



Top Recent Publications in Infectious Disease

(that you may have missed while battling COVID and monkeypox)

Christopher J. Graber, MD MPH FIDSA

Professor of Clinical Medicine, David Geffen School of Medicine at UCLA
Medical Director, Antimicrobial Stewardship Program, VA Greater Los Angeles
Program Director, UCLA Multicampus Fellowship in Infectious Diseases

November 5, 2022

In Memoriam: Nirav Patel, MD

- Graduated from CSMC/VA/OVMC ID Fellowship in 2011 after completing critical care fellowship
- Chief of Staff at SSM Health Saint Louis University Hospital and University Medical Center in New Orleans
- IDSA Journal Club panelist 2013-22



The Winners

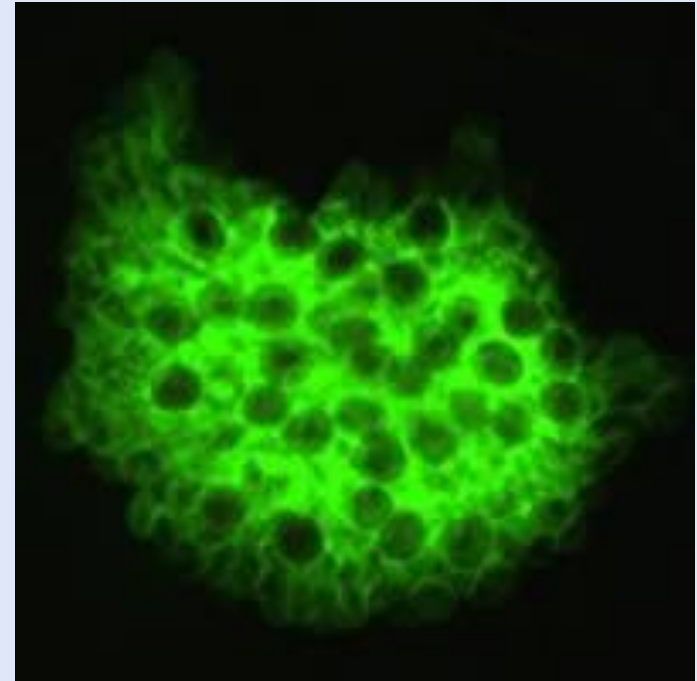
(courtesy of IDSA Journal Club)



- PJP prophylaxis for patients receiving rituximab
- β -lactams before vancomycin
- Dental procedures and PJI risk
- INSTIs and diabetes risk (plus possible mechanism of metabolic effects of INSTIs)
- PET scans for endocarditis
- Meningitis B vaccine vs. gonorrhea
- Gram stain guiding empiric VAP treatment
- Tele-ID consultation
- Duration of antibiotic treatment post-DAIR
- Immunogenetics of disseminated coccidioidomycosis

Pneumocystis Prophylaxis in Immunocompromised Hosts

- Typically recommended in most cases of impaired cell-mediated immunity (iatrogenic or otherwise)
- Need for prophylaxis in the setting of B-cell depletion (as with rituximab) is less clear



Primary Prophylaxis for *Pneumocystis jirovecii* Pneumonia in Patients Receiving Rituximab

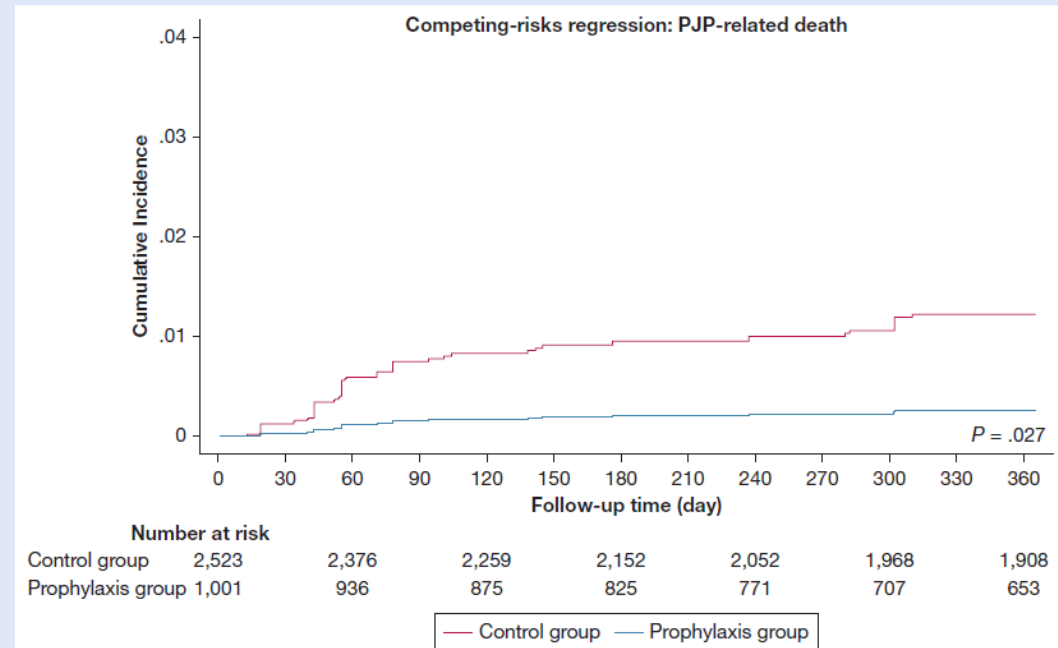
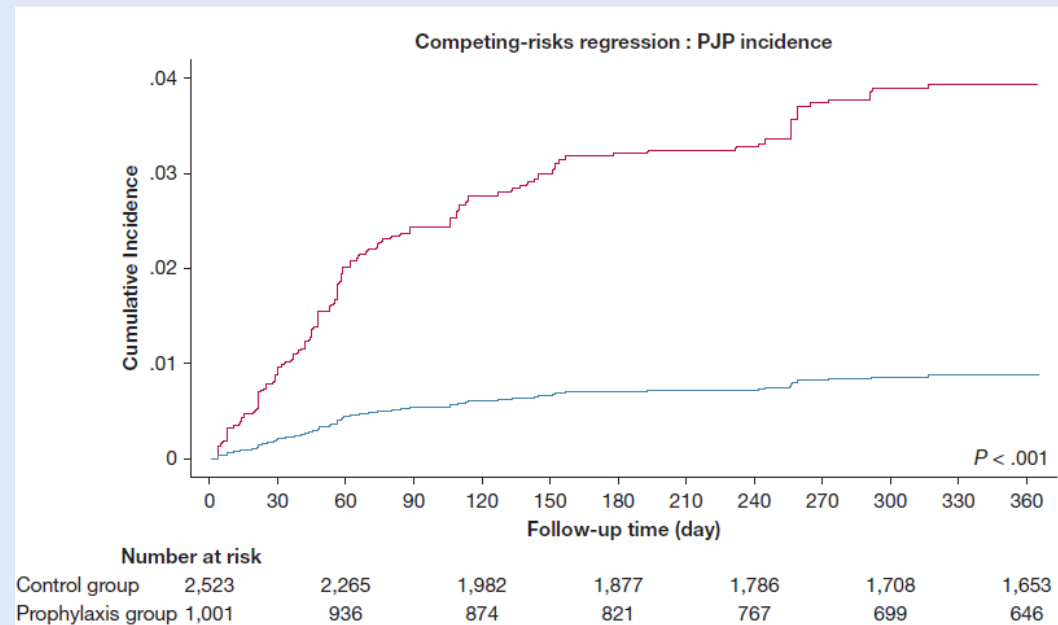


Jun Won Park, MD; Jeffrey R. Curtis, MD; Kang Il Jun, MD; Tae Min Kim, MD; Dae Seog Heo, MD; Jongwon Ha, MD; Kyung-Suk Suh, MD; Kwang-Woong Lee, MD; Hajeong Lee, MD; Jaeseok Yang, MD; Min Jung Kim, MS; Yunhee Choi, PhD; and Eun Bong Lee, MD



- Retrospective study of 3524 patients receiving rituximab at single center in South Korea from 2002-18
 - 1001 received TMP-SMX prophylaxis within 28d of starting rituximab
 - 2269 never got prophylaxis; 254 started after 28d
- Inverse probability treatment weighting, time-varying analysis

- 92 total PJP infections at 1 y
- TMP-SMX prophylaxis associated with HR 0.20 for PJP incidence overall and HR 0.01 in time-varying analysis (only 1 pt got PCP while on TMP-SMX)



Safety of TMP-SMX prophylaxis

- 18.1 adverse drug events related to TMP-SMX per 100 person-years, most mild-to-moderate in severity
- 10 total severe ADRs (6 cases of pancytopenia; 1 SJS) → number needed to harm 101
- Number needed to prevent one PJP infection: 32

Empiric combination vancomycin/ β -lactam therapy

- Theoretical advantages to giving the β -lactam first
 - Faster administration (get at least some drug aboard faster in patients with single IV access)
 - Gram-negative pathogens more likely to cause systemic inflammatory response?
 - A lot of Gram-positive pathogens are going to be covered with the β -lactam anyways
 - Faster killing??

Administration of a β -Lactam Prior to Vancomycin as the First Dose of Antibiotic Therapy Improves Survival in Patients With Bloodstream Infections

Joe Amoah,¹ Eili Y. Klein,² Kathleen Chiotos,³ Sara E. Cosgrove,⁴ and Pranita D. Tamma¹; for the Centers for Disease Control and Prevention's Prevention Epicenters Program

¹Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; ²Department of Emergency Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; ³Department of Anesthesia and Critical Care Medicine, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA; and ⁴Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

- Retrospective cohort of 3,376 patients from 5 JHU-affiliated hospitals treated with a β -lactam-vancomycin combination <6h of blood culture collection and found to be bacteremic with a Gram-positive or Gram-negative organism from 7/2016-6/2020

Study Characteristics

- Inverse probability of treatment weighting accounting for:
 - Demographics
 - Comorbidities
 - Illness characteristics (including time from emergency department arrival to first dose of antibiotics)
- 2,685 (79.5%) patients received β -lactam first
 - 47.9% piperacillin-tazobactam
 - 42% cefepime
 - Most common causes of bacteremia:
 - *Staphylococcus aureus* (22.5%, 42.3% of which was methicillin-resistant)
 - *Escherichia coli* (20.8%)
 - *Klebsiella pneumoniae* (13.9%)

Study Findings

- Administration of β -lactam before vancomycin associated with lower 7-day mortality in weighted regression analysis
 - Adjusted odds ratio (aOR) of 0.48 (95% CI, 0.33-0.69)
 - Results for 48-hour mortality were similar (aOR, 0.45 95% CI, 0.24-0.83)
- In patients with methicillin-resistant *S. aureus* bacteremia, aOR for 7-day mortality among patients who received the β -lactam first was 0.93 (95% CI, 0.33-2.63)

Simple intervention with likely potential benefit!

Dental Procedures and Risk for Prosthetic Joint Infection

- Long-standing recommendation by the American Academy of Orthopaedic Surgery to recommend antibiotic prophylaxis for dental procedures for patients with prosthetic joints
- Guidelines have evolved over the past few years:

1. The practitioner might consider discontinuing the practice of routinely prescribing prophylactic antibiotics for patients with hip and knee prosthetic joint implants undergoing dental procedures.

Grade of Recommendation: Limited



Christopher Graber

@glavaidguy



Got an e-consult from PCP to explain to patient with THA undergoing dental cleaning why he wasn't filling outside prescription for amox that his orthopedist recommended. Turns out orthopod is my wife. Stewardship starts at home!

5:04 PM · Feb 28, 2019 · Twitter for iPhone

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Tweet your reply

Reply



Monica Mahoney @mmPharmD · Mar 1, 2019



Replying to @glavaidguy

"So, honey, how was your day? Prescribe any inappropriate antibiotics? ... no?"

EXHIBIT AMOX!"



1



2





Original Investigation | Orthopedics

Analysis of Prosthetic Joint Infections Following Invasive Dental Procedures in England

Martin H. Thornhill, MBBS, BDS, PhD; Annabel Crum, BSc; Saleema Rex, BA, MSc; Tony Stone, BSc; Richard Campbell, MPH; Mike Bradburn, MSc; Veronica Fibisan, PhD; Peter B. Lockhart, DDS; Bryan Springer, MD; Larry M. Baddour, MD; Jon Nicholl, DSc

- Antibiotic prophylaxis for dental procedures in patients with prosthetic joints is not recommended by NHS
- Study identified 9427 admissions for late (>3mo after implantation) prosthetic joint infections and examined frequency of invasive dental procedures in the 3mo prior to PJI admission as compared to the 12mo prior

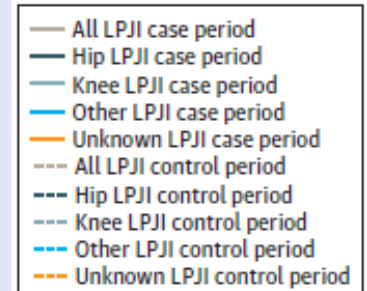
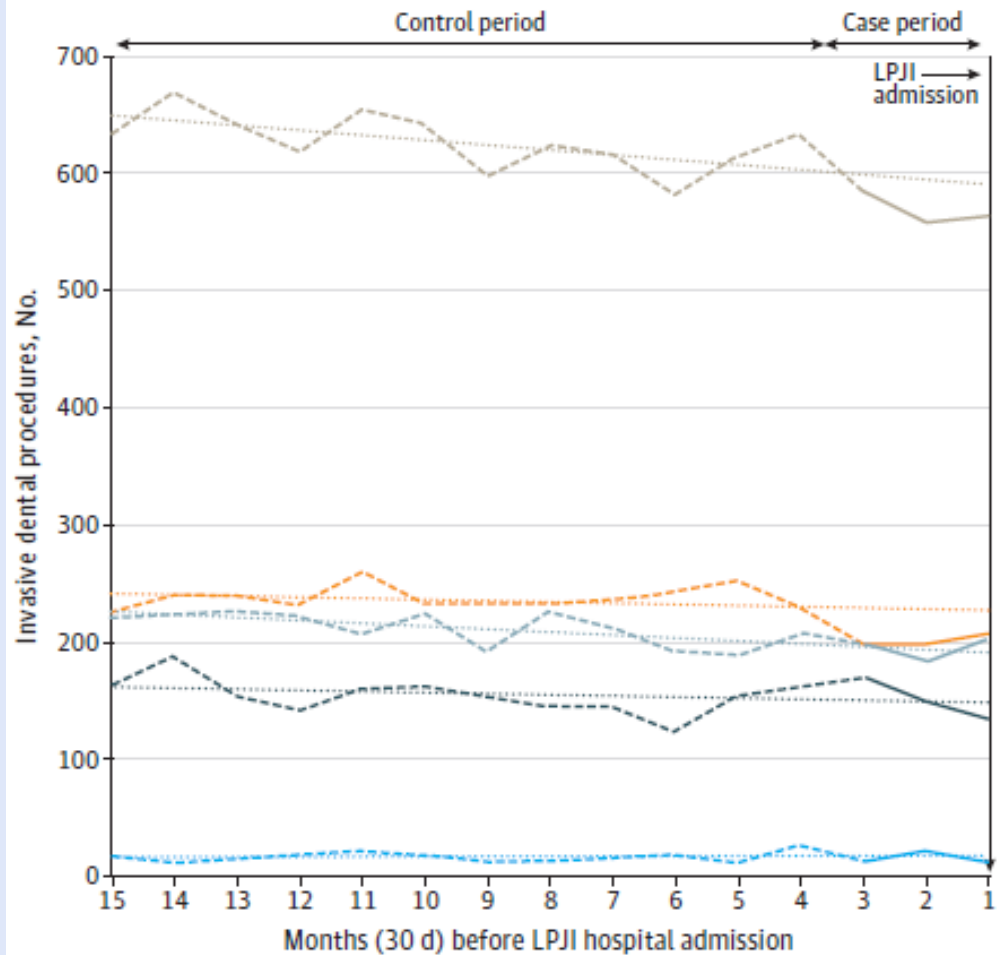
Study Characteristics

- Invasive dental procedure definition:
 - Tooth extraction
 - Scaling
 - Endodontic procedure
- Joints involved:
 - 25.3% hip
 - 33.6% knee
 - 2.8% other
 - 38.4% unknown
- Infecting PJI organisms:
 - 53.3% staphylococci
 - 9.4% oral streptococci
 - 4.9% other streptococci
 - 19.9% other organisms
 - 12.5% mixed

Study results

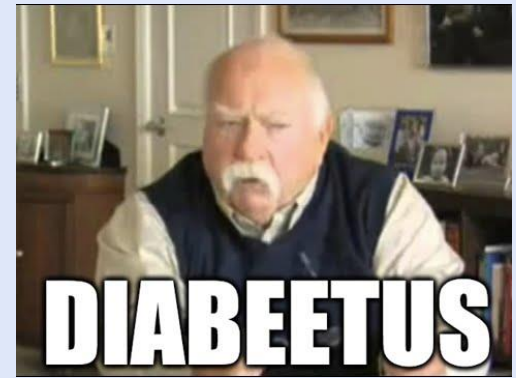
- No association between IDPs and PJI
- Incidence of IDPs actually *lower* in the 3mo prior to the PJI (IRR 0.89, 95% CI 0.82-0.96)
- Sensitivity analysis found no difference with 4- or 5-month followup

Figure 2. Monthly Incidence of Invasive Dental Procedures During 15 Months Before Admission to Hospital With Late Prosthetic Joint Infection (LPJI)



INSTI

Metabolic Issues



- Increased recognition of promotion of weight gain with INSTI use (especially in combination with tenofovir alafenamide)
- Relationship between incidence of hypoglycemia and development of diabetes mellitus is less clear

Integrase Strand Transfer Inhibitors Are Associated With Incident Diabetes Mellitus in People With Human Immunodeficiency Virus

Jane A. O'Halloran,^{1,a} John Sahrman,^{1,a} Luis Parra-Rodriguez,¹ Daniel T. Vo,¹ Anne M. Butler,^{1,2} Margaret A. Olsen,^{1,2} and William G. Powderly¹

¹Department of Medicine, Washington University School of Medicine, St. Louis, Missouri, USA; and ²Department of Surgery, Washington University School of Medicine, St. Louis, Missouri, USA

- Review of IBM MarketScan data from 2007-19 and Medicaid Multi-State data from 2011-19 for incidence of new-onset DM/hyperglycemia within 6mo of initiating INSTI-based regimens
- Propensity scoring to account for confounders (demographics, geographic region, Medicaid status, comorbidities, etc.)

Study Results

- 42,382 patients initiated ART
 - 54% INSTI-based
 - 74% male
 - 19% Medicaid-insured
- INSTI-based regimens were 31% more likely to develop new-onset DM/hyperglycemia (HR 1.31, 95% CI 1.15-1.48)
 - HR 1.54 (1.32-1.79) with elvitegravir
 - HR 1.26 (1.03-1.55) with dolutegravir
 - HR 1.19 (1.03-1.37) with raltegravir
- No notable difference seen with TAF

Mechanism of INSTI-Induced Metabolic Derangements?

- Primary weakness of epidemiologic data implicating INSTIs in weight gain/diabetes has been lack of a clear underlying mechanism
- Possible role in suppression of uncoupling protein 1 (UCP1) transporter
 - UCP1 uncouples cellular respiration from ATP generation in mitochondria in brown and “beige” adipocytes
 - Part of body’s response to cold challenge and body temperature maintenance

Dolutegravir Suppresses Thermogenesis via Disrupting Uncoupling Protein 1 Expression and Mitochondrial Function in Brown/Beige Adipocytes in Preclinical Models

IkRak Jung,^a Becky Tu-Sekine,^a Sunghee Jin, Frederick Anokye-Danso, Rexford S. Ahima, Todd T. Brown, and Sangwon F. Kim[®]

Department of Medicine, Division of Endocrinology, Diabetes, and Metabolism, Johns Hopkins University, Baltimore, Maryland, USA

- Dolutegravir given subcutaneously to mice for 2wk, resulting in ~15% increase in fat mass
- UCP1 expression in intracellular brown adipose tissue and inguinal white adipose tissue were reduced
- Brown adipose cells directly exposed to dolutegravir had reduced UCP1 mRNA expression

Other Notable Study Findings

- DTG-treated mice had attenuated heat generation in response to β -adrenergic stimulus despite adrenergic receptor response being intact
- Glucose uptake and insulin signaling not affected in hepatocytes or myocytes
- DTG disrupted mitochondrial respiratory chain protein and insulin functions

PET/CT Scans As Routine Part of Endocarditis Workup?

- Data accumulating on the role of PET/CT scans in the management of *S. aureus* bacteremia
 - CID study from 2020 (<https://doi.org/10.1093/cid/ciaa929>) noted that PET/CT scans found new foci of infection in almost half of patients with *S. aureus* bacteremia and resulted in new source control interventions in ~18% of patients, resulting in significant reductions in mortality
- Evidence for utility of PET/CT in suspected endocarditis (from any organism) less clear

Impact of Systematic Whole-body ¹⁸F-Fluorodeoxyglucose PET/CT on the Management of Patients Suspected of Infective Endocarditis: The Prospective Multicenter TEPvENDO Study

Xavier Duval,^{1,2,3,4} Vincent Le Moing,⁵ Sarah Tubiana,^{1,2,3} Marina Esposito-Farèse,^{1,2,6} Emila Ilic-Habensus,^{1,2} Florence Leclercq,⁷ Aurélie Bourdon,⁸ François Goehringer,⁹ Christine Selton-Suty,¹⁰ Elodie Chevalier,¹¹ David Boutoille,¹² Nicolas Piriou,^{13,14} Thierry Le Tourneau,¹³ Catherine Chirouze,¹⁵ Marie-France Seronde,¹⁶ Olivier Morel,¹⁷ Lionel Piroth,¹⁸ Jean-Christophe Eicher,¹⁹ Olivier Humbert,²⁰ Matthieu Revest,^{21,22} Elise Thébaud,²² Anne Devillers,²³ François Delahaye,²⁴ André Boibieux,²⁵ Bastien Grégoire,²⁶ Bruno Hoen,⁹ Cédric Laouenan,^{1,2,3,4,6,a} Bernard Jung,^{1,2,3,4,a} and François Rouzet^{1,2,3,4,27,a}; for the AEPeI-TEPvENDO study group

¹INSERM CIC 1425, Paris, France, ²AP-HP, University Hospital of Bichat, Paris, France, ³INSERM UMR-1137 IAME, Paris, France, ⁴University Paris Diderot, Paris 7, UFR de Médecine-Bichat, Paris, France, ⁵Department of Infectious Diseases, University Hospital of Montpellier, Montpellier, France, ⁶Unité de Recherche Clinique, AP-HP, HUPNVS, Hôpital Universitaire Paris Nord-Val de Seine, Paris, France, ⁷Department of Cardiology, University Hospital of Montpellier, Montpellier, France, ⁸Department of Nuclear Medicine, University Hospital of Montpellier, Montpellier, France, ⁹Department of Infectious Diseases, University Hospital of Nancy, Nancy, France, ¹⁰Department of Cardiology, University Hospital of Nancy, Nancy, France, ¹¹Department of Nuclear Medicine, University Hospital of Nancy, Nancy, France, ¹²Department of Infectious Diseases, CIC UIC 1413 INSERM, University Hospital of Nantes, Nantes, France, ¹³Thorax Institute, INSERM, UMR 1087, University Hospital of Nantes, Nantes, France, ¹⁴Department of Nuclear Medicine, Nantes University Hospital, G. et R. Laennec Hospital, Nantes, France, ¹⁵University Hospital of Besançon, France, UMR CNRS 6249 Chrono-Environnement, Bourgogne University, Franche-Comté, Dijon, France, ¹⁶Department of Cardiology, University Hospital of Besançon, Besançon, France, ¹⁷Department of Nuclear Medicine, University Hospital of Besançon, Besançon, France, ¹⁸Department of Infectious Diseases, University Hospital of Dijon, INSERM CIC 1432, CHU Dijon, France, ¹⁹Department of Cardiology, University Hospital of Dijon, Dijon, France, ²⁰Department of Nuclear Medicine, University Hospital of Dijon, Dijon, France, ²¹Infectious Diseases and Intensive Care Unit, University Hospital of Rennes France, INSERM U1230 CHU Rennes, France, ²²INSERM CIC 1414, University Hospital of Rennes, France, ²³Department of Nuclear Medicine, University Hospital of Rennes, France, ²⁴Department of Cardiology, University Hospital of Lyon, Lyon, France, ²⁵Department of Nuclear Medicine, University Hospital of Lyon, Lyon, France, ²⁶Department of Infectious Diseases, University Hospital of Lyon, Lyon, France, and ²⁷Department of Nuclear Medicine, AP-HP, University Hospital of Bichat, Paris, France

- Prospective evaluation of utility of PET/CT in 140 patients suspected of endocarditis (70 native valve; 70 prosthetic valve) at 8 tertiary care hospitals in France from April 2015-March 2016
- Experts classified pts according to modified Duke criteria and management plan before and after PET/CT and at 6mo (when all data except PET/CT were reviewed)

Study Procedures

- Any change in classification resulting from PET/CT data was considered beneficial if the patient was correctly reclassified compared to the 6-month gold standard classification
- Standardization in preparation and acquisition of PET/CT scans
- PET/CT results interpreted by trained physicians quantitatively and qualitatively using valve uptake patterns

Study Findings

- At inclusion, IE classified as definite in 80 patients (34 PV, 46 NV), possible in 56 (33 PV, 23 NV)
- Modified Duke classification changed in 21 patients (24.5% of prosthetic valve and 5.7% of native valve suspected IE)
 - Upgraded in 18, downgraded in 3
 - At 6mo, upgrade confirmed as adequate in 16/18, downgrade adequate in 1/3

Study Findings

- Extracardiac uptake detected in 69 (49.3%); portal of entry detected in 33 (23.6%), which was previously unknown in 12 (8.6%)
- Therapeutic management altered in 37 patients (21.4% PV, 31.4% NV)
 - 22 antibiotic modifications
 - 7 changes to surgical management
 - 5 changes to both
- Overall benefit seen in 40%, typically more frequently in those with noncontributing baseline echocardiography and in those classified as “possible” IE at inclusion
- Useful tiebreaker?

Meningitis B Vaccination: Protection vs. *Neisseria gonorrhoeae*?

- *N. gonorrhoeae* gaining resistance, sustained prevalence despite public health efforts
- Meningococcal B vaccines are based on outer membrane vesicle-based antigens that are similar to that of *N. gonorrhoeae* (ACWY vaccines are polysaccharide-based)
- Some cross-protection suggested in prior cohorts in New Zealand and Norway but concerns for “healthy vaccine” effects and ecological fallacy

Prevention of *Neisseria gonorrhoeae* With Meningococcal B Vaccine: A Matched Cohort Study in Southern California

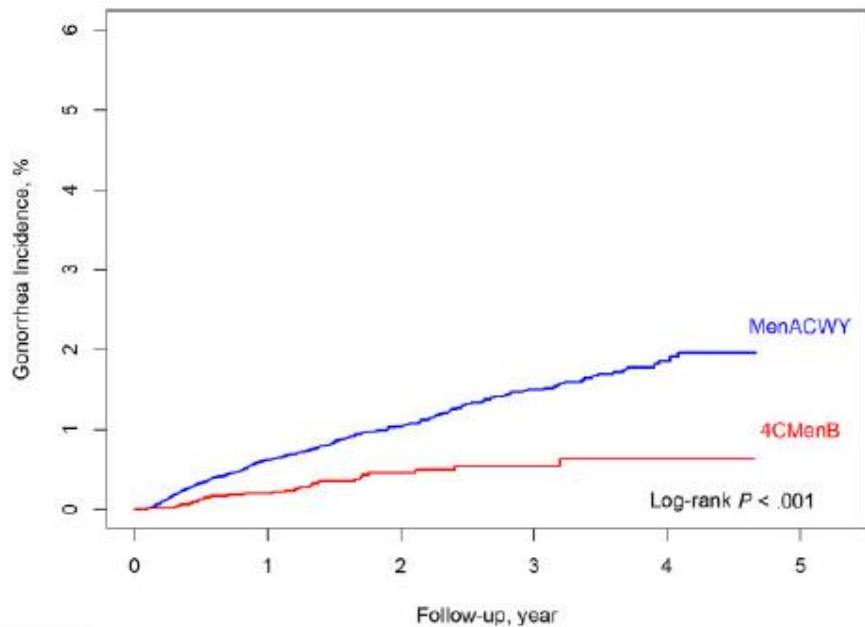
Katia J. Bruxvoort,^{1,2} Joseph A. Lewnard,^{3,4,5} Lie H. Chen,² Hung Fu Tseng,^{2,6} Jennifer Chang,⁷ Jeanne Mrazo,⁸ and Lei Qian²

¹Department of Epidemiology, University of Alabama at Birmingham, Birmingham, Alabama, USA; ²Department of Research & Evaluation, Kaiser Permanente Southern California, Pasadena, California, USA; ³Division of Epidemiology, School of Public Health, University of California–Berkeley, Berkeley, California, USA; ⁴Division of Infectious Diseases & Vaccinology, School of Public Health, University of California–Berkeley, Berkeley, California, USA; ⁵Center for Computational Biology, College of Engineering, University of California–Berkeley, Berkeley, California, USA; ⁶Department of Health Systems Science, Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, California, USA; ⁷Department of Infectious Diseases, Los Angeles Medical Center, Southern California Permanente Medical Group, Los Angeles, California, USA; and ⁸Division of Infectious Diseases, University of Alabama at Birmingham Heersink School of Medicine, Birmingham, Alabama, USA

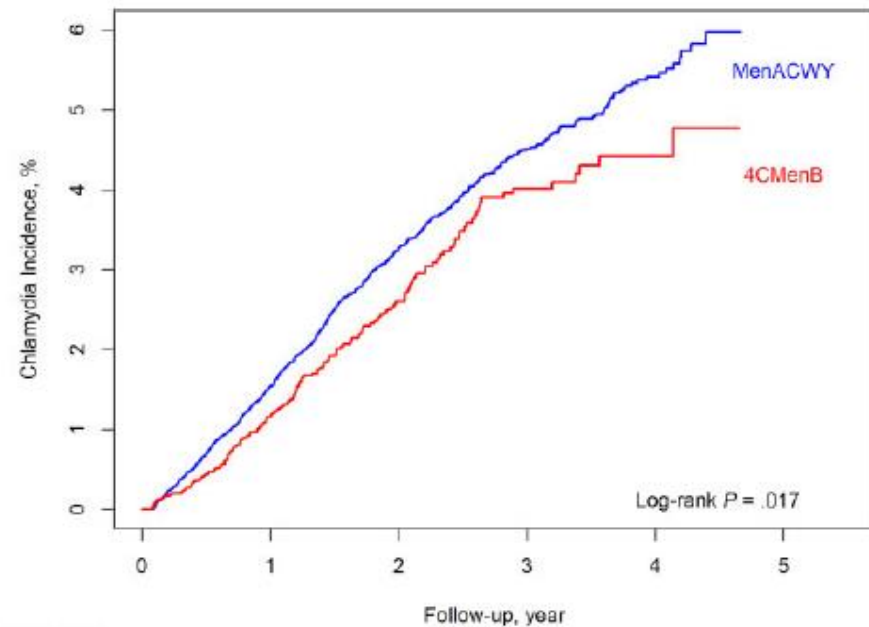
- Retrospective cohort study matching 6641 Kaiser Southern California teen and young adult recipients of meningitis B vaccine to 26,471 who only received meningitis ACWY vaccine by age, sex, and year of vaccination examining subsequent acquisition of gonorrhea

Study Characteristics

- Gonorrhea incidence compared to chlamydia incidence
- Meningitis B vaccine cohort different demographically from ACWY cohort
 - Higher income/education/healthcare utilization
 - More non-Hispanic White and Asian/Pacific Islander and fewer Hispanic
 - Fewer prior year HIV diagnoses, STI infections, HIV PrEP, male reporting male sexual partners



Number at Risk										
	0	1	2	3	4	5	6	7	8	9
MenACWY	26471	26383	23284	17010	13063	9063	6136	3853	2190	430
4CMenB	6641	6630	6125	4006	2785	1958	1622	914	568	37



Number at Risk										
	0	1	2	3	4	5	6	7	8	9
MenACWY	26471	26383	23063	16706	12742	9797	6956	3728	2129	411
4CMenB	6641	6608	6056	3837	2728	1804	1567	881	557	35

- Meningitis B cohort had a similar rate of chlamydia acquisition (12.4 vs. 15.2 cases per 1000 person-years) but lower rate of gonorrhea acquisition (2.0 vs. 5.2 cases per 1000PY)
- Multivariable analysis adjusting for confounders:
 - HR 0.54 (0.34-0.86) for incident gonorrhea
 - HR 0.98 (0.82-1.17) for incident chlamydia
- RCT currently enrolling patients

Ventilator-Associated Pneumonia

- Associated with high morbidity/mortality and often associated with multidrug-resistant bacteria (though often difficult to tell colonizers from true pathogens)
- IDSA/ATS guidelines fairly aggressive in targeting MRSA, resistant GNRs
- Can Gram stains be used to tailor therapy?



Original Investigation | Critical Care Medicine

Effect of Gram Stain–Guided Initial Antibiotic Therapy on Clinical Response in Patients With Ventilator-Associated Pneumonia

The GRACE-VAP Randomized Clinical Trial

Jumpei Yoshimura, MD; Kazuma Yamakawa, MD, PhD; Yoshinori Ohta, MD, PhD; Kensuke Nakamura, MD, PhD; Hideki Hashimoto, MD, PhD; Masahiro Kawada, MD; Hiroki Takahashi, MD; Takeshi Yamagiwa, MD, PhD; Akira Kodate, MD; Kyohei Miyamoto, MD, PhD; Satoshi Fujimi, MD, PhD; Takeshi Morimoto, MD, PhD, MPH

- Multicenter open-label RCT in Japan (2018-20) in which 206 patients with VAP (mCPIS ≥ 5) were randomized to receive empiric guideline-based antibiotics or have therapy guided by Gram stain of endotracheal aspirate
 - If GmPos orgs in clusters observed \rightarrow anti-MRSA Rx
 - If GmNeg orgs observed \rightarrow anti-pseud β -lactam Rx
 - If neither observed \rightarrow both anti-MRSA/anti-pseud Rx

Patient Characteristics

- Low rate of immunocompromise (3-4%)
- Septic shock in 3-6%
- High rates of any GPCs/GNRs observed on Gram stain (91-95%)
- *S. aureus* (50%, 18% of which was MRSA) most frequently isolated, followed by *Klebsiella* (16.5%) and *H. influenzae* (9.7%)

Study Findings

- 76.7% clinical response in Gram stain-guided group vs. 71.8% clinical response in guideline-based group (risk difference 0.05%, 95% CI: -0.07-0.17)
- 28d mortality similar (13.6% vs. 17.5%; HR 0.74 (0.37-1.48))
- 30% reduction in antipseudomonal use and 39% reduction in anti-MRSA agents
- Gram stain had 83.5% sensitivity/75.7% specificity in detecting *S. aureus* and 83% sensitivity/60.7% specificity in detecting GNRs

Subgroup Analyses/Adverse Events

- Among patients with previous antibiotic therapy, clinical response rate trended more favorable with Gram-stain guided treatment (risk difference 0.26; 95% CI 0.01-0.50, $p=.08$)
- Results similar for patients with ICU stay of 5 or more days vs. less
- 69 adverse events in Gram stain group vs. 79 in guideline group
 - Diarrhea 26% vs. 37%
 - Kidney impairment 16.5% vs. 18.4%
 - Thrombocytopenia 15.6% vs. 10.7%
 - C. diff in 1% vs. 3%

Infectious Diseases Consultations Delivered via Telehealth

- Became increasingly relevant during pandemic
 - Synchronous: real-time audio-video interaction
 - Asynchronous: review of digital data only
- Comfort levels differ according to stakeholder
 - Patients/consultors appreciate convenience
 - Consultant may not feel they are getting the whole story
- Workload capture/billing issues

Clinical Infectious Diseases

BRIEF REPORT

Provider Satisfaction With Infectious Diseases Telemedicine Consults for Hospitalized Patients During the Coronavirus Disease 2019 (COVID-19) Pandemic

Joseph E. Canterino,¹ Kaicheng Wang,² and Marjorie Golden¹

¹Department of Medicine, Yale University School of Medicine, New Haven, Connecticut, USA; and

²Yale Center for Analytic Sciences, Yale School of Public Health, New Haven, Connecticut, USA

- In March 2020, Yale ID section transitioned consultations on hospitalized patients to telemedicine (with rare exceptions)
- Synchronous vs. asynchronous at discretion of consultant
- Consultants surveyed June/July 2020

Survey Findings

Consultors

- Quality of the telemedicine consult was the same or better than a traditional consult: 76%
- Timeliness same or better: 99%
- Communication same or better: 80%

ID Consultants

- Quality of telemedicine consult worse than traditional consult: 74% (those with >10y experience more opinionated)
- Consults more timely: 91%
- 88% felt there were specific situations where F2F was necessary (vs. 34% consultors)

Duration of Antibiotic Therapy After Debridement and Retention of Orthopedic Implants

- Controversial topic: IDSA guidelines in 2012 were divided regarding approach, with respect to:
 - Duration of IV vs. oral therapy
 - Role of rifampin (and duration thereof)
- Lots of literature since then that influences thoughts on utilization of oral therapy

Truth in DAIR: Duration of Therapy and the Use of Quinolone/Rifampin-Based Regimens After Debridement and Implant Retention for Periprosthetic Joint Infections

Don Bambino Geno Tai,^{1,●} Elie F. Berbari,^{1,●} Gina A. Suh,^{1,●} Brian D. Lahr,^{2,●} Matthew P. Abdel,^{3,●} and Aaron J. Tande¹

¹Division of Public Health, Infectious Diseases and Occupational Medicine, Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA, ²Department of Quantitative Health Sciences, Mayo Clinic, Rochester, Minnesota, USA, and ³Department of Orthopedic Surgery, Mayo Clinic, Rochester, Minnesota, USA

- Retrospective review of 247 cases of PJI managed by DAIR at Mayo Clinic from 2008-18 with median 4.4-year followup
- Estimated 5-year cumulative incidence of failure was 28.1%

Baseline Population Characteristics

- Median age 70; 54.3% male
- Diabetes mellitus in 25.9%
- 25% prior history of revision arthroplasty due to infection
- Median duration of symptoms 7 days
- Associated bloodstream infection in 23.3%
- *S. aureus* in 35.6%, coag-neg staph in 23.4%
- Modular components exchanged in 59.1%

Antimicrobial Management

- Intravenous therapy used in all but 2 patients; median duration 42 days (IQR 38-42)
 - Beta-lactams used in 66.8%, vancomycin in 32.4%
- Oral antibiotics prescribed after IV antibiotics in 91.9% for a median duration of 2.1 years (IQR 0.9-4.1)

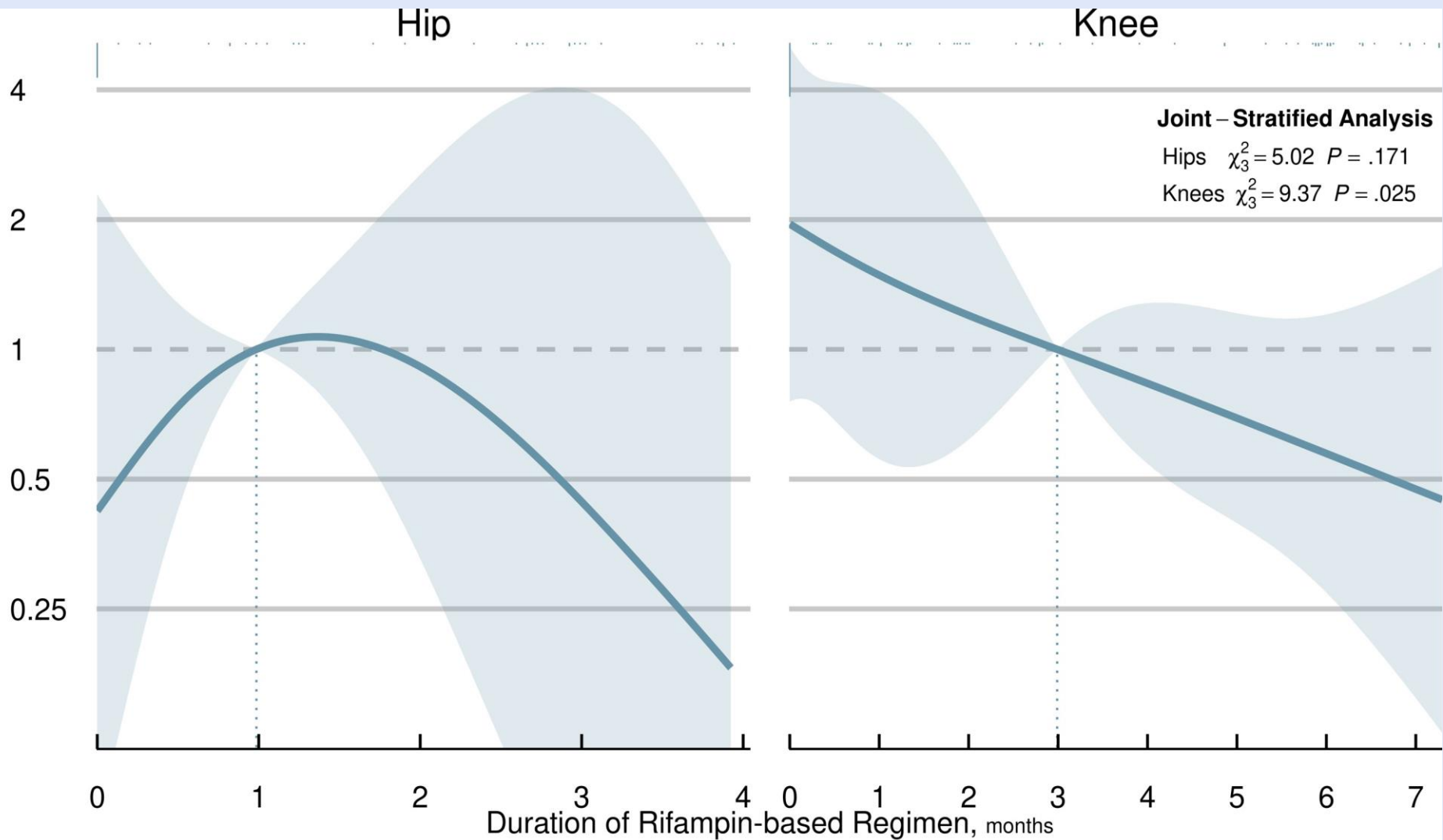
Post-DAIR Failure/Timing

- 65 failures over median 4.4y followup (IQR 2.3-7.0)
 - 5-year cumulative failure rate 28.1%
 - 35.9% failure rate in knees
 - 16.2% failure rate in hips
 - 36 failures within the first year, 13 while on IV abx
- No association seen between duration of IV therapy and failure (HR 1.01 for 4 vs. 6wk)
- Shorter duration of oral antibiotics associated with increased risk of failure ($p=.005$), mostly driven by failures in the 90d-1 y window

Staphylococcal Infections

- Comprised 60.7% of all cases
- No association seen with fluoroquinolone therapy vs. non-fluoroquinolone therapy but wide CI (HR 0.62, 95% CI 0.31-1.24)
- Use of rifampin showed protective effect overall ($p=.025$), driven by use in knee PJI (hip not significant), with longer duration being more protective ($p=.025$)

Treatment Failure Hazard Ratio



Time-dependent Cox analysis included 150 joints from 147 patients (48 events)

Predisposition to Disseminated Coccidioidomycosis

- Correlation observed between disseminated disease and some racial and ethnic backgrounds
- Is there an underlying genetic cause for this increased risk?
 - Failure of immune system to properly recognize pathogen?
 - Maladaptive response to pathogen once recognized?

Immunogenetics associated with severe coccidioidomycosis

Amy P. Hsu, ... , Michail S. Lionakis, Steven M. Holland

JCI Insight. 2022. <https://doi.org/10.1172/jci.insight.159491>.

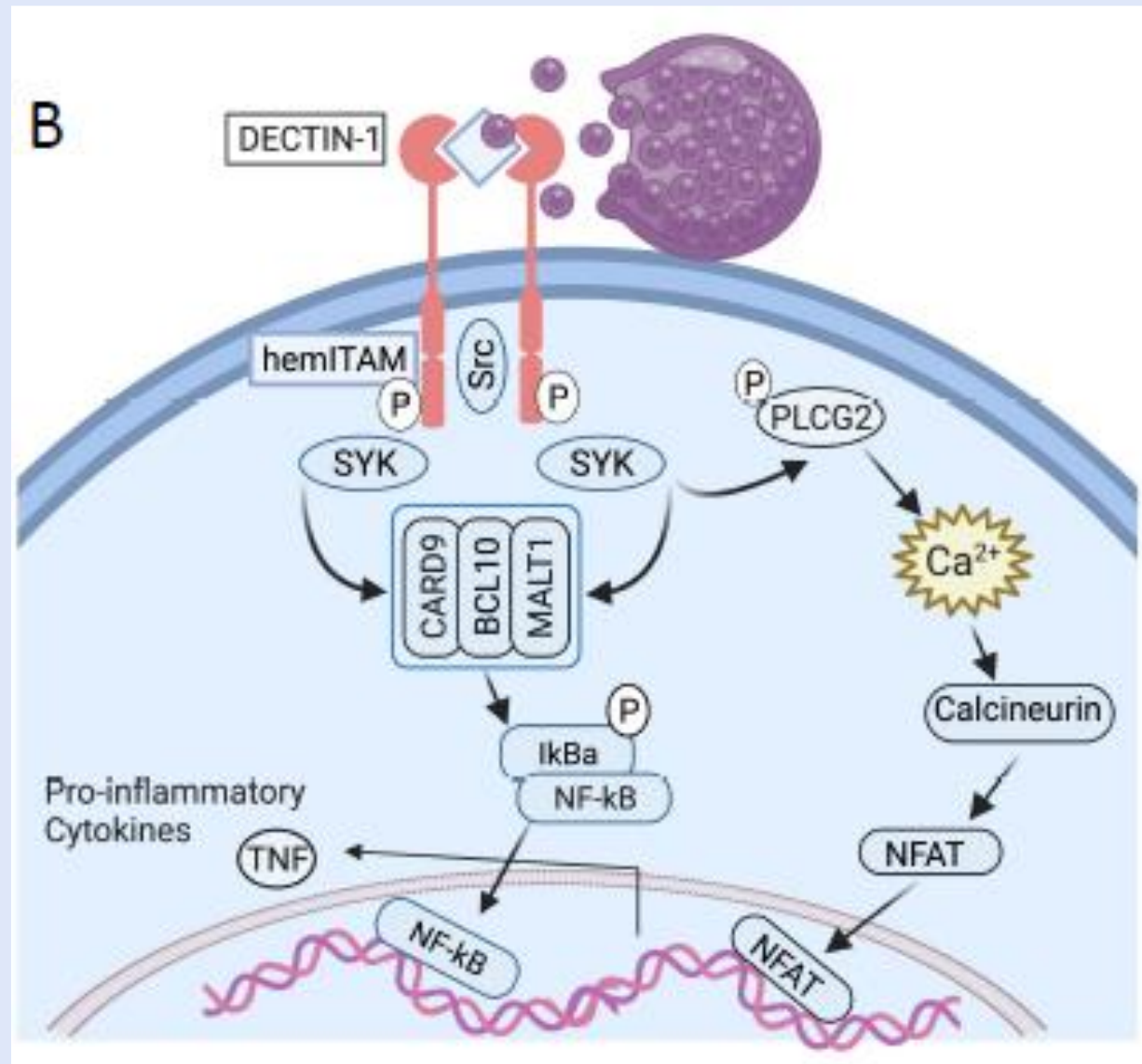
Research In-Press Preview Genetics Infectious disease

- Whole-exome sequencing performed on 67 patients with disseminated cocci
 - 20 European ancestry
 - 20 admixed American/Latino
 - 18 African/African-American
 - 4 East Asian
 - 3 South Asian
 - Subsequent validation on another 111 disseminated cocci patients
- | Sites of dissemination | |
|-------------------------------|--|
| 13 bone | |
| 28 CNS | |
| 17 soft tissue | |
| 9 multiple | |

Key Pathways Where Mutations Were Seen

- Signal transducer and activation of transcription-3 (STAT3): 2 haploinsufficient mutations, both assoc w/fatal disease
- DECTIN-1: C-type lectin pattern recognition receptor for β -glucan
 - 13 patients either homozygous or heterozygous for a p.Y238* mutation previously associated with familial mucocutaneous candidiasis, increased susceptibility to invasive aspergillosis after HSCT, and chronic allograft dysfunction after lung transplant

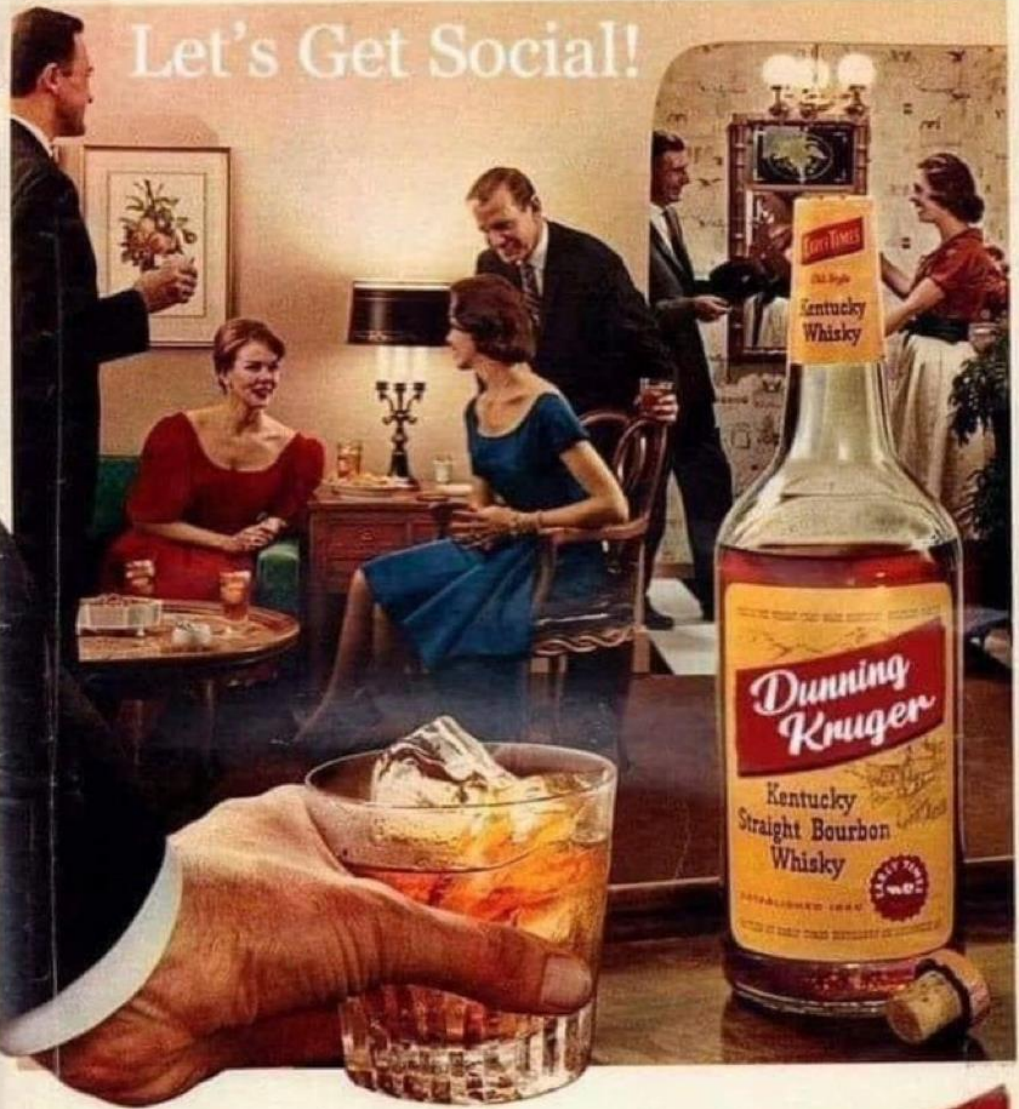
DECTIN-1 Signaling Pathway



More Abnormalities Seen in DECTIN-1 Signaling Pathway

- Heterozygous p.1223S mutation (n=1)
- Predicted damaging PLCG2 variants (n=15)
(confirmed with PBMC stimulation studies)
- Heterozygous variants in downstream NADPH-oxidase complex DUOX1 /DUOXA1 (present in pulmonary epithelium) that impair H₂O₂ production also overrepresented in discovery and validation cohorts

Let's Get Social!



When you know more than the doctors who've spent their entire careers studying infectious diseases, it's time for Dunning Kruger.



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christopher.graber@va.gov