emphasizes the importance of continued surveillance of antimicrobial resistance and antibiotic stewardship programs to curb the emergence of multidrug-resistant strains.

1613 Helminth Infections Encountered in Anatomic Pathology: An 37-Year Institutional Experience Including 104 Cases

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Background: Although helminths are a frequent cause of infection worldwide, they are uncommonly encountered in anatomic pathology, particularly in the United States. For this reason, clinical suspicion for and pathologic knowledge of these organisms may be lacking in some cases. In this study, we examined our institutional experience at a large tertiary care facility with helminth infections to better outline cases which may be encountered in anatomic pathology services.

Design: A comprehensive list of broad as well as specific helminth related terms was used to search anatomic pathology reports within our institutional archives over a 37-year period. Pathology reports and available medical record data were reviewed for clinical and pathologic features.

Results: A total of 104 reports were identified with each case representing an individual patient. Within anatomic pathology, most cases were identified in surgical pathology (96.2%) with the remaining cases occurring in cytology (1.9%), autopsy (1.0%) and hematopathology (1.0%). The most common helminth identified was *Enterobius vermicularis*/pinworm in 51 cases (49.0%). The second most frequent diagnosis, with 13 cases (12.5%), were reported as unspecified helminth/parasitic worm. The additional organisms/diagnoses identified included *Dirofilaria* sp. (7.7%), *Taenia* sp. (6.7%), *Strongyloides* sp. (5.8%), *Schistosoma* sp. (4.8%), *Trichuris sp.* (3.8%), *Echinococcus* sp./hydatid cyst (2.9%), *Spirometra* sp./sparganosis (1.9%), cutaneous larva migrans (1.9%), *Ascaris* sp. (1.0%), *Trichinella spiralis* (1.0%) and visceral larva migrans (1.0%). Most helminths were encountered within the tubular gastrointestinal tract (67.0%). Nonconventional sites of involvement were frequently noted in *Dirofilaria* sp. cases with 62.5% (5/8) occurring outside the lung or skin. Additionally, while 46 cases of Enterobiasis were identified in appendectomy specimens, the remaining instances were appreciated in the cervix or other portions of the gastrointestinal tract. Of note, only 18.3% of cases had a clinical concern for helminth infection provided on the specimen requisition form.

Conclusions: Although helminth infections are largely considered to be of low incidence in anatomic pathology, a diverse variety of organisms may be encountered in tertiary care facilities. As these infections may not be suspected clinically, and may present in unexpected anatomic locations, knowledge of helminths in anatomic pathology settings is warranted.

1614 Universal PCR Optimization and Source Comparison

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Background: Microbial identification using "universal" polymerase chain reaction (uPCR) has become a popular method for investigating infection. uPCR uses primers specific for conserved regions of the 16sRNA unit of the prokaryotic ribosome to amplify the variable regions of the genome that can be matched to a known bacterium. Similarly, fungal uPCR uses broad range primers for 28s and Internal Transcribed Spacer sequence DNA for fungal identification. While uPCR is in use, there has been little discussion regarding the most appropriate specimen type that would be of the highest yield and greatest utility. Our study aims to clarify the most appropriate uses for

uPCR testing for our patient population, and the impact of results on patient management and antimicrobial usage.

Design: All cases sent to a reference laboratory for uPCR testing since 2012 at our institution were included. Clinical data was obtained via chart review of the electronic medical record. uPCR results from formalin fixed paraffin embedded (FFPE) tissues and fresh tissue/body fluids were compared with combined culture and histology results as the gold standard for diagnosis.

Results: 18 of 72 (25%) uPCR cases sent to a reference laboratory yielded positive results; 7 of 19 (36.8%) were from FFPE tissues and 11 of 53 (20.7%) were from fresh tissues/body fluids. While the highest percentage of positive uPCR cases were from FFPE tissues, fresh tissues/body fluids correlated better with true infection based on the gold standard (42.8% vs. 70.0% respectively). These differences are largely due to the relatively higher number of false negative uPCR results on the FFPE tissues and the greater total number of true negatives in the fresh tissue/body fluids. Thus, the negative predictive value for fresh tissue/body fluids is higher at 92.6% compared to 33.3% for FFPE tissues. Conversely, the positive predictive value for FFPE tissues was higher at 85.7% compared to 63.6% for fresh tissue/body fluids. The overall sensitivity and specificity of uPCR testing for all samples compared to conventional methods (culture and histology) were 54.2 and 89.6% respectively. In only 9 (12.5%) cases did the results of uPCR alter patient management by changing, starting, or stopping antimicrobial treatment.

Conclusions: Based on our results, we propose that uPCR should be performed on samples with microorganisms clearly visible and histologic evidence of an infectious process such acute or granulomatous inflammation.

1615 Data-Driven Diagnostic Algorithms for Invasive Fungal Infections: Start with Fungal PCR for High-Risk Patients

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Background: Invasive fungal sinusitis is highly morbid. Diagnosis relies on both microbiology and histopathology. Rapid initiation of optimal antifungal therapy decreases mortality and can minimize drug toxicity. This study was conducted to design a diagnostic testing algorithm based on assay performance and utilization. Three hypotheses were tested: 1) molecular fungal assays have shorter turnaround time (TAT) than culture; 2) molecular assays are more sensitive than culture; and 3) molecular assays performed on pathologist-selected FFPE blocks are as sensitive as fresh tissue without histologic review due to increased pre-test probability.

Design: Laboratory information system data for clinical fungal assays performed on paranasal sinus specimens 1/1/11 – 6/30/16 were identified by a custom script and analyzed with Kruskal-Wallis ANOVA and Fisher's Exact tests. Molecular assays included broad-range fungal and zygomycete group-specific PCR and Sanger sequencing, as well as *Aspergillus fumigatus*-specific real time PCR.

Results: We identified 1158 unique specimens from 789 patients. Of 922 cultures performed, 12.0% were positive vs 31.9% of 335 total PCRs ($p < 0.001$). Of 77 PCRs performed on FFPE specimens, 41.6% were positive vs 29.1% of 258 PCR assays performed on 258 fresh specimens ($p = 0.0507$); 71.6% were broad-range fungal PCR. TATs to first genus- or genus-species level identification were calculated from both time received and collection time. In laboratory TAT was 108.8 h for positive cultures and 92.2 h for all PCR assays ($p < 0.01$). *In-laboratory* TAT for PCR on FFPE vs fresh tissue was not significantly different. TAT from *collection* time was significantly longer for PCR performed on FFPE (median 314.0 h) compared to fresh (147.1 h, $p < 0.001$) or culture (113.5 h, $p < 0.001$). By the same metric, culture was not significantly faster than PCR on fresh tissue collected in-house.

Conclusions: Molecular fungal assays are 2.6 times more likely than culture to identify an organism and have slightly faster in-laboratory TAT. Thus, our proposed diagnostic algorithm prioritizes fungal PCR as a primary laboratory test for high-risk patients in conjunction with culture and histopathology and emphasizes rapid referral of FFPE samples containing fungus for fungal PCR. Longer pre-analytical lead times for FFPE specimens suggest opportunities to speed organism identification, improve antifungal selection, and possibly improve clinical outcomes.

1616 Identification of Tissue Invasive Fungi by 2D and 3D Light Sheet Microscopy

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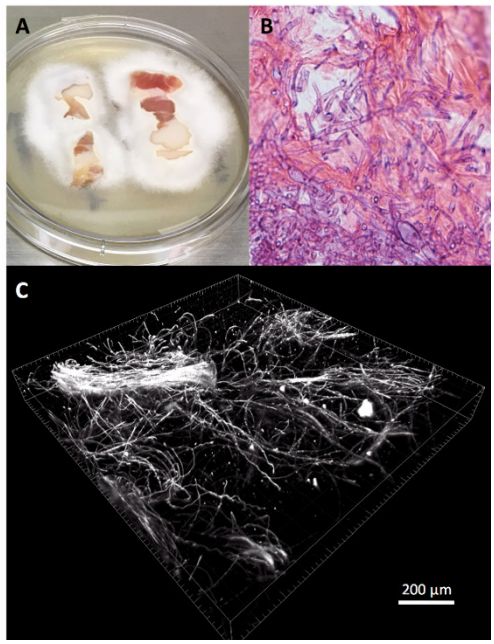
Background: Tissue invasive fungal infections (IFI) are a grave complication for immunosuppressed patients, have high morbidity and mortality, and require both surgical debridement and prompt, optimal antifungal therapy. Treatment decisions integrate histopathologic evaluation for tissue invasion and accurate organism identification. Histopathology has unacceptably high diagnostic error rates in identifying fungal genera; thus, complete diagnosis requires culture and/or molecular identification, requiring coordination and sharing of samples across laboratories. Light sheet microscopy (LSM) is an emerging, rapid fluorescence imaging tool with the capacity to identify histologic structures in 3D, hundreds of microns deep within tissue. LSM may be an ideal tool for identifying organisms in infected tissue, thus improving the histopathologic diagnosis of invasion as well as selecting regions with high organism burden for microbiologic identification.

Design: We developed an *ex vivo* model of IFI by inoculating full-thickness porcine abdominal skin with clinical isolates of two fungi with potential for systemic spread and significant lethality in neutropenic patients - *Mucor spp* and *Fusarium spp.* Infected tissue was fixed and stained with the fluorescent dyes Acridine Orange, which stains nucleic acids of both fungi and procine tissue, and Calcolfuor-KOH, which stains chitinous fungal cell walls. Tissue was imaged by LSM at multiple time points.

Results: Tissue invasion in the *ex vivo* culture system was confirmed on day 6 post-inoculation by histopathologic analysis of fixed specimens frozen in OCT and H&E stained. Fungal organisms invading tissue were detected by LSM using fluorescent dye staining in less than 5 min. LSM imaging demonstrated both the 2D and 3D architecture of infection. Image resolution was equivalent to a 20X - 40X objective lens.



Conclusions: Our results demonstrate 1) a successful *ex vivo* culture system to model IFI; 2) rapid, multispectral imaging to identify invasive fungal organisms using commonly pathogenic stains; and 3) potential diagnostic utility of LSM for rapid microbe detection in tissue, speeding appropriate triage for downstream testing; and 4) potential for LSM to elucidate 2D and 3D architecture of IFI.

1617 PREVIOUSLY PUBLISHED

1618 Utility of Frozen Section in the Identification of Invasive Fungal Rhinosinusitis

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Background: Fungal infections are an important cause of morbidity and mortality in immunocompromised hosts. Angioinvasive disease and dissemination leading to thrombosis, infarction, and tissue destruction carries a high mortality rate and early diagnosis is critical. Microbiologic recovery from tissue takes time and is not always successful, making tissue diagnosis the most accessible diagnostic tool. Frozen sections (FS) are used in some instances for timely diagnosis and monitoring of margins during surgical debridement but significant rates of false negatives have been reported. This study aims to evaluate the usefulness of FS in the diagnosis fungal infections.

Design: The surgical pathology archives of our institution from 2002 to 2017 were searched to identify cases in which FS was performed

for the evaluation of fungus. A total of 96 samples were identified from 40 patients, most of them from sinonasal and oral cavity. The FS diagnoses were compared with final diagnoses (FD). All FS diagnoses were rendered after H&E examination and FD were rendered after evaluation with H&E stained sections and in some cases, GMS and PAS stains. The results of concurrent culture results were recorded when available.

Results: An overall concordance of 87.5% was identified between FS diagnoses and FD. Twelve of 96 samples were discordant (12.5%). In 10 of the discordant cases, fungal organisms were not identified on FS and were detected on permanent section. Of these, 5 were invasive, one of them angioinvasive. The FD in 8 of these cases was achieved with the use of special stains. The two remaining discordant cases were false positives. Fifty-five cases were negative on both FS and FD and 29 cases were positive on both. FS diagnosis correctly identified 20/29 (69%) samples of invasive infection. When comparing FS diagnosis to the FD, including use of special stains, FS had a sensitivity of 74% and a specificity of 96%. Concurrent cultures were available for 60 cases with *Rhizopus* spp. being most commonly isolated followed by *Aspergillus* spp.

Conclusions: In this study, the sensitivity of FS diagnosis for the detection of fungal organisms is comparable with prior studies. False negative results can be a result of technical challenges such as frozen artifact, obscuring inflammation and necrosis, and sampling. FS is a useful tool for diagnosis of fungal infections including invasive fungal infections allowing for a rapid and early diagnosis.

1619 Microbiological Signatures Identified in Rosai-Dorfman Disease via Pan-Pathogen Array Technology

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Background: Sinus histiocytosis with massive lymphadenopathy or Rosai-Dorfman disease (RDD) is classically manifested by painless cervical lymphadenopathy. Due to the disease's prevalence in tropical regions, non-malignant course, and manifestation in patients of all ages in multiple organs, an infectious entity has been thought to be a precipitating factor in the illness. This hypothesis is further supported by the role of infectious agents in other lymphoproliferative disorders and early preliminary investigations in RDD. Our goal was to identify infectious agents in RDD using a metagenomics microarray technology (PMID:25227467) that screens for all viral, bacterial, fungal and parasitic infectious agents known to infect humans and understand their impact on the pathophysiology of the disease.

Design: Twenty cases of RDD were identified from multiple institutions using an Informatics Technology for Cancer Research supported tool. Representative tissue from these cases as well as control tissue was obtained. Pan-pathogen array technology with 60,000 probe sets to selected microorganisms was used to identify the microbial signatures associated with RDD cases and compared to controls representative of the tissue types affected by RDD.

Results: Overall detection of microbial signatures was increased in RDD compared to control tissue. Poxvirus, specifically deerpox virus, and Reovirus, specifically rotavirus strain J19, had the highest total hybridization among viral families. Additional viral signatures of papillomavirus and herpes virus were also identified. Within these families, HPV18, HPV6b, HPV112, HHV5, HHV4 and HHV6a had the highest hybridization values. Bacterial, fungal and parasitic signatures were also identified. No single agent was uniformly found across all cases, suggesting multiple infectious etiologies may be at play in RDD.

Conclusions: Understanding infectious etiologies that underlie Rosai-Dorfman disease is an important step in gaining a better understanding of this elusive disorder and its clinical course. This work suggests that infectious agents are more frequently present in RDD and provides an initial identification of the specific microorganisms seen. Further investigation into the agents underlying RDD may provide important diagnostic and therapeutic targets.

1620 PAX-8 Antibody as a Useful Adjunct in Detection of Cystoisospora in Formalin Fixed Paraffin Embedded Tissue: A Study on Cholecystectomies with Cystoisospora Infection

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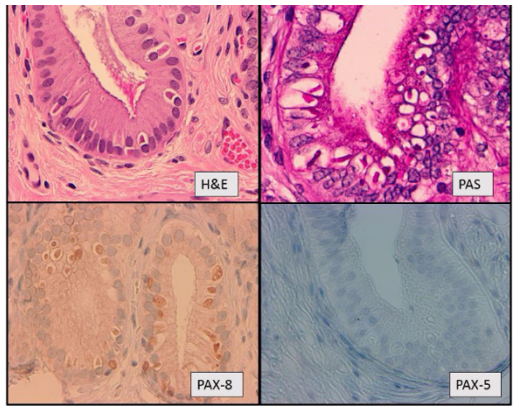
Background: *Cystoisospora belli* is an obligate intracellular coccidian parasite which can cause chronic life threatening diarrhea in immunocompromised. In immunocompetent patients, it causes a self-limited diarrheal illness. Recently, it has been detected in gallbladders of immunocompetent patients including our study on 1500 consecutive cholecystectomies presented at USCAP 2017. Studies on gallbladder have suggested a possible etiologic role in biliary dyskinesia. Special stains like PAS-D in conjunction with H & E are used to identify the organism. However, the distribution of the organism can be very focal. Organism specific immunohistochemistry is available only for research purposes. CD117 staining of Giardia lamblia has been reported recently by Sinelnikov et al. In the process of validating PAX-8 stain in our lab, we noted positive staining of Cystoisospora with PAX-8 antibody. To further substantiate our finding, immunohistochemical expression of PAX-8 and PAX-5 were analyzed on 19 cholecystectomy specimen with Cystoisospora infection.

Design: Formalin fixed paraffin embedded (FFPE) sections of 19 cholecystectomies with Cystoisospora infection and 10 control cases of chronic cholecystitis were analyzed for expression of PAX-8 and PAX-5. PAX-8 (mouse monoclonal, clone MRQ-50, Cell Marque) and PAX-5 (rabbit monoclonal, clone EP-156,Cell Marque) were used.

Results: Eighteen patients were immunocompetent while one was immunocompromised. Three cases were excluded due to lack of representative organism on immunohistochemistry slides. Out of the 16 remaining cases, 11 were positive for PAX-8 (68.8 %) and 5 were negative (31.2%). The organism demonstrated diffuse granular staining. All cases were negative for PAX-5.



Conclusions: Immunohistochemical staining with PAX-8 antibody can be a useful adjunct in detection of Cystoisospora organisms in FFPE sections. The better contrast provided by the immunostain can help in the screening and detection under lower power and may have added advantage over PAS-D staining especially when the organism is focally present.

1621 Unexpectedly High Prevalence of Cystoisospora belli in Acalculous Gallbladders of Younger Patients

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Background: A recent review of the NY State Planning and Research Cooperative System Longitudinal Administrative Database (spanning 1995-2013) revealed that indications for cholecystectomy have changed dramatically. Calculous cholecystitis has declined (-20% p<0.0001), while other indications increased: acalculous cholecystitis (+94%; p<0.0001), biliary dyskinesia (331.74%; p<0.0001), and biliary colic (+55%; p=0.0013). There has been a concomitant shift toward operating on a younger patient population. The etiology for these changes in the clinical context and patient population undergoing cholecystectomy remains unknown.

Given the recently reported association of *Cystoisospora belli* (Cb) infection with acalculous disease of young, we undertook a single institution retrospective review of cholecystectomies lacking stones by gross examination in patients less than 30 years of age.

Design: Archival slides from 219 cholecystectomies without gallstones were reviewed, 29 were excluded due to autolysis of greater than 50% of the biliary epithelium. 190 well-preserved cholecystectomies without gallstones were scored for the presence/absence of parasitophorous vacuoles characteristic of Cb. Location of the vacuoles (cystic duct vs other) was recorded. Correlation of the presence of Cb with patient factors was determined by Fisher Exact Test.

Results: The 190-patient cohort comprised 136 females and 54 males (mean age 18.8 yrs; range <1 to 29). Of the entire cohort, 19 (10%) were positive for Cb infection, ranging in age from 7 to 29 years of age.

Of the 54 males, 10 (18.5%) were positive for Cb; of the 136 females, 9 (6.6%) were positive. Cb infection was positively associated with male sex (p=0.028).

Conclusions: Cb infection is more prevalent amongst immunocompetent humans than previously recognized. Further studies are warranted to determine whether the presence of Cb in acalculous gallbladder disease represents an etiologic agent, or a consequence of factors predisposing to acalculous gallbladder disease.

1622 Histologic Characteristics of Human Intestinal Spirochetosis in Operatively Resected Specimens

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Background: Human Intestinal Spirochetosis (HIS) is an infectious disease of the large intestine caused by *Brachyspira* species bacteria. The histologic diagnosis of HIS is usually established by finding the "fringes" on the colonic surface epithelium in biopsy specimens, although the histologic characteristics, especially beneath the colonic mucosa, have not been elucidated.

Design: To examine the histologic characteristics of HIS in the present specimens, we reviewed operatively resected, colectomy or appendectomy specimens obtained in three consecutive years at a medical center. HIS was diagnosed histologically by finding "fringes". Immunohistochemical study using anti-*Treponema pallidum* antibody, which cross-reacts with *Brachyspira,* was additionally performed for the HIS cases.

Results: A total of 424 (M:F=242:182; median age, 61years; 12-93 years) colectomy and/or appendectomy cases were examined in the present study, and the five cases (1.2%) diagnosed as having HIS were all men (2.1% of men-cases). Three HIS cases [1.1% of 266 colectomy cases (2.0% of 151 men-cases)] were colectomy cases for cancers, and the other two [1.3% of 158 appendectomy cases (2.2% of 91 men-cases)] were appendectomy cases for acute appendicitis. Not all sections in the large intestine exhibited the diagnostically important "fringes". In the immunohistochemical study, immunopositive spiral organisms were located not only on the surface epithelium but also within the mucus, and in the lumens of crypts, and strongly immunopositive materials were also observed within the lamina propria of the mucosa, although the degree of this bacterial presence differed among sections even in the same case. Such spiral organisms could be found within the mucus and lumens of crypts of ileal sections, where "fringes" had not formed. Strongly immunopositive materials were usually limited to within the mucosal layer, but were also observed beneath the mucosal layer near the cancer-invasion sites and also in the dissected lymph nodes.

Conclusions: The present study suggests: 1) heterogeneous distribution of "fringes" in the large intestine, 2) detection of *Brachyspira* not limited to the large intestine, and 3) in cancer-laden HIS patients, *Brachyspira* or its derivatives travel to beneath the mucosal layer of the intestinal wall and even to the regional lymph nodes.

1623 Pretreatment Molecular Determination of Helicobacter pylori Clarithromycin Resistance Mutations Predicts Risk of Laboratory Confirmed Eradication Failure

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Background: *Helicobacter pylori* (HP) infection remains one of the world's most common chronic bacterial infections and predisposes to gastric malignancy. Despite increasing antibiotic resistance and treatment failure, clarithromycin triple therapy remains the primary empiric first-line treatment. Since there is limited recent data in the United States, we sought to determine the prevalence of resistance mutations and the impact on eradication failure in a well-characterized patient population.

Design: A retrospective cross-sectional cohort study was performed to evaluate patients in San Diego County diagnosed with HP infection. During a 2-year period, 130 patients were identified who met the following inclusion criteria: underwent gastric endoscopic biopsy that was found to be positive for HP, received a clarithromycin based antibiotic treatment regimen post biopsy, and had laboratory confirmation of eradication status after treatment. Biopsy material was evaluated by molecular analysis to determine the presence of clarithromycin resistance mutations via PCR then sequencing of HP 23S rRNA domain V.

Results: 130 patients diagnosed with HP via gastric biopsy were treated with a clarithromycin based treatment then underwent a laboratory confirmation of eradication status. Clinical laboratory confirmation included HP stool antigen testing (N=102), repeat endoscopic biopsy (N=30), or urease breath testing (N=3). 5 cases were tested by more than one modality and were concordant. Molecular analysis identified mutations in 26.9% (35 of 130) of patients, including the following: 2143A>G (N=30, 85.7%), and A2142>G (N=4, 11.4%) and both (N=1, 2.86%). 12.5% (12 of 96) of patients with wild-type 23S rRNA failed therapy, while 45.7% (16 of 35) of patients harboring a clarithromycin resistance mutation in 23S rRNA failed therapy, resulting in a 3.6-fold higher rate of eradication failure among mutation carriers (p<0.0001).

Conclusions: HP clarithromycin resistance mutations are common and represent a strong, significant predictor of increased risk of laboratory confirmed treatment failure in this study. The findings demonstrate that although a minority of patients harbor clarithromycin resistance, these patients have a markedly increased risk of treatment failure and nearly one half will fail therapy. Since pretreatment HP resistance testing accurately identifies these patients, broad implementation of such testing has the potential to decrease overall rates of treatment failure in the population.

1624 Histological Features Predictive of Positive 16S rRNA Sequencing in Bacterial Endocarditis FFPE Specimens

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Background: Infective endocarditis causes significant morbidity and mortality in individuals with native and prosthetic heart valves. Appropriate antibiotic selection relies on the identification of a specific causative organism; however, blood and valve tissue cultures are often negative, due to prior antibiotic treatment or involvement by a fastidious organism, or are not submitted due to lack of clinical suspicion. 16S rRNA sequencing of formalin-fixed paraffin-embedded (FFPE) tissue has been effectively utilized in these scenarios, although no histologic guidelines currently exist to determine which cases should be referred for testing.

Design: Endocarditis resection specimens and controls from a five-year period were histologically reviewed for the presence of microorganisms by Gram and methanamine silver stains (MSS). Representative cases associated with a variety of organisms by blood and valve cultures were selected for sequencing using a clinically validated in-house assay targeting the V1/V2 region of the 16S rRNA gene.

Results: In all valves with acute inflammation (n=68), 16S rRNA sequencing identified a specific pathogenic organism in 33 cases (49%), and in 0/10 (0%) controls. Predominantly Gram positive cocci (n=28) and occasional Gram negative bacilli (n=3) were molecularly detected. In 33/58 (57%) cases with organisms identified by MSS and 28/43 (65%) cases with Gram positivity 16S sequencing was positive. Decreased sensitivity of 16S was associated with histological evidence of antibiotic treatment effect (28%, 7/25 cases) and decalcification prior to tissue processing (29%, 4/14 cases). Molecular identifications were concordant with blood culture results in 26/29 cases (90%), and a positive 16S result was obtained in 16/34 (47%) cases with negative valve cultures.

Histological Findings	16S Positive (n)	Total (n)	%
Gram+ MSS+ AI+	28	43	65
Gram- MSS+ AI+	5*	15	33
Gram- MSS- AI+	0	10	0
Gram- MSS- AI-	0	10	0

*Includes 3 cases of Gram negative bacilli (*Cardiobacterium hominis*, *Haemophilus parainfluenzae*, and *Streptobacillus moniliformis).*
Abbreviation: acute inflammation (AI)

Conclusions: Molecular testing of FFPE tissue can produce clinically useful data in a high percentage of cases when histological criteria are used for screening. In this retrospective cohort of real world cases, positive results were most likely to be obtained with the presence of acute inflammation and definitive organisms detected by Gram and MSS stains. Lack of visible organisms, presence of antibiotic treatment effect, and specimen decalcification were significantly less likely to result in a positive identification, and alternative samples should be tested whenever possible.

1625 The Utility of Third Sputum Collection in the Workup of Pulmonary Tuberculosis: A One-Year Retrospective Analysis in a Large Urban Safety-Net Hospital

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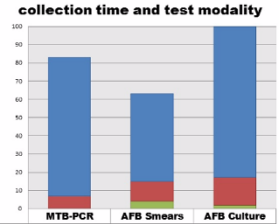
Background: Identification of patients with active pulmonary tuberculosis (PTB) is a major public health concern. However, ruling out PTB has traditionally required the collection of three sputum samples collected at 8-hour intervals, resulting in at least 1 hospital day and airborne precautions. Although two negative Xpert MTB-Rif nucleic acid amplification (PCR) assay results may be used to remove a patient from airborne precautions in less than 1 hospital day, collection of a third sputum specimen for culture continues to be recommended.

Design: We investigated the diagnostic yield of the third sputum collection. A retrospective analysis of consecutive PTB workups over a 1-year period in a large urban safety-net hospital in the United States was performed.

Results: From July 2015 to June 2016, 873 consecutive unique patients underwent a PTB workup. There were 46 culture confirmed PTB cases (incidence rate = 5.4%; 3/46 were HIV positive). *Mycobacterium tuberculosis* complex (MTBC) was isolated from at least one of the first two specimens sent in 45/46 patients (97.8%). Importantly, there were no cases where two MTB/Rif tests were negative but the third AFB smear result was positive. A single patient (2.2%) had MTBC isolated after 7 weeks of incubation from the 3rd specimen only (i.e. two negative specimens followed by a positive third specimen). The patient was HIV-positive with chronic cough and a right upper lung lobe consolidation. Among non-HIV-positive patients (43/46), there were no cases of MTBC isolated from the third sputum culture only. (See **Figure 1**).

Figure 1. Diagnostic sensitivity by collection time and test modality



Conclusions: The third AFB-smear did not identify any active or communicable PTB cases in the context of negative MTB/Rif results. Submission of a third specimen for culture identified only one case of active PTB in a HIV patient with a high clinical suspicion for PTB. The impact of third sputum collection on hospital length of stay was significant, resulting in at least an extra hospital day in the 827 patients who did not have PTB. Our data is in keeping with the current recommendation that two negative MTB/Rif tests (or two specimen collections) is sufficient to rule out communicable TB and active PTB in cases of low clinical suspicion. Additionally, our data supports that collection of two sputum specimens may be sufficient for the PTB workup in immunocompetent patients.

1626 Routine Testing for Anaerobic Bacteria in Shoulder Cultures Improves Recovery of Clinically Significant Propionibacterium Acnes

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Background: In the past 20 years, *Propionibacterium acnes* (*P. acnes*) has been associated with postoperative shoulder arthritis based on sporadic case reports followed by clinical studies. *P. acnes* is a fastidious organism requiring prolonged, anaerobic culture.

Design: In our institution, before 2014, anaerobic bacterial cultures included a pre-reduced Brucella blood agar (BBA) medium for cultures from normally sterile body sites, or three pieces of anaerobic media for other body sites, which were examined daily from day 2 to day 5. In early 2014, our standard practice changed so that anaerobic media were held for 10 days for shoulder specimens or if the physician noted *P. acnes* as the suspected pathogen. To reduce the chance of contamination, if no growth after 3 days, the media were placed into anaerobic bags until final examination on day 10 (**Figure**). We assessed joint cultures submitted over 24 months (Jan 2012 to Dec 2013) before the implementation, and 33 months (Jul 2014 to Mar 2017) after it.

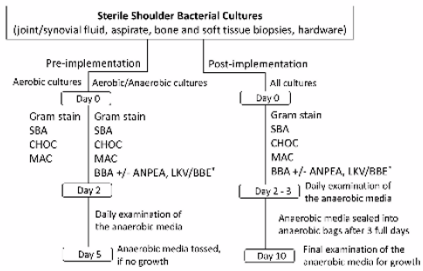
Results: In the pre- and post-implementation years, 2872 cultures (1401 patients) and 4374 cultures (2111 patients) from five joint sites (shoulder, elbow, acetabular/hip, knee, and ankle) were received, respectively, of which 46 of 199 (23.1%) and 171 of 552 (31.0%) shoulder cultures were positive, respectively (**Table**). When comparing the pre- and post-implementation culture results by sub-category, a statistically significant difference is observed in positive shoulder cultures (p=0.036, OR 1.493 [95% CI 1.035-2.166]), as well as in *P. acnes* identified in shoulder cultures (p=0.010, OR 2.589 [95% CI 1.208-5.430]), but not in overall anaerobes in shoulder, *Staphylococcus* spp. in shoulder, or *P. acnes* identified in non-shoulder cultures. Overall, *P. acnes* was more likely to be identified in the shoulder joint compared to other joints (p<0.0001 for both pre- and post-implementation years, not shown in table) and was exclusively recovered on anaerobic media, i.e., BBA and ANPEA. The majority (>95%) of anaerobic organisms were recovered on anaerobic media. Chart review of patients with positive shoulder cultures in the pre- and post-implementation years showed no statistically significant difference in characteristics such as gender, race, history of prior procedures, indwelling hardware, or concurrent bloodstream infection.

Number of Cultures	Data by Pre- and Post-implementation		p[a]
	Pre- (24 months)	Post- (33 months)	
Total	2872	4374	
Total positive	641	1189	
Shoulder	199	552	
Shoulder positive	46	171	0.036[b]
Non-shoulder	2673	3822	
Non-shoulder positive	595	1018	<0.0001[c]
P. acnes - shoulder	8	54	0.010[b]
Other Propionibacterium spp. – shoulder	0	3	
Overall anaerobes – shoulder	12	57	0.085[b]
Staphylococcus spp. – shoulder	25	75	0.808[b]
P. acnes – non-shoulder	3	13	0.078[c]
Other Propionibacterium spp. – non-shoulder	9	3	

[a] p values that are statistically significant (<0.05) in bold type

[b] Fisher's exact test, pre- vs. post-implementation shoulder cultures

[c] Fisher's exact test, pre- vs. post-implementation non-shoulder cultures



Abbreviations: SBA – Sheep Blood Agar; CHOC – Chocolate agar; MAC – MacConkey Agar; BBA – Brucella Blood Agar; ANPEA – Anaerobic Phenyl-Ethyl-Alcohol Agar; LKV/BBE – Laked Blood with Kanamycin Vancomycin/Bacteroides Bile Esculin Agar
* Additional ANPEA and LKV/BBE plates were employed for specimens with a high likelihood of contamination

Conclusions: The implementation of routine 10-day anaerobic cultures independently improved the recovery rate for *P. acnes* from shoulder specimens.