ID WATCH

by Ed Septimus, MD

Editor's Choice

1 ID add-on code proposed in new CMS fee schedule

CMS announced its proposed 2025 Physician Fee Schedule in July, which includes a cut to physician payments — this year, of 2.93% — for the fifth straight year. According to the AMA, physician payments have dropped 29% since 2001, which experts have said will worsen ongoing workforce shortages and strain physician practices. CMS says the new add-on code, HCPCS code GIDXX, could be applied to hospital and inpatient evaluation and management (E/M) services to describe service elements, including disease transmission risk assessment and mitigation; public health investigation, analysis and testing; and complex antimicrobial decisions and treatment. The proposed relative value for the new code is 0.89. Under the proposed conversion factor, that translates to a $28.80 boost to hospital and inpatient E/M services

where the code is appended. Current E/M codes do not adequately capture the complexity of ID physician services. This add-on code is intended to help better account for that complexity and provide a mechanism for ID physicians to receive additional reimbursement (on top of what E/M codes provide) when providing this complex inpatient care. CMS is accepting public comments on the rule through September 9th. CMS is expected to publish its final rule later this year, and it will take effect next year.

Dr. Septimus's Annotations

Ensuring fair compensation for ID clinicians that accurately reflects the value and complexity of ID care is long overdue. ID care is undervalued, and inadequate compensation is one of the key elements hindering ID recruitment and retention. To earn this recognition, ID clinicians must uphold the highest standards of diagnostic and antimicrobial stewardship as well as infection prevention.

2

Opportunities to Improve Antibiotic Prescribing for Adults with Acute Sinusitis, United States, 2016–2020

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The investigators set out to characterize antibiotic prescribing patterns for acute sinusitis among commercially insured adults and explored differences by patient and prescriber-level factors. Outpatient encounters among adults aged 18–64 years diagnosed with sinusitis between 2016–2020 were identified using national administrative claims data. They classified first-line (amoxicillin-clavulanate or amoxicillin) and second line (doxycycline, levofloxacin, or moxifloxacin) antibiotic agents and ≤7 day durations as guideline-concordant based on clinical practice guidelines. Modified Poisson regression was used to examine the association between patient- and prescriber-level factors and guideline-concordant antibiotic prescribing. The primary outcomes were receipt of an antibiotic prescription for acute sinusitis within three days of the sinusitis diagnosis date and whether that antibiotic selection was guideline concordant as defined by the IDSA clinical practice guideline for acute bacterial rhinosinusitis. The secondary outcome was guideline-concordant duration of therapy.

Among 4,689,850 sinusitis encounters, 53% resulted in a guideline-concordant antibiotic, 30% in a guideline-discordant antibiotic, and 17% in no antibiotic prescription. About 75% of first line agents and 63% of second-line agents were prescribed for >7 days, exceeding the length of therapy recommended by clinical guidelines. Adults with sinusitis living in a rural area were less likely to receive a prescription with guideline-concordant antibiotic selection (adjusted risk ratio [aRR], 0.92; 95% confidence interval [CI], 0.92–0.92) and duration (aRR, 0.77; 95% CI, 0.76– 0.77). Compared to encounters in an office setting, urgent care encounters were less likely to result in a prescription with guideline-concordant duration (aRR, 0.76; 95% CI, 0.75–0.76)

Dr. Septimus's Annotations

Sinusitis is the most common indication for antibiotics in adults in the outpatient setting, with almost 3.7 million antibiotic courses dispensed per year in the US. [JAMA 2016; 315:1864-73] The Infectious Diseases Society of America (IDSA) clinical practice guideline recommends 5 to 7 days of therapy for adult patients with an uncomplicated infection

and a favorable initial response (i.e., improvement or no worsening of symptoms after 3–5 days). [Clin Infect Dis. 2012;54: e72-e112] In 2016, about 70% of antibiotics prescribed for adults with sinusitis were for ten days or longer, and about 36% of prescriptions were for guideline-discordant agents.[JAMA Intern Med. 2018;178:992-994] In addition, antibiotic therapy for acute sinusitis is often unnecessary.

In this nationwide cohort study of commercially insured adults diagnosed with acute sinusitis in the outpatient setting, most encounters resulted in an antibiotic prescription, with nearly one-third of encounters resulting in a guideline-discordant agent. Additionally, about 75% of encounters with a guideline-concordant agent had a prescription with a longer-than-recommended duration. They were unable to assess the clinical criteria used to diagnose acute bacterial sinusitis, but this percentage likely reflects the overtreatment of adults with antibiotic therapy. Most cases of acute sinusitis have a viral etiology, and a recent cross-sectional study showed that approximately 50% of encounters for sinusitis do not warrant an antibiotic prescription.[Clin Infect Dis. 2021;72:311-314] Patients with bacterial sinusitis have persistent symptoms without improvement for ≥10 days, severe signs or symptoms (i.e., high fever and purulent nasal discharge of facial pain) for at least 3–4 consecutive days at the beginning of illness, or experience worsening symptoms after initial improvement. In this study, only encounters at an ED had such high proportion, with 57% of them not resulting in an antibiotic prescription. Watchful waiting and delayed prescribing are reasonable strategies for the initial management of patients with acute sinusitis with mild symptoms who do not meet the stringent clinical criteria for establishing a bacterial infection. Clinical guidelines recommend against the use of macrolides for acute sinusitis due to increased resistance to S pneumoniae. [Clin Infect Dis. 2012;54: e72-e1129] Despite this, they found that azithromycin was the second most prescribed antibiotic.

Using ICD-10 diagnosis may result in misclassification. In addition, administrative claims cannot ascertain the severity of infection and other factors (e.g., signs or symptoms of infection) that could influence antibiotic prescribing and the assessment of whether the antibiotic prescriptions were clinically indicated. Therefore, they were unable to assess the clinical criteria used to diagnose acute bacterial sinusitis, but this percentage given an antibiotic likely reflects the overtreatment of adults with antibiotic therapy.

BOTTOM LINE

Opportunities still exist to optimize antimicrobial selection and treatment duration for adults with acute sinusitis, especially in rural areas and urgent care settings. We can and must do better.

Nasal sprays and behavioural interventions compared with usual care for acute respiratory illness in primary care: a randomised, controlled, open-label, parallel-group trial

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Although respiratory tract infections are frequently caused by viruses, they are a significant driver of unnecessary antibiotic prescribing, since primary care providers don't have a quick way to distinguish viral from bacterial infections and often feel pressure to prescribe antibiotics.

This study was an open-label, parallel-group Immune Defence trial, led by investigators at the University of Southampton, which recruited 13,799 adults who had at least one comorbidity or risk factor that increased their risk of adverse outcomes due to respiratory illness from December 12, 2020, to April 7, 2023. The participants were randomized to four intervention groups on a 1:1:1:1 basis—usual care, gel-based nasal spray, saline nasal spray, or a behavioral website promoting physical activity and stress management—and instructed to use the interventions at the first sign of symptoms or when they came into close contact with someone with a respiratory tract infection. The primary outcome was the total number of days of illness due to self-reported respiratory-tract illnesses since randomization, reported at a 6-month survey. Key secondary outcomes included days when work or normal activities were impaired, reported incidence of respiratory tract illness, possible adverse events, and use of antibiotics. Neither investigators nor medical staff were aware of treatment allocation.

A total of 11,612 participants had complete data for the primary outcome and were included in the final analysis (3,451 assigned to the usual-care group, 3,448 to gel-based nasal spray, 3,450 to saline nasal spray, and 3,450 to the digital intervention). Compared with the participants in the usual-care group, who had a mean of 8.2 days of illness, participants who received gel-based nasal spray (mean 6.5 days of illness; adjusted incidence ratio [IRR], 0.82; 99% confidence interval [CI], 0.76 to 0.90) and saline spray (mean, 6.4 days; IRR, 0.81; 99% CI, 0.74 to 0.88) had significantly fewer days of illness. The group allocated to the behavioral website did not see a significant reduction in days of illness (mean, 7.4 days; IRR, 0.97; 99% CI, 0.89 to 1.06). In addition, the number of lost workdays or lost days of normal activity was lower in the gel-based spray group (IRR, 0.81; 95% CI, 0.67 to 0.98) and the saline spray group (IRR, 0.72; 95% CI, 0.59 to 0.87) than in the usual care group.

Antibiotic use was lower for all three interventions than with usual care, with an IRR of 0.65 (95% CI, 0.50 to 0.84) for the gel-based spray group, 0.69 (95% CI, 0.45 to 0,88) for the saline spray group, and 0.74 (95% CI, 0.57 to 0.94) for the behavioral website group. Of those with available data, the most common adverse effect was headache or sinus pain, which was experienced by 4.8% of participants in the usual-care group, 7.8% in the gel-based spray group (risk ratio [RR], 1.61; 95% CI, 1.30 to 1.99), 4.5% in the saline spray group (RR, 0.81; 0.63 to 1.05), and 4.5% in the behavioral website group (RR, 0.95; 95% CI, 0.74 to 1.22).

Dr. Septimus's Annotations

The trial, conducted at 332 UK practices, found that the use of two types of over-the-counter nasal sprays and a digital behavioral intervention reduced antibiotic use by as much as 35% in patients diagnosed as having upper respiratory tract infections. The nasal sprays, when used at the first sign of infection, also reduced illness duration and the number of workdays lost compared with usual care. These findings are important because these interventions are simple, and they decrease the unfavorable outcomes from respiratory tract infections, and they enable clinicians to provide proactive treatment while avoiding unnecessary antibiotics.

In a prior study, patients were randomized to 1200 mg guaifenesin/120 mg pseudoephedrine hydrochloride extended release, or matching placebo for 7 consecutive days. Eligible patients met physician's criteria for antibiotic therapy but were considered suitable for a wait and see approach (withholding antibiotics for 48 hours). [Curr Thera Res 2017; 84:54-61] On day 8, significantly fewer patients receiving guaifenesin/ pseudoephedrine versus placebo desired antibiotics (4.2% vs 8.0%). Like nasal spray, the use of a guaifenesin pseudoephedrine provided effective symptom control compared to a placebo and an effective first-line strategy for the management of respiratory tract infections decreasing antibiotic use.

"Compared with the participants in the usual-care group... participants who received gel-based nasal spray and saline spray had significantly fewer days of illness. "

BOTTOM LINE

The use of either nasal spray reduced illness duration and both sprays and the behavioral website reduced antibiotic use.

Oral Antibiotics and Risk of Serious Cutaneous Adverse Drug Reactions

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The purpose of this study was to explore the risk of serious cutaneous adverse drug reactions (cADRs) associated with commonly prescribed oral antibiotics, and to characterize outcomes of patients who had an ED visit or were hospitalized because of cADRs.

The investigators performed a nested case-control study using population-based linked administrative datasets among adults aged 66 years or older who received at least 1 oral antibiotic between 2002 and 2022 in Ontario, Canada. To identify antibiotic use, they used the Ontario Drug Benefit database, which contains data on outpatient prescription drugs dispensed to all Ontario residents aged 65 years or older. To identify ED visits for cADRs, they used the Canadian Institute for Health Information (CIHI) National Ambulatory Care Reporting System, which contains details regarding ED visits including diagnostic information. To identify hospitalization for cADRs, they used the CIHI Discharge Abstract Database, which contains detailed diagnostic and procedural information. Cases were those who had an ED visit or hospitalization for serious cADRs within 60 days of the prescription, and each case was matched with up to 4 controls who did not. Conditional logistic regression estimates of the association between different classes of oral antibiotics and serious cADRs, using macrolides as the reference group.

During the 20-year study period, they identified 21,758 older adults (median age, 75 years; 64.1% female) who had an ED visit or hospitalization for serious cADRs following antibiotic therapy and 87,025 matched controls who did not. In the primary analysis, sulfonamide antibiotics (adjusted odds ratio [aOR], 2.9; 95% CI, 2.7-3.1) and cephalosporins (aOR, 2.6; 95% CI, 2.5-2.8) were most strongly associated with serious cADRs relative to macrolides. Additional associations were evident with nitrofurantoin (aOR, 2.2; 95% CI, 2.1-2.4), penicillins (aOR, 1.4; 95% CI, 1.3-1.5), and fluoroquinolones (aOR, 1.3; 95% CI, 1.2-1.4). The crude rate of ED visits or hospitalization for cADRs was highest for cephalosporins (4.92 per 1000 prescriptions; 95% CI, 4.86-4.99) and sulfonamide antibiotics (3.22 per 1000 prescriptions; 95% CI, 3.15-3.28). Among the 2852 case patients hospitalized for cADRs, the median length of stay was 6 days (IQR, 3-13 days), 9.6% required transfer to a critical care unit, and 5.3% died in the hospital.

Table 2. Crude Rate of Serious cADRs Within 60 Days of Antibiotic Prescription[a]

Antibiotic class	No. of exposures	No. of serious cADRs	Events per 1000 exposures (95% CI)
Cephalosporins	5 076 176	24 997	4.92 (4.86-4.99)
Sulfonamides	2 730 810	8780	3.22 (3.15-3.28)
Fluoroquinolones	6 825 283	16 939	2.48 (2.44-2.52)
Nitrofurantoin	3 627 644	8464	2.33 (2.28-2.38)
Penicillins	8 666 828	16 822	1.94 (1.91-1.97)
Macrolides	4 709 840	8483	1.80 (1.76-1.84)
Other antibiotics[b]	2 477 673	9786	3.95 (3.87-4.03)
All antibiotics	34 114 254	72 449	2.12 (2.11-2.14)

Dr. Septimus's Annotations

This study is the first to use population-based data to provide estimates of the relative and absolute risks of serious cADRs following outpatient antibiotic therapy. cADRs are a group of rare but potentially life-threatening

drug hypersensitivity reactions involving the skin and, frequently, other organs. Typically delayed in onset, these reactions include drug reaction with eosinophilia and systemic symptoms, Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN)—the most severe cADR, which has a reported mortality of 20% to 40%. [JAMA. 2014; 311:2231-2232] While many drugs can cause serious cADRs, antibiotics are among the most commonly implicated triggers.[JAMA Dermatol. 2023; 159:384-392] The majority of antibiotic prescribing occurs in the community, and older adults receive more antibiotic prescriptions than younger people. Older age is also associated with polypharmacy and various comorbidities that can increase the risk of serious cADRs.

The rate of antibiotic-associated serious cADRs leading to an ED visit or hospitalization has not been previously studied. They found that at least 2 hospital encounters for serious cADRs ensued for every 1000 antibiotic prescriptions. This rate is considerably higher than suggested by studies that examine only SJS/TEN and drug reactions with eosinophilia and systemic symptoms. [J Allergy Clin Immunol Pract. 2020; 8:1302-1313] A surprising finding of this study was the association between serious cADRs and use of nitrofurantoin, which has not been previously reported as a common cause of severe drug reactions. They also found that up to 20% of hospitalized patients with SJS/TEN were treated in a critical care unit, a lower rate than previously reported. We observed in-hospital mortality of 20% among these patients, in accordance with previous estimates. [J Invest Dermatol. 2018; 138:2315-2321]

They did not have access to detailed hospital records for case ascertainment, relying instead on ICD-10 codes to identify cADR. Because dedicated ICD-10 codes do not exist for serious cADRs other than SJS and TEN, they developed a study-specific definition by restricting our outcome to instances in which cADRs were the primary reason for seeking medical attention. Some patients may not have sought care for cADRs that improved after antibiotic cessation and were presumably mild. Lastly, they did examine the use of nonprescription medications such as nonsteroidal anti-inflammatory drugs, which can also cause cADR.

BOTTOM LINE

Many commonly prescribed oral antibiotics are associated with an increased risk of serious cutaneous adverse drug reactions (cADRs) compared with macrolides, with sulfonamide antibiotics and cephalosporins carrying the highest risk.

5

Should Blood Cultures Be Drawn Through an Indwelling Catheter?

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Clinicians in many US hospitals are discouraged from obtaining blood cultures from indwelling central venous catheters to reduce the likelihood of positive blood cultures resulting from catheter colonization/contamination, which may lead to reporting a central line-associated bloodstream infection (CLABSI) to the NHSN. A positive catheter-drawn blood culture in the absence of growth from a percutaneously drawn culture may reflect contamination, especially with growth of common skin commensals. When there is growth from both catheter-drawn and percutaneously drawn blood cultures, a differential time to blood culture positivity may assist in identifying the catheter as the source of the bloodstream infection. [Clin Infect Dis 2023; 77:428-437]

When encountering a patient with possible CLABSI, an important question is how many lumens should be sampled if the CVC is thought to be a likely source of infection. This is important because many critically ill patients with fever or sepsis have multiple intravascular catheters, often with multiple lumens. Approximately one-third of CRBSIs will be missed if only 1 lumen of a multilumen catheter is sampled [Clin Infect Dis 2010; 50:1575–79.]. Despite controversy regarding which lumen and how many lumens should be sampled for blood culture collection, the lumen used for administration of total parenteral nutrition and/ or blood products may have the highest yield. [Infection 2013; 41:49–52]

Key Recommendations:

- Percutaneously drawn blood cultures should be obtained when blood cultures are indicated.
- Blood cultures should be drawn from a catheter if there is reasonable clinical suspicion that the catheter could be the source of infection: there is evidence of localized infection (e.g., purulent drainage, suspected tunnel infection); fever, and/or hypotension during or shortly after infusion through a catheter, or without obvious source based on careful assessment of the patient; unexplained change in a patient's status during hemodialysis; or if one simply cannot obtain blood cultures percutaneously.
- Catheter-drawn blood cultures should be accompanied by percutaneously drawn cultures whenever possible.
- Avoid catheter-drawn blood cultures if a nonvascular catheter source of infection is likely.
- Catheter-drawn blood culture contamination can be minimized by using care to reduce risk of contamination by removal of existing connector valves, disinfection of the catheter hubs, and obtaining the blood through a fresh sterile connector or disinfected hub. Additionally, passive port protectors should be used more widely to prevent catheter colonization and blood culture contamination.
- In patients with a multilumen CVC, more than 1 lumen should be sampled. However, the clinician must balance the likelihood of CRBSI and the need to sample multiple lumens against the downsides of increased cost, iatrogenic anemia, and increased risk of contamination.
- Because approximately 90% of blood cultures are without growth, blood culture diagnostic stewardship programs should be employed to avoid blood cultures with low pretest probability

Dr. Septimus's *Annotations*

Infectious Diseases Society of America (IDSA) guidelines for diagnosis and management of catheter-related bloodstream infections [Clin Infect Dis 20-09; 49:1-45] and Society of Critical Care Medicine/ IDSA guidelines[Crit Care Med 2023;51:15710-1586] for evaluation of fever in critically ill patients both recommend drawing blood cultures from a central venous catheter and percutaneously if the catheter is a suspected source of infection. Central venous catheter drawn blood cultures may be more likely to be positive reflecting catheter hub, connector, or intraluminal colonization/ contamination. Therefore, many hospitals in the US discourage blood culture collection from catheters in an effort to reduce reporting possible CLABSI to the CDC.

BOTTOM LINE

Blood cultures should be drawn from a catheter if there is reasonable clinical suspicion that the catheter could be the source of infection and catheter-drawn blood cultures should be accompanied by percutaneously drawn cultures whenever possible.

6

Treatment of positive catheter tip culture without bloodstream infections in critically ill patients. A case-cohort study from the OUTCOMEREA network

Intensive Care Medicine (2024)
DOI: 10.1007/s00134-024-07498-1

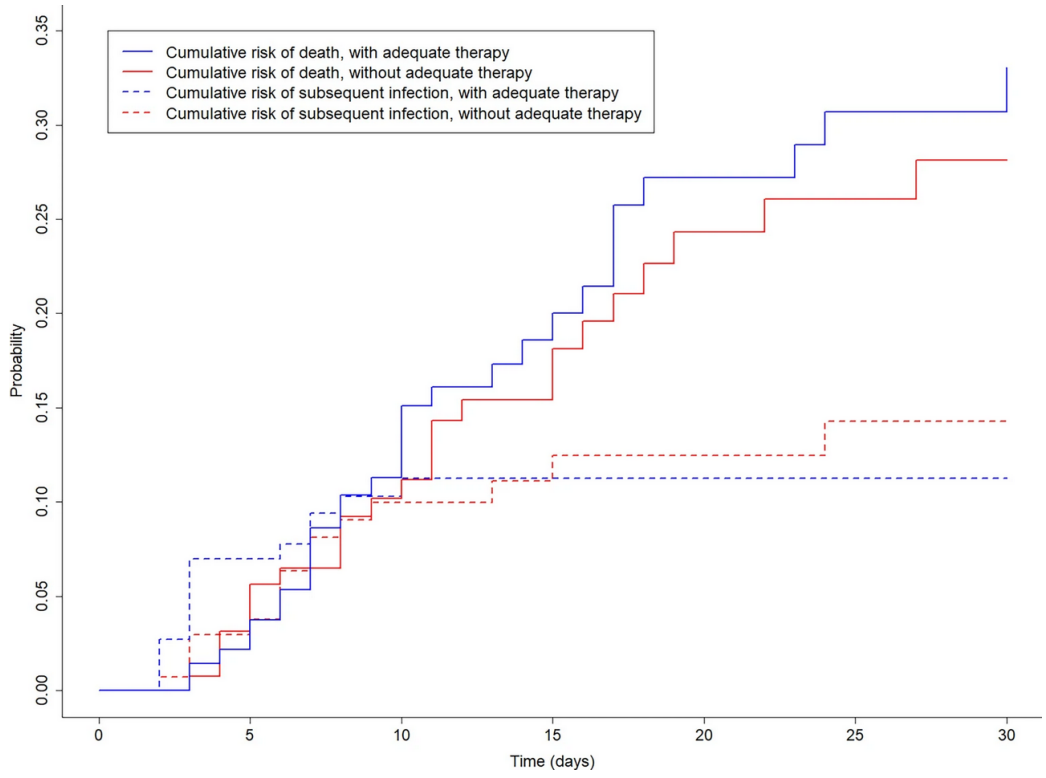
The purpose of this study was to evaluate the impact on subsequent infections and mortality of adequate antimicrobial therapy within 48 h after catheter removal in ICU patients with positive catheter tip culture. They performed a retrospective analysis of prospectively collected data from 29 centers of the OUTCOM EREA network. They developed a propensity

score (PS) for adequate antimicrobial treatment, based on expert opinion of 45 attending physicians. They then conducted a 1:1 case-cohort study matched on the PS score of being adequately treated. A PS-matched subdistribution hazard model was used for detecting subsequent infections and a PS-matched Cox model was used to evaluate the impact of antibiotic therapy on mortality.

Patients were enrolled for the current study if they had a positive quantitative intravascular catheter tip culture, with at least one potentially pathogenic microorganism but not with BSI. Potentially pathogenic microorganisms included *S. aureus*, Streptococcus spp., *Enterococcus spp.*, *Enterobacterales*, *P. aeruginosa*, *Acinetobacter spp.*, and *Candida spp.* Of note, *S. aureus*, *P. aeruginosa*, *A. baumannii*, other non-fermentative Gram-negative bacteria and Candida spp. were classified as high-risk microorganisms for subsequent infections. Coagulase-negative staphylococci, *Neisseria spp.*, *Corynebacterium spp.* (except Corynebacterium JK), *Bacillus spp.*, unspecifed Gram-positive cocci were not included. Patients with central venous catheters (CVCs), short-term dialysis catheters and arterial catheters were included. Positive intravascular catheter tip culture was defined as a positive quantitative device tip culture showing at least one microorganism yielded≥1000 cfu/ml by vortexing or sonication. [many hospitals in the US still use the Maki roll plate semi quantitation of >15 colonies] Only the first positive catheter tip culture was considered in this study. Patients with positive blood cultures with a potentially pathogenic microorganism also identified on the catheter tip culture within 48 h before and 48 h after catheter removal (i.e., CRBSI) were excluded.

They included 427 patients with a catheter tip culture positive with potentially pathogenic microorganisms. They then matched 150 patients with adequate antimicrobial therapy with 150 controls. In the matched population, 30 (10%) subsequent infections were observed, and 62 patients died within 30 days. Using subdistribution hazard models, the daily risk to develop subsequent infection up to day-30 was similar between treated and non-treated groups (subdistribution hazard ratio [sHR] 1.08, 95% [CI] 0.62–1.89, p=0.78). Using Cox proportional hazard models, the 30-day mortality risk was similar between treated and non-treated groups (HR 0.89, 95% CI 0.45–1.74, p=0.73).

Treatment of positive catheter tip culture without bloodstream infections in critically ill patients. A case-cohort study from the OUTCOMEREA network



Dr. Septimus's Annotations

Colonization of central catheters in the ICU is a common phenomenon, affecting more than 10% of intravascular catheter, depending on the study.[Clin Microbiol Infect 2021;27:1279–1284] Colonization is not sufficient by itself to define catheter infection, but some consider it as an acceptable surrogate for catheter infection, although it poorly correlates with catheter-related infections which has a positive blood culture with same organisms.[Clin Infect Dis 2002; 35:1053–1058]. Since CVC colonization can be a risk for CVC infection, it is likely that CVC colonization may predispose to catheter-related bloodstream infections (CRBSIs). [Semin Respir Crit Care Med 2019; 40:508–523]. There is no uniform approach to the management of colonized catheters, and the consequences in terms of bacteremic or non-bacteremic subsequent infections following catheter removal remain controversial. [Intensive Care Med 2018; 44:742–759]

This large study demonstrates that detection of potentially pathogenic pathogens on a removed catheter tip probably does not warrant systemic antimicrobial therapy if simultaneously drawn blood cultures do not grow the same pathogen a finding relevant to diagnostic and antimicrobial stewardship. The results underline the decision-making importance of drawing blood cultures if a catheter-related infection is suspected, and not just sending tips for culture.

BOTTOM LINE

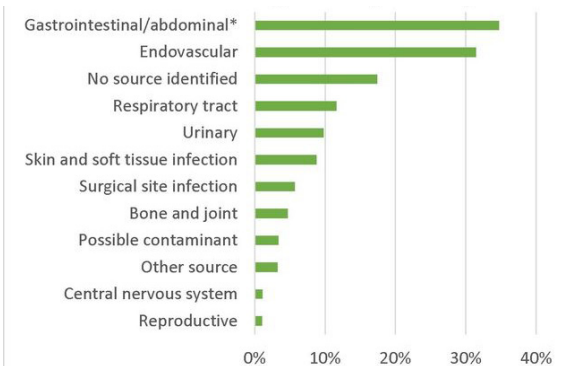
Using a large multicenter cohort, the investigators showed that early antimicrobial therapy was not associated with decreased risk of subsequent infection or death in short-term catheter tip colonization in critically ill patients without bloodstream infections.

Evaluation of hospital-onset bacteraemia and fungaemia in the USA as a potential healthcare quality measure: a cross sectional study

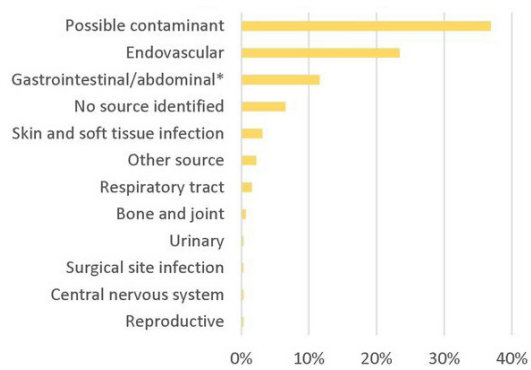
BMJ Quality & Safety 2024;33:487–498.
DOI: 10.1136/bmjqs-2023-016831

The investigators conducted a cross-sectional study of hospital-onset bacteremia and fungemia (HOB) events at 10 academic and three community hospitals using structured chart review. HOB was defined as a blood culture on or after hospital day 4 with growth of one or more bacterial or fungal organisms. HOB events were stratified by commensal and non-commensal organisms. HCPs reviewed charts to determine HOB source, and infectious disease physicians with training in infection prevention/hospital epidemiology rated preventability from 1 to 6 (1=definitely preventable to 6=definitely not preventable) using a structured guide. Ratings of 1–3 were collectively considered 'potentially preventable' and 4–6 'potentially not preventable.

Sources of hospital-onset bacteremia and fungemia events with non-commensal organisms (n=1789)



Sources of hospital-onset bacteremia and fungemia events with commensal organisms (n=320)



Among 1789 HOB events with noncommensal organisms, gastrointestinal (GI) (including neutropenic translocation) (35%) and endovascular (32%) were the most common sources. Overall, 636/1789 (36%) non-commensal and 238/320 (74%) commensal HOB events were rated potentially preventable. In logistic regression analysis among non-commensal HOB events, events attributed to intravascular catheter-related infection, indwelling urinary catheter-related infection and surgical site infection had higher odds of being rated preventable while events with neutropenia, immunosuppression, GI sources, polymicrobial cultures and previous positive blood cultures in the same admission had lower odds of being rated preventable, compared with events without those attributes. Of 636 potentially preventable non-commensal HOB events, 47% were endovascular in origin, followed by GI, respiratory and urinary sources. Approximately 40% of those events would not be captured through existing healthcare-associated infection surveillance.

Dr. Septimus's Annotations

Among 1789 HOB events with non-commensal organisms, gastrointestinal (including neutropenic translocation) (35%) and endovascular (32%) were the most common sources, and overall, 36% of noncommensal HOB events were rated potentially preventable. Among potentially preventable non-commensal HOB events, intravascular catheter-related infection was the most common source, followed by GI, respiratory and urinary sources. Among HOB events with only commensal organisms, the most common source was contaminated blood cultures, with perceived preventability of 92%.

While intravascular catheter-related infections (including central line infections) constituted nearly half of all potentially preventable non-commensal HOB events, they estimated that approximately 40% of potentially preventable non-commensal HOB events would not be identified through routine HAI surveillance currently in place in most US hospitals. GI sources of HOB need to be mentioned given their high frequency overall and a lower relative odd of preventability.

The investigators believe the use of HOB as a modifiable infectious outcome is also supported by well-designed multicenter studies, showing that daily chlorhexidine bathing significantly reduces the risk of all-cause hospital onset BSI in adult and pediatric ICU patients, including 'primary' bacteremia or fungaemia without identified source. [N Engl J Med 2013; 368:2255–65. N Engl J Med 2013; 368:533–42. Lancet 2013; 381:1099–106] In addition several years later the ABATE infection trial was conducted to evaluate the role of CHG bathing among patients in non-ICU settings. In a post-hoc analysis, the investigators identified a high-risk sub-group of patients with medical devices including central lines and midlines which significantly decreased all-cause bacteremia by 32%. [Lancet, 2019;393:1205-1215]

BOTTOM LINE

The investigators conclude these studies support the use of hospital onset bacteremia and fungemia (HOB) as an expanded outcome for hospital infection prevention programs when compared with the smaller proportion attributed to central line associated bloodstream infections (CLABSIs).

8

Hospital-Onset Bacteremia Among Neonatal Intensive Care Unit Patients

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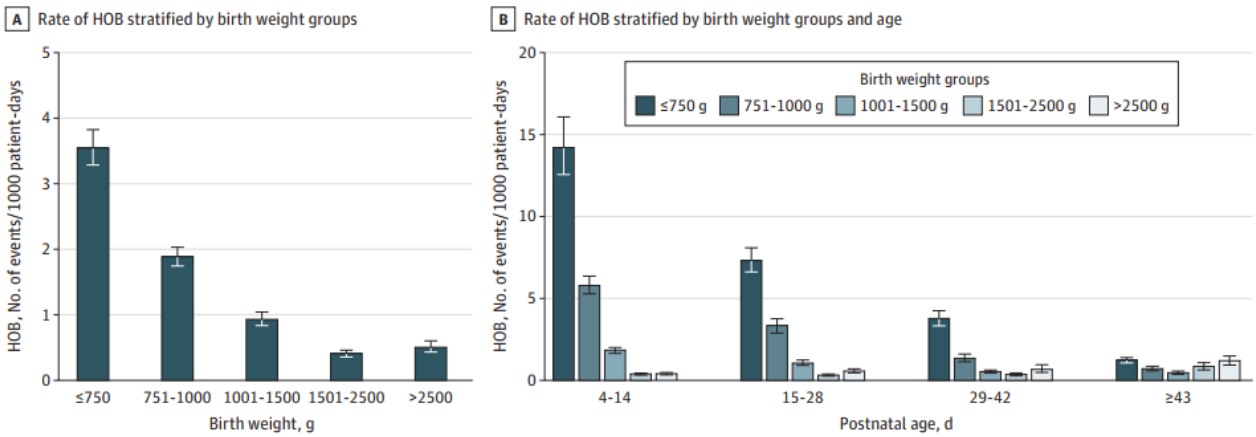
The purpose of this study was to estimate the rate of hospital-onset bacteremia (HOB) among infants admitted to the NICU, measure the association of HOB risk with birth weight group and postnatal age, and estimate HOB-attributable mortality. To answer this question the investigators did a retrospective multicenter cohort study and emulated trial from 2016 to 2021 including sampling of 322 NICUs in the US. Participants were infants admitted to a NICUs for at least 4 days. The primary study outcomes were HOB and HOB-attributable mortality.

Of 451,443 included infants, 250,763 (55.6%) were male, 200,680 (44.4%) were female, and 62,091 (13.8%) were born 1500 g or less. Of 9015 HOB events that occurred among 8356 infants (2%) 4888 HOB events (54.2%) occurred in the absence of a central line. Within the first 2 weeks after birth, the HOB rate was 14.2 per 1000 patient-days (95% CI, 12.6-16.1) among infants born 750 g or less, to 0.4 events per 1000 patient-days among infants born more than 2500 g (95% CI, 0.4-0.5). Among infants born 750 g or less, the relative HOB risk decreased by 90% after day 42 compared with days 4 to 14. Conversely, among infants born more than 2500 g, the relative HOB risk increased by 50% after day 42 compared with days 4 to 14. Compared with otherwise similar infants without HOB, infants with HOB had an absolute difference in attributable mortality of 5.5% (95% CI, 4.7-6.3).

Figure 2. Unadjusted Hospital-Onset Bacteremia (HOB) Rate Stratified by Birth Weight Groups



Dr. Septimus's Annotations

Two percent of eligible infants had HOB, at an unadjusted HOB rate of 1.1 per 1000 patient-days. Birth weight, presence of a central line, and postnatal age were associated with HOB risk. However, more than half of the HOB events in this cohort occurred in infants without a central line in place at time of HOB event. A first-time HOB event was associated with an increased attributable mortality. They estimated a 5.5% absolute difference in attributable mortality among infants with and without HOB. Putting it another way, HOB is a common and an important cause of mortality among infants admitted to the NICU.

Currently, the CDC collects and reports national CLABSI and LOS rates; however, only CLABSI is CMS mandated and represents a subset of all bacteremia events. HOB is an anticipated, CDC health care–associated infection measure that will use electronically available data, capture a larger number of events, and provide nationally representative data. They documented a predominance of gram-positive pathogens in this cohort, with CoNS and S aureus being the 2 most common causes of HOB. This is consistent with prior late-onset sepsis studies. [Pediatrics. 2022;150(6): e2022058813] The majority of HOB events and HOB-attributable deaths occurred within the first several weeks after birth, so they were not able to estimate cumulative attributable mortality from HOB after postnatal day 28.

"...[hospital-onset bacteremia] is a common and an important cause of mortality among infants admitted to the [neonatal intensive care unit]."

BOTTOM LINE

This study found that hospital onset bacteremia (HOB) events in the NICU are associated with increased mortality and not associated with a central line. Birth weight is an important risk factor for HOB; however, the relative rate of HOB decreases over postnatal age among low-birth-weight infants and increases among infants born more than 2500 g. Identifying interventions to prevent HOB and programs to decrease HOB risk are needed.

9

Hospitalizations among family members increase the risk of MRSA infection in a household

Infection Control & Hospital Epidemiology published online August 7, 2024
DOI: 10.1017/ice.2024.106

To determine the extent to which recent MRSA diagnosis and hospitalization might increase the risk of MRSA transmission in households, investigators extracted patient data from a large commercial insurance database from 2001 through 2021, limiting the population to households with two or more family members on the same insurance plan. They then identified cases of MRSA in both inpatient and outpatient settings and compared the monthly incidence of MRSA between individuals in households where another member had been diagnosed with MRSA in an inpatient or outpatient setting within the last 30 days, and individuals in households with no recent MRSA exposure. In a second analysis, they looked at MRSA incidence in households where a family member had recently been hospitalized but not diagnosed with MRSA.

Among the more than 157 million enrollees included in the study, the investigators identified 424,512 MRSA cases in 343,524 individuals. Of the MRSA cases identified, 4,724 (1.1%) represented a possible transmission linked to a recent MRSA diagnosis in a separate family member, and 8,064 (1.9%) represented possible transmission after recent hospitalization of a separate family member. A stratified regression analysis found that the estimated incidence rate of MRSA among those exposed to a family member with a MRSA diagnosis was more than 71 times the rate compared with those not exposed to a family member with MRSA (incidence rate ratio [IRR], 71.03; 95% confidence interval [CI], 67.73 to 74.50). Among those individuals who had a family member who was recently hospitalized but not diagnosed with MRSA, the IRR of MRSA was 1.44 (95% CI, 1.39 to 1.49). The analysis also found that the risk of MRSA among household members increased the longer the recently hospitalized family member was in the hospital. The IRR increased from 1.34 (95% CI, 1.28 to 1.40) when a family member was hospitalized for 1 to 3 days to 1.49 (95% CI, 1.41 to 1.57) when hospitalization lasted 4 to 10 days. Other factors associated with MRSA infection in household members included the number of comorbidities, prior antibiotic usage, and having young children in the family.

Dr. Septimus's Annotations

This study found that household members exposed to a family member recently diagnosed with MRSA were more than 71 times more likely to get a MRSA infection than those who had not been exposed to a family member with MRSA. But the study also found that exposure to recently hospitalized patients with no MRSA diagnosis was associated with an increased risk of MRSA infection, likely because those patients had become colonized with MRSA during their hospital stay. The investigators noted that the findings are limited by the inability to determine exact exposure status among family members and the lack of sequencing data to study potential transmission events. However, the link found between hospitalization and household MRSA transmission highlights why hospital infection prevention practices are so important. Hand hygiene, environmental cleaning, and CHG bathing are few prevention measures to preventing the spread of resistant bacteria in the hospital.

BOTTOM LINE

Exposure to a recently hospitalized and discharged family member increased the risk of MRSA infection in a household even when the hospitalized family member was not diagnosed with MRSA.

10

Put the Vanc Down, Flip It and Reverse It: Comparison of Vancomycin and Daptomycin Health Care Utilization and Cost in Outpatient Parenteral Antimicrobial Therapy.

Open Forum Infectious Disease published online July 25, 2024
DOI: 10.1093/ofid/ofae438

Vancomycin and daptomycin are frequently used in outpatient parenteral antimicrobial therapy (OPAT). The investigators analyzed health care utilization and cost to the health care system for vancomycin vs daptomycin in the outpatient setting. This study was a single-center, retrospective cohort study included adult patients who received at least 72 hours of vancomycin or daptomycin via home infusion or at an infusion center or skilled nursing facility (SNF) through the OPAT program at Oregon Health & Science University (OHSU). Patients who received concurrent antimicrobials (except for rifampin), who received OPAT via alternative settings such as dialysis centers, or who were transferred to the care of an outside provider during their OPAT treatment course were excluded from the study. The primary outcome was a composite of events requiring intervention, including adverse drug reactions, elevated laboratory markers, line complications, ED visits, and hospital readmissions during the OPAT course. Secondary outcomes included the rates of interventions, additional phone calls, changes to alternative antimicrobial therapy, and cost for medication and management. ADE included acute kidney injury (serum creatinine >1.5 mg/dL or a 1.5-fold increase from baseline), tinnitus, neutropenia (absolute neutrophil count 0.5 K/cu mm or 3% of the differential), myalgias, or other specific reactions noted by the ID physician in the patient chart.

Four hundred nine OPAT patients met inclusion criteria; 290 received vancomycin and 119 daptomycin. The mean age of the vancomycin group was 60 years vs 54 years in the daptomycin group ($P < .0001$). Patients in the vancomycin group had a significantly higher proportion of comorbid coronary artery disease. The most common indication in both groups was bone and joint infection (64% vancomycin vs 62% daptomycin), and the most common pathogen was MRSA (36% vancomycin vs 40% daptomycin). There were no statistically significant differences between groups in total events requiring intervention. However, they identified differences in line complications (vancomycin vs daptomycin: RR, 0.51; 95% CI, 0.34–0.74) and ED visits (RR, 1.73; 95% CI, 1.19–2.53). Patients receiving daptomycin experienced fewer laboratory events requiring intervention than those receiving vancomycin (RR, 0.34; 95% CI, 0.18–0.62). Rates of additional interventions and phone calls were lower for patients receiving daptomycin compared with vancomycin (interventions: RR, 0.38; 95% CI, 0.3–0.49; phone calls: RR, 0.72; 95% CI, 0.72–0.79).

The medication acquisition cost for daptomycin was higher than for vancomycin (mean cost per course, $744.24 vs $289.29); however, once time spent on interventions and dose adjustments, additional laboratory monitoring, and line complications were totaled, the cost of a course of daptomycin ($996.76) was lower than the cost of an outpatient course of vancomycin ($1351.98).

Dr. Septimus's Annotations

Rates of intervention required by the OPAT team and overall health care utilization and cost were lower for patients receiving daptomycin than those receiving vancomycin. In 2014 a retrospective cohort study reported that adult patients receiving daptomycin as home infusion therapy experienced 60% fewer antimicrobial adverse events and required 80% fewer antimicrobial interventions than similar patients receiving vancomycin.[J Antimicrob Chemother 2014; 69:1407–15] In 2018, another retrospective cohort study also found that patients receiving vancomycin experienced more ADEs compared with daptomycin-treated patients.[[Infect Control Hosp Epidemiol 2018; 39:947–54] Additionally, a recent cost study [reviewed in ID Watch several months ago] conducted in the inpatient setting reported both time and cost-savings with the use of daptomycin compared with vancomycin. [Open Forum Infect Dis 2024; 11] Of interest patients with

Medicare coverage are more likely to receive OPAT in an SNF, given that home infusion services are not always covered by Medicare parts A & B, thereby increasing the likelihood of receiving vancomycin, as SNFs have historically discourage daptomycin on the basis of cost. Although daptomycin carries a higher medication cost, it requires less health care utilization in terms of additional labs and required care management by the OPAT team, as demonstrated by their cost analysis. Furthermore, daptomycin is infused over 2 to 5 minutes compared with longer infusion times with vancomycin and more frequent daily doses for vancomycin, as well as need to draw lab for vancomycin levels. As a retrospective study, data was limited to the information available in the electronic health record. This may have led to an underestimation of the actual rate of adverse drug reactions, complications, interventions, and additional phone calls.

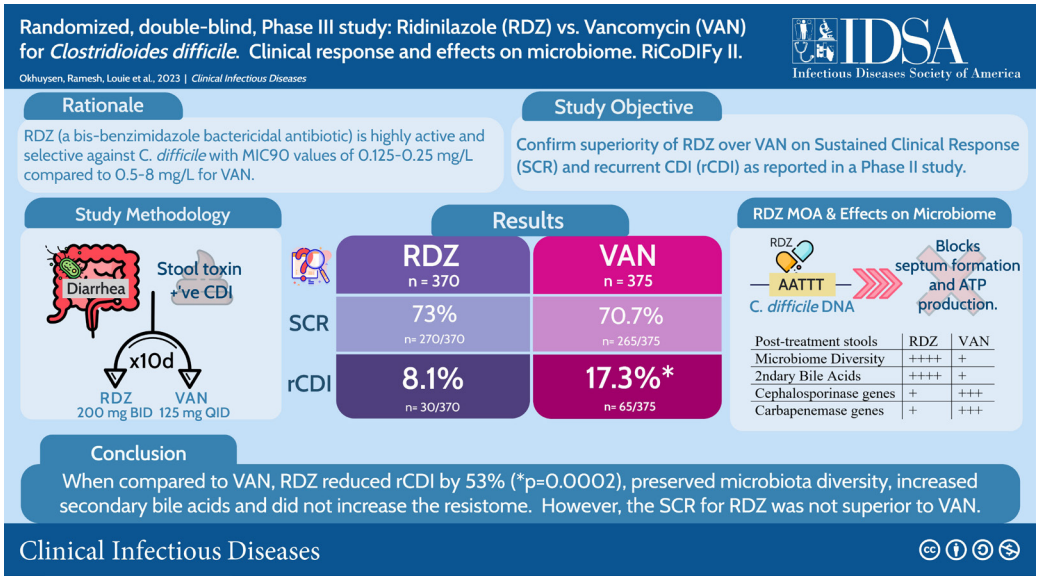
BOTTOM LINE

Daptomycin is a reasonably good alternative to vancomycin for the treatment of gram-positive infections in the OPAT setting.

A Randomized, Double-Blind, Phase 3 Safety and Efficacy Study of Ridinilazole Versus Vancomycin for Treatment of *Clostridioides difficile* Infection: Clinical Outcomes With Microbiome and Metabolome Correlates of Response.

Clinical Infectious Disease 2024;78:1462–72
DOI: 10.1093/cid/ciad792

This is a phase 3 superiority trial of adult patients with CDI confirmed with a stool toxin test. They were randomized to receive 10 days of ridinilazole (200 mg twice daily) or vancomycin (125 mg 4 times daily). The primary endpoint was sustained clinical response (SCR), defined as clinical response and no recurrent CDI (rCDI) through 30 days after end of treatment. Secondary endpoints included rCDI and change in relative abundance of (secondary bile acid) SBAs production. rCDI was defined as a new episode of diarrhea (≥3 [unformed bowel movements] UBMs) in a 1-day period with a positive C. *difficile* free toxin test or cell cytotoxicity neutralization assay (CCNA) that required CDI treatment in subjects who achieved clinical response. Sustained clinical response (SCR) was defined as clinical response and no rCDI through 30 days post-EOT(end of therapy) (day 40 [D40]). Predefined secondary endpoint included change in the relative abundance of microbiome-derived SBAs in stool samples from baseline to EOT. Exploratory endpoints included changes in relative abundance of primary, conjugated primary BAs, and SBAs and in microbiome composition in stool samples at days 40, 70, and 100. Bile acid and microbiome results up to D40 are presented here because the primary endpoint is determined at D40.



Ridinilazole and vancomycin achieved an SCR rate of 73% versus 70.7%, respectively, a treatment difference of 2.2% (95% CI: -4.2%, 8.6%). However, ridinilazole resulted in a 53% reduction in recurrence compared with vancomycin (8.1% vs 17.3%; 95% CI: -14.1%, -4.5%; P = .0002). Subgroup analyses revealed consistent ridinilazole benefit for reduction in rCDI across subgroups. Ridinilazole preserved microbiota diversity, increased SBAs, and did not increase the resistome. Conversely, vancomycin worsened CDI-associated dysbiosis, decreased SBAs, increased Proteobacteria abundance (~3.5-fold), and increased the resistome.

Dr. Septimus's Annotations

RDZ is a bis-benzimidazole bactericidal antibiotic that preferentially binds to AATTT-rich sequences in the *C. difficile* DNA minor groove impacting downstream cell septum formation and, likely, the ability to generate ATP. In vitro, RDZ exhibits a narrow spectrum of activity and is highly active against *C. difficile*. Exposure to antibiotics predisposes to dysbiosis and CDI that can be severe, recurrent (rCDI), and life-threatening. Nonselective drugs that treat CDI and perpetuate dysbiosis are associated with rCDI, in part due to loss of microbiome-derived secondary bile acid (SBA) production. Ridinilazole is a highly selective drug designed to treat CDI and prevent rCDI. Since CDI recurs in 15% to 30% of cases, successful outcomes following therapy require treating the initial episode and preventing rCDI. Central to both outcomes is the need to selectively eradicate *C. difficile* and avoid additional long-lasting dysbiosis. In this study, the investigators showed that RDZ is well tolerated, safe, and effective for the treatment of both CDI and the prevention of rCDI. reflecting the activity and selectivity of RDZ against C. difficile. Although RDZ did not meet the primary endpoint of superiority for SCR versus VAN, RDZ decreased the incidence of rCDI by 53% when compared with VAN, an effect that is likely due to the RDZ microbiome-sparing specificity seen in previous studies.[Am J Physiol Gastrointest Liver Physiol 2020; 319:G227–G37] A key factor leading to rCDI is a decrease in the relative abundance of bacteria capable of resisting *C. difficile* overgrowth. At EOT, RDZ preserved baseline microbiota alpha-diversity, had minimal impact on the baseline taxonomic composition compared with VAN, and increased the relative abundance of protective SBAs. Furthermore, RDZ did not result in an expansion of the gut resistome. In contrast, dysbiosis worsened with VAN at the expense of potentially harmful gram-negative Proteobacteria (e.g., *E coli*, *K pneumoniae*, *K oxytoca*) and decreased the abundance of protective SBAs. Importantly, VAN was associated with an increased relative abundance of genes coding for resistance to antibiotics, notably to carbapenems and third-generation cephalosporins.

"At [end of therapy], [ridinilazole] preserved baseline microbiota alpha-diversity, had minimal impact on the baseline taxonomic composition compared with [vancomycin], and increased the relative abundance of protective [secondary bile acid]s."

Among the currently available CDI therapies, metronidazole is no longer recommended in adults, and vancomycin has a high rate of recurrent CDI episodes. Fidaxomicin is now considered a first-line option for the treatment of initial CDI or rCDI, in part due to its relative microbiome-sparing activity but is not as efficacious against hypervirulent ribotype 027. [J Antimicrob Chemother 2020; 75:1824–32

BOTTOM LINE

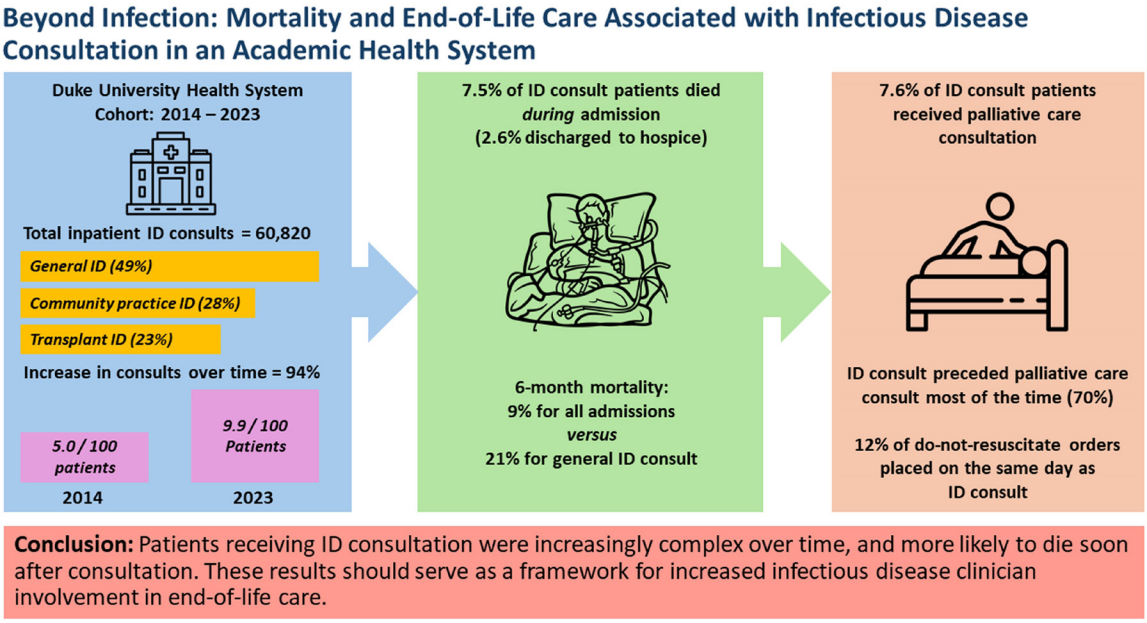
Treatment with ridinilazole preserved microbiome diversity and thus protective secondary bile acids, resulting in a 53% relative reduction in recurrent C difficile infection when compared with vancomycin.

12

Beyond Infection: Mortality and End-of-Life Care Associated With Infectious Disease Consultation in an Academic Health System

Clinical Infectious Diseases published online June 13, 2024
DOI: 10.1093/cid/ciae325

ID physicians are increasingly faced with the challenge of caring for patients with terminal illnesses, incurable infections, and/or end-of-life care. To examine this question the authors conducted a retrospective cohort of all patients with an ID consult within an academic health system from January 1, 2014 through December 31, 2023, which included community, general, and transplant ID consult services. There were over 60,000 inpatient ID consults (17,235 community, 29,999 general, and 13,586 transplant) involving almost 38,000 patients. The number of consults increased by 94% and the rate rose from 5.0 to 9.9 consults per 100 inpatients (P < .001). In total, 7.5% of patients receiving an ID consult died during admission and 1006 (2.6%) of patients were discharged to hospice. In hospital mortality was 5.2% for community ID, 7.8% for general ID, and 10.7% for transplant ID patients (P < .001). Six-month mortality was 9% for all nonobstetric admissions versus 19% for community ID, 21% for general ID, and 22% for transplant ID. In total 2866 (7.6%) of all patients receiving ID consultation also received palliative care consultation during the same hospitalization. The index ID consult preceded any palliative consult in the majority (69.5%) of cases. A total of 16.3% of patients had a do-not-resuscitate order during the index hospitalization; 12.2% of all patients with a do-not-resuscitate order had this placed on the same day as the ID consult!



Smith AG, et al. *Clinical Infectious Diseases*, 2024

Dr. Septimus's Annotations

There has been increased interest in and discussion around the roles ID physicians play in end-of-life care and the challenges of antimicrobial management. [Clin Infect Dis 2024; 78: e27-e36 reviewed March 2024 ID Watch] ID Watch wrote ongoing collaborative discussions between ID and palliative care teams should allow for more meaningful conversations with patients at each phase of their evolving condition. Patients receiving ID consultation in general during the past decade are increasingly complex, sicker, and more likely to die relatively soon after the consultation was performed. The

increasing rate of ID consultation emphasizes the increasing importance of ID in complex inpatient care. ID consultants are often called to reassure medical teams and families that "everything is being done," even when the prognosis is poor. ID is frequently asked to prescribe antibiotics despite impending death. This is generally inappropriate. They also found that a relatively high proportion of both palliative care consults (8.1%) and DNR orders (12.2%). There is compelling evidence that effective palliative care involvement can reduce inappropriate or aggressive antibiotic use in hospitalized patients at the end of life. [J Antimicrob Chemother 2022; 78:302–8] Inappropriate antibiotics can also promote selection of antimicrobial resistance and adverse side effects. In an ICU setting this can increase colonization pressure and impact other patients.

BOTTOM LINE

Patients receiving ID consultation were increasingly complex and more likely to die soon after consultation. These results provide a framework for ID clinicians to consider their role in end-of-life care.

13

Benefits and Harms of Procalcitonin- or C-Reactive Protein-Guided Antimicrobial Discontinuation in Critically Ill Adults With Sepsis: A Systematic Review and Network Meta-Analysis

Critical Care Medical published online July 1,2024
DOI: 10.1097/CCM.0000000000006366

The objective was to compare the effectiveness and safety of procalcitonin or CRP-guided antibiotic cessation strategies with standard of care in sepsis. A systematic review with network meta-analyses was performed. Randomized controlled trials involving adults with sepsis in intensive care were selected.

Eighteen studies involving 5023 participants were included. Procalcitonin-guided and CRP-guided strategies shortened antibiotic treatment (−1.89 days [95% CI, −2.30 to −1.47], −2.56 days [95% CI, −4.21 to −0.91]) with low- to moderate-certainty evidence. In procalcitonin-guided strategies, this benefit was consistent even in subsets with shorter baseline antimicrobial duration (7–10 d) or in Sepsis-3, and more pronounced in procalcitonin cutoff of 0.5 µg/L and 80% reduction. Procalcitonin-guided strategies lowered mortality (−27 per 1000 participants [95% CI, −45 to −7]) and this was pronounced in Sepsis-3, but CRP-guided strategies led to no difference in mortality. Recurrence did not increase significantly with either strategy (very low to low certainty).

A Duration of antibiotic therapy

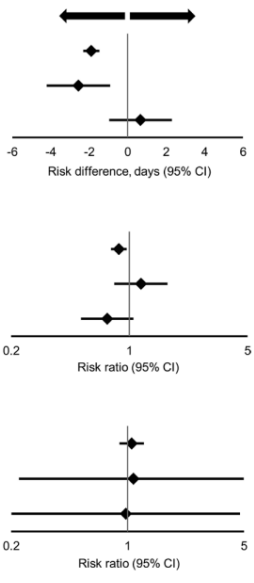
	No. of patients	No. of RCTs	Certainty of the evidence	Estimated absolute risk difference, days (95% CI)	Network risk ratio (95% CI)
Compared with SOC					
PCT	4739	15	Moderate	-1.89 (-2.30 to -1.47)	—
CRP	130	1	Low	-2.56 (-4.21 to -0.91)	—
Additional comparison					
PCT vs CRP	94	1	Low	0.67 (-0.96 to 2.30)	—

B Mortality

	No. of patients	No. of RCTs	Certainty of the evidence	Estimated absolute risk difference, per 1000 patients (95% CI)	Network risk ratio (95% CI)
Compared with SOC					
PCT	4739	15	Moderate	-27 (-45 to -7)	0.87 (0.78 to 0.97)
CRP	130	1	Low	+35 (-38 to +140)	1.17 (0.82 to 1.68)
Additional comparison					
PCT vs CRP	154	2	Low	-53 (-99 to +12)	0.74 (0.52 to 1.06)

C Sepsis recurrence

	No. of patients	No. of RCTs	Certainty of the evidence	Estimated absolute risk difference, per 1000 patients (95% CI)	Network risk ratio (95% CI)
Compared with SOC					
PCT	3162	10	Low	+2 (-4 to +10)	1.06 (0.89 to 1.25)
CRP	130	1	Very low	+3 (-31 to +171)	1.08 (0.22 to 5.27)
Additional comparison					
PCT vs CRP	94	1	Very low	-1 (-32 to +150)	0.98 (0.20 to 4.74)



Dr. Septimus's Annotations

In this analysis of RCTs involving adults with sepsis, procalcitonin- and CRP-guided antimicrobial cessation strategies demonstrated shortened antibiotic treatment from approximately 10 days to 7–8 days; the evidence was of low to moderate certainty. The procalcitonin-guided strategy was also associated with a significant reduction in mortality with moderate certainty. Recurrence did not significantly increase with either strategy. For the procalcitonin cutoffs, the antimicrobial shortening effect was most pronounced in the subset of 0.5 µg/L and 80% reduction. The authors postulate the mortality benefit might stem from reduced antibiotic-resistant bacteria development. In a RCT by Kyriazopoulou et al assessing infection-related clinical adverse events due to drug-resistant organisms and Clostridioides difficile, they demonstrated that procalcitonin-guided strategies reduced both these events and mortality.[Am J Respir Crit Care Med 2021; 203:202–210] These findings are consistent with other publications which demonstrated that streamlining antimicrobial treatment can decrease mortality [Intensive Care Med 2014; 40:32–40] and that prolonged use of antimicrobials may worsen outcomes. [Intensive Care Med 2007; 33:1369–1378]

They found few RCTs where CRP-guided strategies were compared directly with SOC and with procalcitonin-guided strategies; therefore, the evidence was not robust. Second, the proportion of septic shock varied in the included trials. In addition, the included RCTs excluded sources/microorganisms or immunocompromised.

BOTTOM LINE

This review revealed that procalcitonin- or CRP-guided antimicrobial cessation strategies shorten antimicrobial therapy without increased mortality or recurrence.

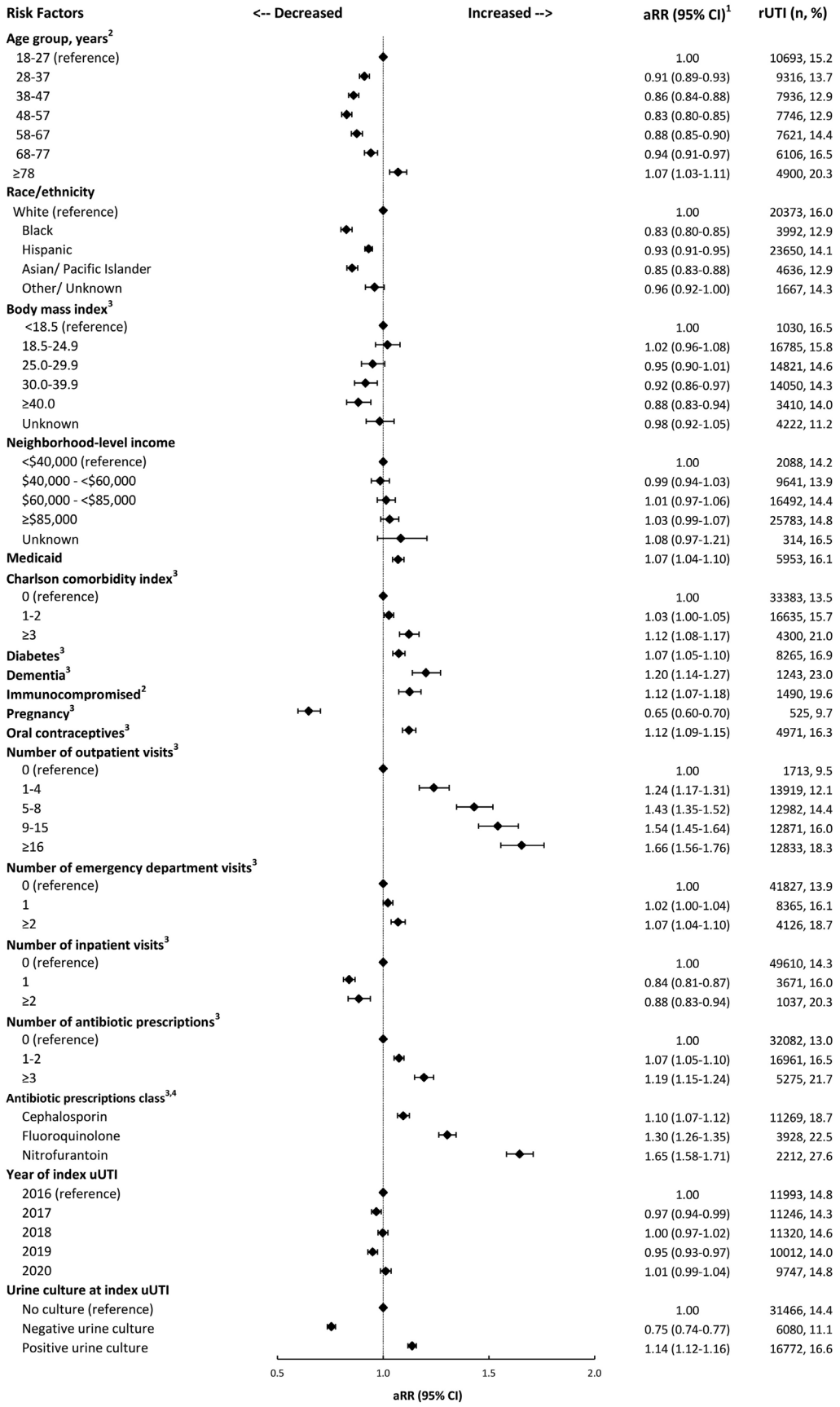
Risk Factors for Recurrent Urinary Tract Infections Among Women in a Large Integrated Health Care Organization in the United States

The Journal of Infectious Diseases published online June 28, 2024
DOI: 10.1093/infdis/jiae331

Between January 1, 2016, and December 31, 2020, index uncomplicated UTIs (uUTIs) from office, emergency department, hospital, and virtual care settings were identified from the electronic health records of women at Kaiser Permanente Southern California. They defined rUTI as ≥3 UTIs within 365 days or ≥2 UTIs within 180 days. They determined the proportion of women with cystitis index uUTI who had rUTI, and they examined factors associated with rUTIs using modified multivariable Poisson regression. UTI was defined as 1 of the following: (1) occurrence of a UTI diagnosis code with a prespecified antibiotic prescription order (aminoglycoside, carbapenem, cephalosporin, fluoroquinolone, fosfomycin, nitrofurantoin, penicillin, trimethoprim-sulfamethoxazole, or other) ±3 days of a UTI diagnosis code date, (2) a positive urine culture result with a prespecified antibiotic prescription order ±3 days of culture date, or (3) a positive urine culture result with a UTI diagnosis code ±7 days of culture date. The laboratory at Kaiser defined a positive urine culture result as isolation of ≥1000 colony-forming units (CFU)/mL for normally sterile samples or ≥10 000 CFU/mL for clean-catch specimens. However, the investigators in this study used a higher threshold (e.g., ≥100 000 CFU/mL) to reflect real-world practice.

Among 374,171 women with cystitis index uUTI, 54,318 (14.5%) had rUTI. A higher proportion of women with rUTI vs those without rUTI were aged 18 to 27 or ≥78 years at index uUTI (19.7% vs 18.7% and 9.0% vs 6.0%, respectively), were immunocompromised, or had a positive urine culture result at index uUTI. In multivariable analyses, characteristics associated with rUTI included younger or older age (48–57 vs 18–27 years: adjusted risk ratio [aRR], 0.83 [95% CI, .80–.85]; ≥78 vs 18–27 years: aRR, 1.07 [95% CI, 1.03–1.11]), Charlson Comorbidity Index (≥3 vs 0: aRR, 1.12 [95% CI, 1.08–1.17]), and diabetes mellitus (aRR, 1.07

[95% CI, 1.04–1.10]). More frequent prior-year outpatient and emergency department encounters, oral antibiotic and oral contraceptive prescriptions, positive culture result at index uUTI, and antibiotic-resistant organisms were also associated with increased risk of rUTI.



Dr. Septimus's Annotations

Urinary tract infections (UTIs) are among the most common bacterial infections, with an estimated annual incidence of >150 million cases worldwide. [J Infect Dis 2001; 183(Suppl 1): S1–4] In the US, UTIs result in approximately 10.5 million office visits as well as 3 million emergency department (ED) encounters and 400,000 hospitalizations annually with an estimated annual cost >$4.8 billion.[Open Forum Infect Dis 2017; 4:ofw281] Clinically, UTIs are categorized as uncomplicated or complicated. Uncomplicated UTIs (uUTIs) can be differentiated into lower (cystitis) and upper (pyelonephritis). uUTIs typically affect individuals who are otherwise healthy. Approximately 75% of uUTIs are caused by intestinal pathogenic E coli, followed by K pneumoniae and other pathogens. Complicated UTIs are associated with factors compromising the urinary tract or host defense, such as urinary obstruction, immunosuppression, renal failure/transplantation, and indwelling catheterization. In the US, 70% to 80% of complicated UTIs(cUTIs) are attributable to indwelling catheters, accounting for 1 million cases per year. [Am J Med 2002; 113(Suppl 1A):5S–13S]

In this study the investigators found that rUTI is common, occurring in nearly 15% of women following an incident uUTI. They found a bimodal age distribution for women with the greater risk of rUTIs among the youngest and oldest participants (18–27 and ≥78 years vs 28–67 years). The increased risk of rUTIs among younger women is thought to reflect behavioral risk factors, including sexual activity, and genetic risk factors, including nonsecretor status and personal and familial history of UTI. The higher risk of rUTI among women who received oral contraceptive prescriptions in this study is similar to the greater risk of UTI associated with diaphragm use reported in prior studies [13], reflecting sexual activity as a likely risk factor for rUTI[Am J Public Health 1990; 80:331–3]. In contrast, hormonal changes [30] that increase colonization with uropathogens, as well as structural changes, are thought to have a greater role in increasing the risk of rUTIs among older women. [Clin Infect Dis 2000; 30:152–6] Several comorbidities were associated with an increased risk of rUTI: diabetes, immunocompromised status, dementia, and Charlson Comorbidity Index ≥1. They found that increased use of antibiotics (cephalosporins, fluoroquinolones, or nitrofurantoin), often used in outpatient settings, in the year prior to the index uUTI was associated with increased risk of rUTI in our study population, possibly due to antibiotic-associated changes in the gut and/or vaginal microbiota that appear to raise the risk of rUTI. [Nat Microbiol 2022; 7:630–9] Similarly, multidrug resistance in isolates in women with cystitis whose urine was cultured was associated with an increased risk of rUTI, consistent with findings from previous studies. [Microbiol Spectr 2016; 4:10] Unfortunately, the definition did not include clinical symptoms or dipstick or microscopic urinalysis, which were not consistently captured in the electronic health record.

"In this study the investigators found that [reoccuring urinary tract infection] is common, occurring in nearly 15% of women following an incident [uncomplicated urinary tract infection]."

BOTTOM LINE

The investigators found that recurrent UTI following uncomplicated UTI is common, particularly among younger and older women, those with comorbidities, and those with more antibiotic prescriptions in the year prior to the index uncomplicated UTI or with an index uncomplicated UTI caused by multidrug-resistant organisms.

15

Recurrent Urinary Tract Infection in Older Outpatient Women

JAMA Internal Medicine 2024; 184:971-972 Clinical Insights
DOI: 10.1001/jamainternmed.2024.1069

Recurrent UTI (rUTI) is defined by symptomatic, culture-confirmed UTI occurring at least twice in 6 months or 3 times in a year. rUTI appears twice as common among women older than 65 years as in the general population of women.

Classic symptoms of bladder infection include acute dysuria, urgency, frequency, and suprapubic pain, sometimes accompanied by hematuria or fever. However, more than one-third of older women have chronic overactive bladder or genitourinary syndrome of menopause, and the waxing and waning symptoms of these syndromes should not be confused with acute cystitis symptoms.

Urine testing can be misleading among older women due to high rates of bacterial colonization and contamination. Asymptomatic bacteriuria occurs in 15% to 20% of community-dwelling older women, and more than 90% of older women with asymptomatic bacteriuria also have some degree of pyuria, which limits the discriminant value of urine testing. [J Am Geriatr Soc.

1995; 43:618-622] In addition, the presence of pyuria or bacteriuria cannot rule in an infection, but their absence can help rule out a UTI. Therefore, clinicians should avoid unnecessary testing in older women without symptoms.

Diagnostic challenges arise when bacteriuria is detected in patients with dementia or functional deficits that prevent them from perceiving urinary symptoms. In May 2024, ID Watch reviewed "Bacteremia From a Presumed Urinary Source in Hospitalized Adults With Asymptomatic Bacteriuria" [JAMA Network Open. 2024;7(3): e242283] The study demonstrated that bacteremia from a presumed urinary source was rare in patients with ASB, even those presenting with altered mental status or dementia especially if the patients did not have SIRS, elevated WBC, or hypotension. Unfortunately, many older women are treated for presumptive UTI in the setting of nonspecific presentations, such as falls or functional status changes, but these non-localizing symptoms do not correlate with a positive urine culture in older populations.[Am J Obstet Gynecol. 2018;219:40-51] Consequently, even when bacteriuria is found in older patients with these nonspecific presentations, acute UTI may not be the cause, especially in the absence of signs of sepsis. In fact, in community dwelling women, prior empiric antibiotic therapy for UTI has been associated with increased subsequent risk of antimicrobial resistant organisms, bacteremia, and death. [BMC Infect Dis. 2022;22(1):805]

Prevention Strategies (*see table for details*)

Sustained low-dose antibiotic therapy has been an approach for rUTI. However, while it may be effective, the optimal duration of prophylaxis is unclear ands this approach has been associated with rapid development of antimicrobial resistance.

Vaginal estrogen can decrease rUTI risk in postmenopausal women. However, vaginal estrogen therapy may not be as effective as antibiotic prophylaxis. In one study, there was more than 2-fold higher rate of recurrent cystitis rate among women using a vaginal pessary with estradiol compared with nitrofurantoin. [Clin Infect Dis. 2003;36 (11):1362-1368]

Methenamine, an agent metabolized to formaldehyde in the distal tubules of the kidney, may be an option for rUTI prophylaxis, although prior methenamine research has not focused on older women with comorbidities. Cranberry products are reported to reduce rUTI risk by 26% among women of all ages. However, no single cranberry regimen is known to be superior to any other, and a subgroup analysis of more than 1400 older adults in long-term care facilities found no benefit of cranberry supplementation. [Cochrane Database Syst Rev. 2023;(11):CD001321] Nonprescription supplements, such as D-mannose or Lactobacillus probiotics, have not yet been proven effective. Because rUTI is associated with sexual intercourse in both postmenopausal and premenopausal women, early postcoital voiding may offer benefits in elderly women.

Table. Strategies to Prevent Recurrent Urinary Tract Infection in Women Older Than 65 Years in Outpatient Settings

Agent	Common formulations/regimens	Special considerations for older women
Antibiotic strategies		
Nitrofurantoin	Daily oral dose of 50-100 mg at bedtime or 100 mg as a single dose within 2 h of sexual intercourse[a]	Risk of pulmonary toxic effects, hepatic toxic effects, and peripheral neuropathy if CrCl is <30 mL/min; conversely, lower rates of drug-drug interactions and antimicrobial resistance[b]
Trimethoprim-sulfamethoxazole	Daily or 3 times weekly oral dose of 40 mg or 200 mg (half a single-strength tablet), respectively[a]	Greater risk of kidney failure or hyperkalemia if CrCl is <30 mL/min or with concomitant angiotensin-converting enzyme inhibitor or receptor antagonist therapy; multiple potential other drug-drug interactions[b]
Trimethoprim	Daily dose of oral 100 mg[a]	50% Dose decrease indicated if CrCl is 15-30 mL/min; multiple potential drug-drug interactions[b]
Fosfomycin	Oral dose of 3 g every 7-10 d (or every 3 d to maintain higher blood levels)[a]	Dose adjustment indicated if CrCl is <50 mL/min; lower rates of drug-drug interactions than some alternatives[b]
Cephalexin	Daily oral dose of 125-250 mg or 250 mg as a single dose just before or after sexual intercourse[a]	Potential for increased kidney toxic effects with concomitant loop diuretic therapy; drug-drug interactions with metformin and warfarin[b]
Antibiotic-sparing strategies		
Vaginal estrogen	No evidence to compare formulations; past trials with estradiol cream (0.5 mg nightly for 2 weeks then twice weekly) or estradiol ring (2 mg, every 3 mo)[a]	In contrast to vaginal estrogen, no evidence of reduced UTI risk with oral estrogen, which has other long-term health risks in older women
Methenamine	Oral methenamine hippurate, 1 g, tablet twice daily[a]	Evidence of noninferiority based on trials in women of all ages (only 0.49 more episodes per year with methenamine vs nitrofurantoin),[8] but no age-specific data
Cranberry supplements	No single definitive regimen—past trials reporting benefit with juice, tablets, or powder[a]	Relative risk of 0.74 in a meta-analysis of trials of women of all ages,[9] but unclear benefit in the subgroup of older adults in long-term care
Hydration	A trial reporting benefit with 1.5 L water over daily intake, but other solutions possible	Hydration with water preferable to electrolyte beverages in older women with conditions worsened by salt load; diuretics may be held in acute UTI

Abbreviations: CrCl, creatinine clearance; UTI, urinary tract infection.

[a] Past trials limited to 6 to 12 months for antibiotic prophylaxis, 8 to 9 months for vaginal estrogen, 12 months for methenamine, and 12 months for cranberry products.

[b] Consider evaluation of antimicrobial sensitivities through urine culture before initiating antibiotics in clinically stable older patients.

BOTTOM LINE

Prevention and management of rUTI pose significant challenges in older community-dwelling women. Rather than test and treat liberally, clinicians should focus on acute, localizing urinary symptoms that are most likely to indicate recurrent infection. If asymptomatic do not routinely send urine for culture.

Twice-Yearly Lenacapavir or Daily F/TAF for HIV Prevention in Cisgender Women

The New England Journal of Medicine published online July 24, 2024
DOI: 10.1056/NEJMoa2407001

Adherence to preexposure prophylaxis with daily oral emtricitabine–tenofovir disoproxil fumarate (F/TDF) for human immunodeficiency virus (HIV) prevention among cisgender women has been challenging. Lenacapavir is a novel, first-in-class, multistage HIV-1 capsid inhibitor with high potency and a long half-life, allowing administration by subcutaneous injection twice yearly.

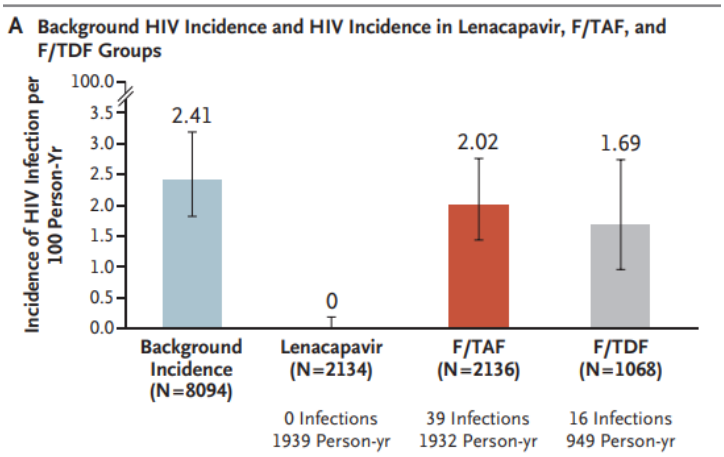
The investigators conducted a phase 3, double-blind, randomized, controlled trial involving adolescent girls and young women in South Africa and Uganda. Participants were assigned in a 2:2:1 ratio to receive subcutaneous lenacapavir every 26 weeks, daily oral emtricitabine–tenofovir alafenamide (F/TAF), or daily oral emtricitabine–tenofovir disoproxil fumarate (F/TDF; active control); all participants also received the alternate subcutaneous or oral placebo. They assessed the efficacy of lenacapavir and F/TAF by comparing the incidence of HIV infection with the estimated background incidence in the screened population and evaluated relative efficacy as compared with F/TDF.

Among 5338 participants who were initially HIV-negative, 55 incident HIV infections were observed: 0 infections among 2134 participants in the lenacapavir group (0 per 100 person-years; 95% CI, 0.00 to 0.19), 39 infections among 2136 participants in the F/TAF group (2.02 per 100 person-years; 95% CI, 1.44 to 2.76), and 16 infections among 1068 participants in the F/TDF group (1.69 per 100 person-years; 95% CI, 0.96 to 2.74). Background HIV incidence in the screened population (8094 participants) was 2.41 per 100 person-years (95% CI, 1.82 to 3.19). HIV incidence

with lenacapavir was significantly lower than background HIV incidence (incidence rate ratio, 0.00; 95% CI, 0.00 to 0.04; P<0.001) and lower than HIV incidence with F/TDF (incidence rate ratio, 0.00; 95% CI, 0.00 to 0.10; P<0.001). HIV incidence with F/TAF did not differ significantly from background HIV incidence (incidence rate ratio, 0.84; 95% CI, 0.55 to 1.28; P=0.21), and no evidence of a meaningful difference in HIV incidence was observed between F/TAF and F/TDF (incidence rate ratio, 1.20; 95% CI, 0.67 to 2.14). Adherence to F/TAF and F/TDF was low as expected. Injection-site reactions were more common in the lenacapavir group (68.8%) than in the placebo injection group (F/TAF and F/TDF combined) (34.9%). 4 participants in the lenacapavir group (0.2%) discontinued the trial regimen owing to injection-site reactions.

There were 510 pregnancies among 487 participants: 193 pregnancies in the lenacapavir group, 219 in the F/TAF group, and 98 in the F/ TDF group. At the time of this analysis, 277 pregnancies (54.3%) were completed, and 233 (45.7%) were ongoing. There were 121 births (23.7%), 66 spontaneous abortions (12.9%), and 90 induced abortions (17.6%). Among pregnant participants, HIV infection occurred in no participants in the lenacapavir group, in 4 participants in the F/TAF group, and in 1 participant in the F/TDF group. A congenital abnormality of polydactyly was observed in an infant born to a participant in the lenacapavir group who had a strong family history of this condition; this abnormality was considered by the investigator to be unrelated to the drug.

The incidence of laboratory-diagnosed C. trachomatis, N. gonorrhoeae, or T. vaginalis infection at asymptomatic screening every 26 weeks was high and similar in all three groups: in the lenacapavir group, 48.7 per 100 person-years (930 events during 1908.8 person-years); in the F/TAF group, 50.8 per 100 person-years (965 events during 1899.4 person-years); and in the F/TDF group, 48.4 per 100 person-years (452 events during 933.4 person-years).



Dr. Septimus's Annotations

Remarkedly, no adolescent girls or young women who received twice-yearly lenacapavir acquired HIV infection in this trial. The HIV incidence with lenacapavir was significantly lower than both background HIV incidence and HIV incidence with F/TDF. Adherence to daily oral F/TAF, and to F/TDF, was poor, a finding that is consistent with previous reports of low adherence to daily oral F/TDF and therefore low effectiveness in cohorts of women, particularly younger women. [Lancet 2022; 399:1779-89; AIDS Care 2021;33:712-20]

BOTTOM LINE

PrEP use remains suboptimal among women, particularly in populations with disproportionate HIV incidence, including young women, women in Africa, and women of color in the US. Twice-yearly lenacapavir offers a highly efficacious choice to potentially improve PrEP use among women.

17

Hepatitis C Virus Reinfection Among Men Who Have Sex With Men With HIV in New York City

Clinical Infectious Diseases Published 18 July 2024, ciae297
DOI: 10.1093/cid/ciae297

The investigators performed a prospective cohort study in NYC of MSM with HIV who cleared HCV to determine the incidence of and risk factors for HCV reinfection. They assessed the risk behaviors for primary HCV in NYC: receipt of semen in the rectum, and sexualized methamphetamine use, along with route of use. They defined HCV clearance as (1)

having an undetectable HCV viral load (VL) ≥12 weeks after the end of treatment, for those who were treated; or (2) having ≥2 not detected HCV VL measurements ≥12 weeks apart, for those who had spontaneous clearance (SC). For participants whose infection cleared, monitoring visits were planned every 3 months for the 6 months after clearance, and then every 6 months. They defined reinfection as new HCV viremia after clearance of the previous infection. The date of onset of reinfection was the date of the first-noted HCV viremia, or first-noted alanine aminotransferase elevation in those who were subsequently determined to be viremic, whichever was earlier. They collected the following data to consider as risk factors for reinfection: Date of birth, race, ethnicity, health insurance type (public or private), HCV genotype, interferon (IFN) λ3 haplotype, calendar year of clearance of primary HCV, mode of clearance of primary HCV (i.e., treatment, including type, or SC), timing of HCV clearance, CD4 cell count, and HIV VL suppression (defined as <50 copies/mL).

From 2000 through 2018, among 304 MSM with HIV who had cleared HCV, 42 reinfections occurred over 898 person years, for an incidence rate of 4.7 per 100 person-years(PY). Assessing 1245 postclearance visits, only receipt of semen into the rectum was associated with reinfection (hazard ratio, 9.7 [95% confidence interval: 3.3–28.3], P < .001); methamphetamine use was not. Participants with reinfection differed significantly from those without reinfection in year of clearance (P < .001), era of clearance (P < .001), mode of clearance (P = .002), and timing of clearance (P = .02). The median time (IQR) to first reinfection was 1.9 (1.2–3.5) years, and the median time to second reinfection was 1.1 (0.6–2.5) years. Although most reinfections occurred within the first 2 years after HCV clearance, reinfections continued to occur for >11 years after clearance.

Dr. Septimus's *Annotations*

In this study of HCV reinfection among MSM with HIV in NYC, the incidence rate of reinfection was high, 4.7 per 100 PY. In addition, receiving semen in the rectum during condomless receptive anal intercourse (CRAI) was strongly associated (HR, 9.7) with this high reinfection rate, which suggested transmission of HCV was sexual. This study was performed at a single institution in a single city. Their cohort had a somewhat lower proportion identied as Black and Hispanic than the total population of MSM with HIV who had primary HCV, as documented by the NYC Department of Health.

BOTTOM LINE

They found the HCV reinfection rate actually was higher than the primary infection rate, similar to the findings from other cohorts in other countries. Risk factor behaviors indicated that receipt of semen into the rectum with CRAI was strongly associated with reinfection, while noninjecting methamphetamine use was not associated with reinfection, and neither was use by the injection route. Condom use, the most effective currently available intervention to prevent semen ejaculation into the rectum, has not been successful as an HCV prevention strategy.

18

JYNNEOS Vaccine Safety Surveillance During the 2022 Mpox Outbreak Using the Vaccine Adverse Event Reporting System and V-safe, United States, 2022 to 2023

Sexually Transmitted Diseases 2024; 51: 509-515
DOI: 10.1097/OLQ.0000000000001978

In response to the mpox outbreak in 2022, CDC recommended vaccination with the JYNNEOS vaccine for people at high risk for infection. JYNNEOS contains an attenuated, nonreplicating orthopoxvirus and was approved by the FDA in 2019 for prevention of smallpox and mpox disease in adults aged ≥18. This vaccine is effective at substantially reducing risk for hospitalization among persons with mpox, including those with HIV. [MMWR Morb Mortal Wkly Rep 2023 Sep

8] To monitor post-licensure vaccine safety, the Vaccine Adverse Event Reporting system (VAERS; a passive surveillance system) and V-safe (a voluntary smartphone-based system) were utilized.

Between May 2022 and March 2023, a total of 1,207,056 JYNNEOS vaccine doses were administered in the US VAERS received 1927 reports, 50% describing administration errors and 48% adverse health events. Administration errors were more common with intradermal than subcutaneous injection. The most common adverse health events were injection site reactions. The 34 serious adverse events included four deaths; of these, three were unrelated to the vaccine (e.g., cocaine toxicity) and one was caused by mpox disease in a person vaccinated after illness onset. In all, seven cases of myocarditis were reported (two confirmed and five probable). All cases occurred in men (median age, 38). Six were hospitalized and all survived. Five cases of pericarditis alone were also reported; two were hospitalized and all survived. Three cases of anaphylaxis were reported, and 30 recipients reported hives.

Dr. Septimus's Annotations

The mpox outbreak of 2022 necessitated administration of many JYNNEOS vaccine doses and, as such, represented an excellent opportunity to monitor for adverse health events outside a clinical trial. The vaccine has proven safe in recipients (mostly men) aged 18 and older. Rates of myocarditis and pericarditis were similar to population background rates (and substantially lower than those associated with the older smallpox vaccines). Based on these and other data, I support the ACIP recommendations on mpox vaccination (two-dose JYNNEOS series for persons aged ≥18 and at risk for mpox) and would remind those at risk (such as gay, bisexual, and other men who have sex with men) that mpox transmission is ongoing (with a new outbreak in the Democratic Republic of Congo of mpox clade 1, against which this vaccine is also effective) — so if you haven't yet been vaccinated or haven't completed the two-dose series, don't wait; get vaccinated! See next review

19

CDC Health Alert Network August 7, 2024, Mpox Caused by Human-to-Human Transmission of *Monkeypox Virus* in the Democratic Republic of the Congo with Spread to Neighboring Countries

August 7, 2024

Since January 2023, the DRC has reported the largest number of yearly suspected clade I mpox cases on record. While clade I MPXV is endemic, or naturally occurring, in Democratic Republic of the Congo (DRC), the current outbreak is more widespread than any previous DRC outbreak and has resulted in clade I mpox transmission to some neighboring countries. The Republic of the Congo (ROC), which borders DRC to the west, declared a clade I mpox outbreak in April 2024, and there have been confirmed cases in the Central African Republic (CAR). While clade I mpox is endemic in ROC and CAR, the epidemiologic pattern of recent cases suggests a possible link to DRC.

No cases of clade I mpox have been reported outside central and eastern Africa at this time. Because there is a risk of additional spread, CDC recommends clinicians and jurisdictions in the US maintain a heightened index of suspicion for mpox in patients who have recently been in DRC or to any country sharing a border with DRC (ROC, Angola, Zambia, Rwanda, Burundi, Uganda, South Sudan, CAR) and present with signs and symptoms consistent with mpox. These can include rash that may be located on the hands, feet, chest, face, mouth, or near the genitals; fever; chills; swollen lymph nodes; fatigue; myalgia (muscle aches and backache); headache; and respiratory symptoms like sore throat, nasal congestion, and cough.

Dr. Septimus's Annotations

MPXV has two distinct genetic clades (subtypes of MPXV), I and II, which are endemic to central and west Africa, respectively. Clade I MPXV has previously been observed to be more transmissible and to cause a higher proportion of severe infections than clade II MPXV. The ongoing global mpox outbreak that began in 2022 is caused by clade II MPXV, and cases continue to be reported worldwide including the US.

Clade I MPXV is endemic in DRC and several other Central African countries, and cases are reported annually. More than 22,000 suspect cases, with more than 1,200 suspected deaths, have been reported in DRC since January 1, 2023, a substantial increase from the median 3,767 suspect clade I mpox cases reported annually in DRC during 2016–2021.. Outbreaks of clade I MPXV associated with sexual contact among men who have sex with men and female sex workers and their contacts have been reported in some provinces. In other provinces, patients have acquired infection through contact with infected dead or live wild animals, household transmission, or patient care (transmitted in the absence of appropriate personal protective equipment); a high proportion of cases have been reported in children younger than 15 years of age. Mpox vaccine, which is expected to be effective against both clades. WHO has decided to call Mpox outbreak in Africa a global emergency.

BOTTOM LINE

Mpox continues to spread in Africa and in the US. Education and vaccinating eligible people as outlined above is critical in limiting the spread of the virus.

20

Clusters of Emerging Multidrug-Resistant Organisms in United States Healthcare Facilities During the Initial Months of the SARS-CoV-2 Pandemic

American Journal of Infection Control published online July 26, 2026
DOI: 10.1016/j.ajic.2024.07.013

Outbreaks of emerging multidrug-resistant organisms (MDROs), including carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant *Acinetobacter baumannii* (CRAB), and *Candida auris*, have been reported among SARS-CoV-2 patients. They describe MDRO clusters in SARS-CoV-2 units and associated infection control (IC) practices early in the SARS-CoV-2 pandemic. To address this question, they conducted a retrospective survey of a convenience sample of health departments in 11 states to describe clusters of MDROs that began before November 1, 2020, and involved SARS-CoV-2 units. Cluster characteristics and IC practices during the cluster period were assessed using a standardized outbreak report form and descriptive analyses were performed. The forms collected facility and cluster characteristics, the number of patients associated with each cluster, patient outcomes, IC practices, changes in IC practices and in frontline HCP staffing due to the pandemic, and the local epidemiology of MDROs and SARS-CoV-2.

Multidrug-Resistant Organisms (MDRO) Clusters in US Healthcare Facilities, 2019-2020

#	MDRO
10	Carbapenem-resistant Enterobacterales (CRE)
1	Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA)
1	Carbapenem-resistant *Acinetobacter baumannii* (CRAB)
6	*Candida auris*

Overall, 18 clusters of carbapenem-resistant Enterobacterales (CRE, 10), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA, 1), carbapenem-resistant *Acinetobacter baumannii* (CRAB, 1), and *Candida auris* (6) were reported by facilities in 10 states. The clusters affected 345 patients in 11 acute care hospitals and 52 patients in 6 post-acute care facilities. A cluster reported in a long-term acute care hospital did not have information available on the number of affected patients.

Among the 17 clusters with information available, 5 (29%) were first recognized in a non-COVID unit, 7 (41%) occurred in facilities located in communities with moderate to substantial SARS-CoV-2 transmission, and 10 (59%) in jurisdictions where the MDRO was considered endemic or regional. The pooled proportion of patients co-infected with SARS-CoV-2 was 54%.

Among the facilities with available information on HCP staffing, 10 (71%) of 15 said they increased the use of contracted or agency HCP relative to pre-pandemic practices, 8 (53%) of 15 reassigned HCP to units with a different patient acuity than where they typically worked, and 7 (58%) of 12 reassigned cleaning duties to HCP who were also providing direct patient care.

Of the facilities with information about PPE availability, 9 (60%) of 15 reported a shortage of isolation gowns, and 11 (69%) of 16 reported extended use of gowns (HCPs wearing the same gown when interacting with more than one patient), irrespective of an actual shortage. And although only 1 (7%) of 15 facilities reported a glove shortage, 3 (19%) of 16 reported extended use of gloves without changing them between patients. In addition, shortages of or difficulty obtaining preferred disinfectants were reported in 8 (67%) of 12 facilities, while 5 (31%) of 16 reported shortages of alcohol-based sanitizer or soap. Compared with pre-pandemic practices in similar units, hand hygiene audit frequency decreased in 85% of affected units during the cluster period.

Dr. Septimus's Annotations

Surges in Covid-19 patients, overcrowding, increased antibiotic use, and actual shortages of HCP and PPE likely played a role in these increases, they suggest changes in staffing practices and PPE conservation strategies may have also contributed. Extended use of gowns and gloves, for example, could have facilitated MDRO transmission among patients. This study was limited to a small number of healthcare facilities, the pathogens documented in the outbreak reports are among those that saw substantial nationwide increases during the pandemic. A 2022 CDC report [COVID-19 : U.S. impact on antimicrobial resistance, special report 2022 (cdc.gov)] found that hospital-onset CRAB cases increased by 78% in 2020 compared with 2019, CRE cases by 35%, multidrug-resistant P aeruginosa by 32%, and combined hospital and community-onset C auris by 60%.

Because of pandemic impacts, 2020 data are delayed or unavailable for 9 of the 18 antimicrobial resistance threats.

- *Clostridioides difficile (C. diff)*
- Drug-resistant *Neisseria gonorrhoeae*
- Drug-resistant *Campylobacter*
- Drug-resistant nontyphoidal *Salmonella*
- Drug-resistant *Salmonella* serotype Typhi
- Drug-resistant *Shigella*
- Drug-resistant *Streptococcus pneumoniae*
- Erythromycin-resistant group A *Streptococcus*
- Clindamycin-resistant group B *Streptococcus*

Available data show an alarming increase in resistant infections starting during hospitalization, growing at least 15% from 2019 to 2020.

- Carbapenem-resistant *Acinetobacter* (↑78%)
- Antifungal-resistant *Candida auris* (↑60%)*
- Carbapenem-resistant Enterobacterales (↑35%)
- Antifungal-resistant *Candida* (↑26%)
- ESBL-producing Enterobacterales (↑32%)
- Vancomycin-resistant Enterococcus (↑14%)
- Multidrug-resistant *P. aeruginosa* (↑32%)
- Methicillin-resistant *Staphylococcus aureus* (↑13%)

BOTTOM LINE

Changes in infection control (IC) practices and supply chain shortages were identified in facilities with MDRO outbreaks during the SARS-CoV-2 pandemic and might have contributed to MDRO transmission. To reverse this trend, healthcare facilities need strong, well-supported IC programs to address the MDRO challenges.

21

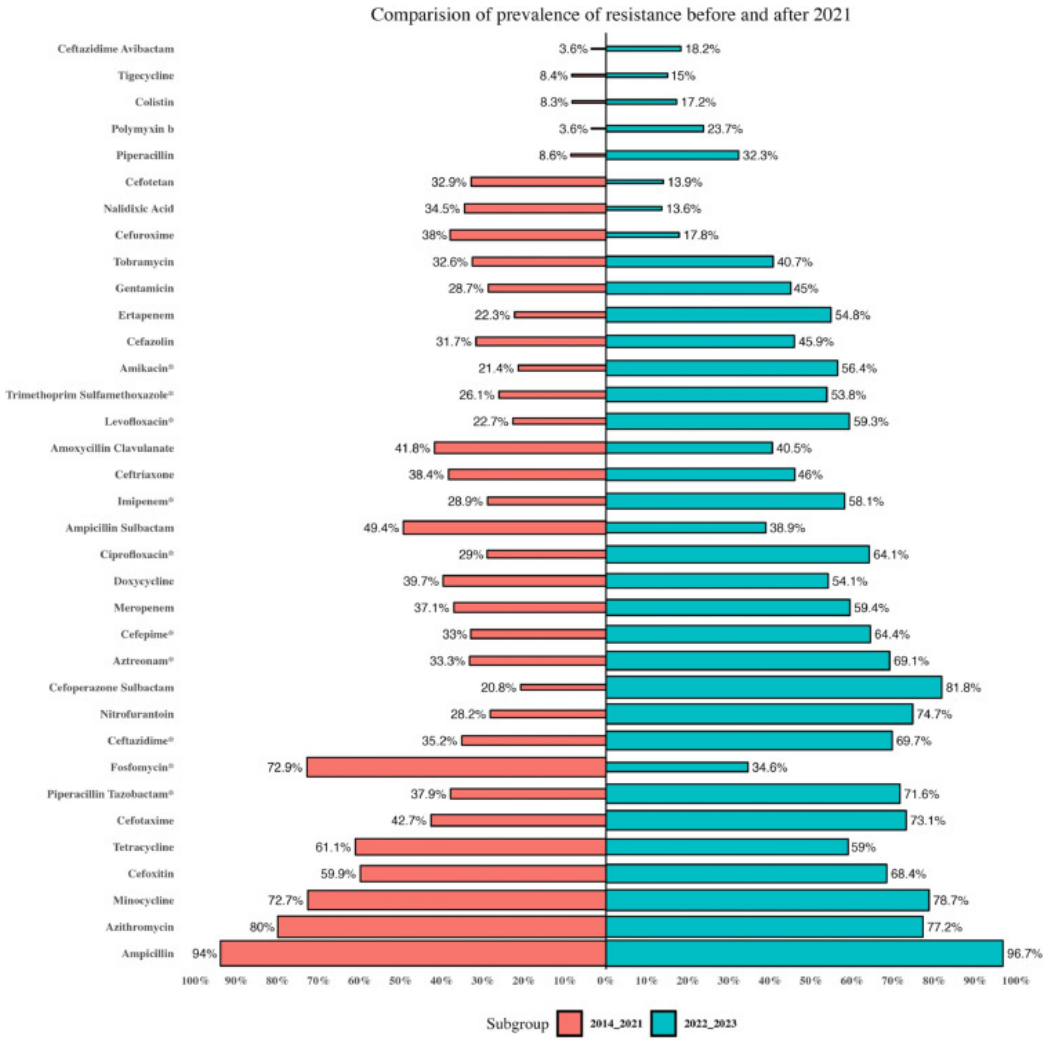
Antibiotic resistance rates in hypervirulent *Klebsiella pneumoniae* strains: a systematic review and meta-analysis

Journal of Global Antimicrobial Resistance published online July 26, 2024
DOI: 10.1016/j.jgar.2024.06.018

In response to the growing global concerns regarding antibiotic resistance, the investigators conducted a meta-analysis to assess the prevalence of antibiotic resistance in hypervirulent *Klebsiella pneumoniae* (hvKp) strains. Eligible studies published in English until April 10, 2023, were identified through a systematic search of various databases. Data extraction included publication details and key information on antibiotic resistance. Data synthesis employed a random-effects model to account for heterogeneity.

This meta-analysis of 77 studies from 17 countries. A high resistance rates have been observed against various classes of antibiotics. Ampicillin-sulbactam faced 45.3% resistance, respectively, rendering them largely ineffective. The first-generation cephalosporin cefazolin exhibited a resistance rate of 38.1%, whereas second-generation cefuroxime displayed 26.7% resistance. Third-generation cephalosporins, cefotaxime (65.8%) and ceftazidime (57.1%), and fourth-generation cephalosporins, cefepime (51.3%), showed substantial resistance. The last resort carbapenems, imipenem (45.7%), meropenem (51.0%), and ertapenem (40.6%), were equally impacted.

Comparative analysis of antibiotic-resistant hvKp isolate prevalence before and after 2021, highlighting statistically significant yearly differences



Dr. Septimus's Annotations

WHO conducted through its Global Antimicrobial Resistance and Surveillance System (GLASS), issued a request for information earlier this year to all countries enrolled in the system after receiving reports of increased identification of hvKp isolates in several countries. Of the 43 countries and territories that responded to the WHO request, 16 reported the presence of hvKp strains. Of the 16 countries that reported the presence of hvKp strains, 12 (Algeria, Argentina, Australia, Canada, India, Iran, Japan, Oman, Philippines, Switzerland, Thailand, and the United Kingdom) specifically reported the presence of the ST23-K1 strain. The United States is among the countries that have reported the presence of hvKp strains. hvKp strains can cause severe invasive infections in healthy individuals that develop quickly and spread to various sites. Infections caused by hvKp strains have been associated with high morbidity and mortality. Although hvKp infections were initially found in community settings in parts of Asia and were susceptible to most antibiotics, recent reports have shown transmission of multidrug-resistant hvKp strains in healthcare settings in several countries. One strain of hvKp, sequence type (ST)23, a strain that carries carbapenemase genes which can confer resistance to carbapenem antibiotics and all available beta-lactam antibiotics. WHO noted that ST23 strains can out-compete other gut bacteria, which can facilitate colonization and spread, and have the capability to cause outbreaks. The WHO said in its assessment that with the concurrence of hypervirulence and antibiotic resistance, we can expect an increased risk of spread of these strains at both the community and in the hospital.

BOTTOM LINE

This study emphasizes the growing issue of antibiotic resistance in hvKp strains, with notable resistance to both older and newer antibiotics, increasing resistance over time. Effective responses must be a multifaceted approach involving international cooperation, standardized testing, and tailored regional interventions.

22

Early Antibiotic Exposure and Bronchopulmonary Dysplasia in Very Preterm Infants at Low Risk of Early-Onset Sepsis

JAMA Network Open 2024;7(6): e2418831
DOI: 10.1001/jamanetworkopen.2024.18831

The question: Is early antibiotic exposure associated with higher risk of bronchopulmonary dysplasia (BPD) in very preterm infants (VPIs) at low risk of early-onset sepsis (EOS)? This national multicenter cohort study utilized data which prospectively collected data from January 1, 2019, to December 31, 2021. VPIs less than 32 weeks' gestational age or with birth weight less than 1500 g at low risk of EOS, defined as those born via cesarean delivery, without labor or rupture of membranes, and no clinical evidence of chorioamnionitis, were included. Data analysis was conducted from October 2022 to December 2023. Early antibiotic exposure was defined as the total number of calendar days antibiotics were administered within the first week of life, which were further categorized as no exposure, 1 to 4 days of exposure, and 5 to 7 days of exposure. The primary outcome was the composite of moderate to severe BPD or mortality at 36 weeks' post menstrual age (PMA). Logistic regression was employed to assess factors associated with BPD or mortality using 2 different models.

In this cohort study that included 27,176 VPIs in China, prolonged early antibiotic exposure (5-7 days) was associated with increased likelihood of moderate to severe BPD or death among VPIs at low risk of EOS. The use of broad-spectrum antibiotics (1-7 days) was also associated with a higher risk of moderate to severe BPD or death.

Dr. Septimus's Annotations

Empirical antibiotic therapy is often initiated as a precaution against EOS. According to American Academy of Pediatrics guidelines, antibiotics should be discontinued by 36 to 48 hours if blood cultures are sterile in infants at low risk of EOS; [Pediatrics. 2018;142(6): e20182896] however, most studies including this current paper show an even higher proportion of low-risk infants (62.9%) receiving prolonged antibiotics, indicating an overuse in this population. EOS poses a substantial risk to very preterm infants, necessitating the prevalent administration of empirical antibiotics in the NICU. Puopolo et al reported that more than one-third of the extremely preterm infants in their study were categorized as low risk for EOS, with an incidence of 0.5%. In these low-risk groups, prolonged empirical antibiotic treatment (>5 days) was observed in approximately 35% of cases. [Pediatrics. 2017;140(5): e20170925] Recent studies have suggested a potential association of prolonged antibiotic therapy with both increased mortality and a higher incidence of adverse neonatal outcomes, including BPD. [J Pediatr. 2022; 243:91-98. e4; Pediatrics. 2019;143(3): e20182286] The reported association may be influenced by factors such as culture-proven sepsis bacteremia, illness severity, and early respiratory disease. One proposed mechanism is that early antibiotic exposure may disrupt the neonatal intestinal microbiome, leading to dysregulation of innate immune mechanisms that protect against airway and systemic inflammation through the intestinal-pulmonary axis, ultimately heightening the risk of BPD. [Microbiome. 2022;10(1):103; Nat Immunol. 2019;20(10):1279-1290] Comparing the potential harm caused by the overuse of broad-spectrum antibiotics on beneficial microbial communities, narrow-spectrum antibiotics may be safer by preserving the integrity of these microbial communities. [Genome Med. 2017;9(1):110]

Limitations include observational design and exclusion of infants with severe illnesses. Also, cases with a potential infection or maternal colonization with group B streptococcus (GBS) were not identified, and the investigators were not able to determine the effect of ventilator-associated pneumonia, fluid overload, and exposure to hemodynamically significant patent ductus arteriosus (PDA).

BOTTOM LINE

The findings in this study highlight a concern about overuse of early antibiotics among very preterm infants at low risk for early-onset sepsis. Prolonged treatment with broad-spectrum antibiotics in these infants was associated with a heightened risk of developing moderate to severe bronchopulmonary dysplasia. This finding underscores the importance of antimicrobial stewardship, especially in the early life stages of this vulnerable population

23

Health Alert Network August 13, 2024: Human Parvovirus B19 Activity in the United States

Parvovirus B19 is a seasonal respiratory virus that is transmitted through respiratory droplets by people with symptomatic or asymptomatic infection. In the first quarter of 2024, public health authorities in 14 European countries observed unusually high numbers of cases of parvovirus B19. In the US, there is no routine surveillance for parvovirus B19, and it is not a notifiable condition. However, recently, CDC has received reports indicating increased parvovirus B19 activity in the US. Parvovirus B19 is highly transmissible in respiratory droplets, with 50% of susceptible people infected after household exposure and 20–50% of susceptible students and staff infected during school outbreaks. Historically, people working in schools and in close contact with children (e.g., daycare workers and teachers) have had high occupational risk of infection. About 50% of adults have detectable antibodies by age 20 years. More than 70% of adults have detectable antibodies by age 40 years. Antibodies from prior infection are thought to protect against reinfection.

Although many people with parvovirus B19 infection are asymptomatic, immunocompetent children and adults with symptomatic disease typically develop a biphasic illness. The first phase of illness is characterized by symptoms of fever, myalgia, and malaise and develops approximately 7 days after infection. This phase lasts approximately 5 days. People with parvovirus B19 infection are most contagious during the first phase, when viral loads in respiratory secretions and saliva are highest. During the second phase of illness (approximately 7–10 days after the first phase), children often present with a characteristic facial rash (erythema infectiosum, or "slapped cheek" appearance), which may be followed by reticulated body rash or joint pain (arthralgia) 1–4 days later. In immunocompetent adults, the most common symptoms of parvovirus B19 disease typically occur during the second phase and include a reticular rash on the trunk and joint pain (arthralgia). Typically, the characteristic facial rash does not appear until after viral loads have declined. Laboratory tests conducted during acute illness can demonstrate a transient decrease in absolute reticulocyte counts lasting approximately 10 days, mild anemia, thrombocytopenia, or leukopenia. Most people require only supportive care during the acute phase of illness and will recover completely. Severe outcomes from parvovirus B19 disease, such as myocarditis, hepatitis, or encephalitis, are rare. No vaccine or specific treatment is recommended for parvovirus B19 infection. Parvovirus B19 infection can lead to adverse health outcomes among people without pre-existing immunity who are pregnant, immunocompromised, or have chronic hemolytic disorders. During pregnancy, most cases of fetal parvovirus B19 infection resolve spontaneously without adverse outcomes. However, the risk of an adverse fetal outcome (e.g., fetal anemia, non-immune hydrops, or fetal loss) is 5–10%, and is highest when acute infection occurs between gestational weeks 9–20. Parvovirus B19 can also cause chronic or transient aplastic anemia among people with severely immunocompromising conditions (e.g., leukemia or other cancers, organ transplant, HIV infection, receiving chemotherapy) or chronic hemolytic disorders (e.g., sickle cell disease, thalassemia, hereditary spherocytosis). Red blood cell transfusions and intravenous immunoglobulin are the mainstays of treatment for aplastic anemia.

Recommendations for Healthcare Providers

1. Have increased suspicion for parvovirus B19 among people presenting with compatible symptoms (i.e., fever, rash, arthropathy, or unexplained anemia with low reticulocyte count).
2. Provide preventive counseling and have a low threshold to test people who present with compatible signs and symptoms if they are at higher risk of severe parvovirus B19 disease, including:
    - Pregnant people
    - People with severely immunocompromising conditions, including leukemia or other cancers, organ transplant, HIV infection, or who are receiving chemotherapy.
    - People with chronic hemolytic blood disorders, including sickle cell disease, thalassemia, and hereditary spherocytosis.

1. When treating people with suspected or confirmed parvovirus B19, inform them or their caregivers about high-risk groups and advise any exposed contacts in those groups (e.g., who may be pregnant) to consult with their healthcare providers.
2. Follow standard of care (e.g., professional society guidelines) for testing pregnant people reporting exposure to parvovirus B19 infection or who present with compatible signs and symptoms of maternal or fetal parvovirus B19 disease.
3. Promote CDC recommendations for core prevention strategies to prevent respiratory illness, including practicing good hand hygiene and taking steps for cleaner air to reduce spread of parvovirus B19 and other respiratory viruses.
    - People at higher risk of severe outcomes or complications who work in settings with higher risk of parvovirus B19 exposure should practice hand hygiene, avoid sharing food or drinks, and consider wearing a respirator or mask while at work. There is no proven benefit to removing someone from work in settings with higher risk of parvovirus B19 exposure.

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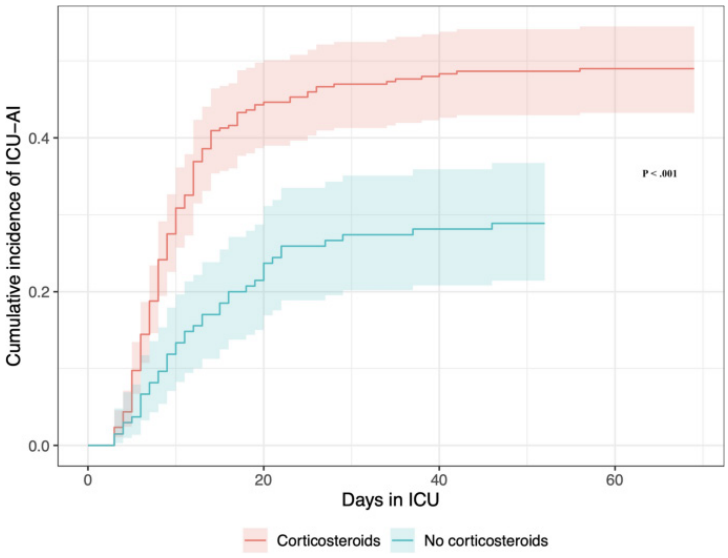
Intensive care unit acquired infections more common in patients with COVID 19 than with influenza

Scientific Reports 2024; 14:16655
DOI: 10.1038/s41598-024-67733-z

In this study the investigators analyzed the incidence, microbiology, and outcome in patients with Covid-19 versus influenza in the ICU included all adult patients treated with invasive mechanical ventilation due to (1) Covid-19 between January 2020 and March 2022, and (2) influenza between January 2015 and May 2023.

Of the 480 participants included in the final analysis, the majority had Covid-19. The incidence rates of ICU-acquired infections were 31.6/1000 and 9.9/1000 ICU-days in the Covid-19 and influenza cohorts, respectively. Ventilator-associated lower respiratory tract infections (VAP) were most common in both groups. In patients with Covid-19, corticosteroid treatment was associated with an increased risk of ICU-acquired infections and with higher 90-day mortality in case of infection. Furthermore, ICU-acquired infection was associated with a prolonged time in the ICU, with more difficult-to-treat gram-negative infections in late versus early VAP. The majority of VAP in the Covid-19 cohort were caused by gram-negative bacteria 66%, compared to 28% for patients with influenza. Staphylococcus aureus was identified as the most common pathogen causing VAP among patients with influenza. Sixty-five BSIs in the Covid-19 group were caused by gram-positive bacteria, 18 by gram-negative bacteria, and 11 by Candida spp. All BSIs in the influenza cohort were caused by either gram-positive bacteria or Candida albicans. Of all patients with an ICU-HAI in the Covid-19 cohort, 15% had MDRO, of which 79% were gram-negative bacteria. None of the infections in the influenza group were caused by an MDRO.

Cumulative incidence of intensive care unit-acquired infections in patients with and without corticosteroid treatment from a competing events analysis using Fine and Gray model with discharge from intensive care or death as competing events.



P < 0.001. ICU-AI ICU-Acquired Infection.

Dr. Septimus's Annotations

The different risk of ICU-HAIs in patients with Covid-19 as opposed to influenza is consistent with other studies. [Clin. Infect. Dis. 75, 2225–2238; Intensive Care Med. 47, 188–198] The possible explanations include factors such as increased demand on the healthcare system during the Covid-19 pandemic, staffing and turnover, alterations of immune responses caused by SARS-CoV-2, a high proportion of ARDS in Covid-19, more frequent prone positioning, and prolonged IMV and ICU stays. Their findings demonstrated an increased risk of mortality with ICU-HAIs in patients with corticosteroid treatment as compared to patients who have not received corticosteroids. The comparison group had relatively few patients on mechanical ventilation with influenza, especially during the first few years of the Covid-19 pandemic. Most samples from the lower respiratory tract were not taken with a protected brush. This may have resulted in some colonization cultures and contaminations being included for analysis. Further research is needed to understand how

the association between corticosteroid treatment and incidence and outcome of ICU-acquired infections varies across different patient categories.

BOTTOM LINE

Secondary bacterial infections among ICU patients with Covid-19 are a well-recognized complication. Covid-19 patients were more likely to have difficult-to-treat gram-negative infections. The high incidence rate during the Covid-19 pandemic may partly be due to overuse of antibiotics and corticosteroid treatment. Given the increased use of corticosteroids for severe viral and bacterial pneumonia and ARDS, their impact on ICU-HAIs merits further study.

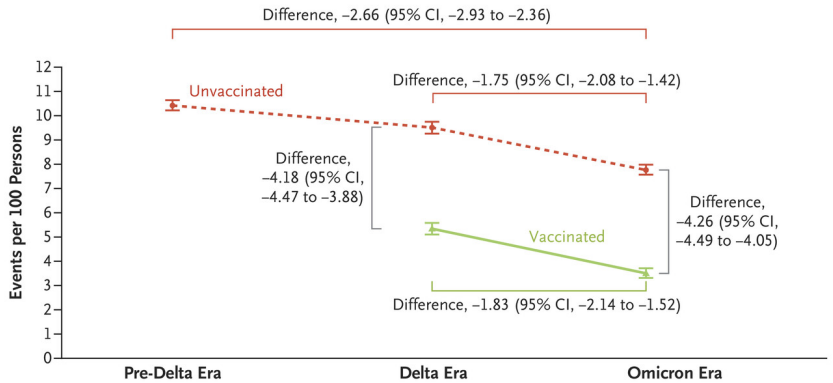
Postacute Sequelae of SARS-CoV-2 Infection in the Pre-Delta, Delta, and Omicron Eras

The New England Journal of Medicine published online July 17, 2024
DOI: 10.1056/NEJMoa2403211

Postacute sequelae of SARS-CoV-2 infection (PASC) remains an ongoing public health concern. Whether the risk and burden of PASC have changed over the course of the pandemic is unclear. The investigators used electronic health records(EHR) of the Department of Veterans Affairs to build a study population of 441,583 veterans with SARS-CoV-2 infection between March 1, 2020, and January 31, 2022, and 4,748,504 noninfected contemporaneous controls. They estimated the cumulative incidence of PASC at 1 year after SARS-CoV-2 infection during the pre-delta, delta, and omicron eras of the Covid-19 pandemic. They studied eight cohorts — five cohorts with SARS-CoV-2 infection between March 1, 2020, and January 31, 2022, and three noninfected contemporaneous control cohorts of 4.7 million persons — to estimate the cumulative incidence of PASC at 1 year after infection. They examined several health outcomes defined based on multiple data domains, including ICD-10 diagnosis codes, laboratory values, and prescription medications. The investigators then divided "points in time" into three eras in which specific SARS-CoV-2 variants were the dominant lineage — the pre-delta era, the delta era, and the omicron era. They examined vaccination records from additional points in time and they included several covariates, including age, race, ethnic group, sex as reported by the participant, area deprivation index, smoking status, BP, BMI, and use of long-term care services.

Among unvaccinated persons infected with SARS-CoV-2, the cumulative incidence of PASC during the first year after infection was 10.42 events per 100 persons in the pre-delta era, 9.51 events per 100 persons in the delta era, and 7.76 events per 100 persons in the omicron era Among vaccinated persons, the cumulative incidence of PASC at 1 year was 5.34 events per 100 persons during the delta era and 3.50 events per 100 persons during the omicron era Vaccinated persons had a lower cumulative incidence of PASC at 1 year than unvaccinated persons. Decomposition analyses showed 5.23 (95% CI, 4.97 to 5.47) fewer PASC events per 100 persons at 1 year during the omicron era than during the pre-delta and delta eras combined; 28.11% of the decrease (95% CI, 25.57 to 30.50) was attributable to era-related effects (changes in the virus and other temporal effects), and 71.89% (95% CI, 69.50 to 74.43) was attributable to vaccines.

Cumulative Incidence of Postacute Sequelae of SARS-CoV-2 Infection (PASC) in the Pre-Delta, Delta, and Omicron Eras According to Vaccination Status



Events per 100 Persons			
Unvaccinated	10.42 (95% CI, 10.22–10.64)	9.51 (95% CI, 9.26–9.75)	7.76 (95% CI, 7.57–7.98)
Vaccinated		5.34 (95% CI, 5.10–5.58)	3.50 (95% CI, 3.31–3.71)

Dr. Septimus's Annotations

The prevalence of long Covid is estimated to be 6.9% among noninstitutionalized persons in the US who were previously infected with SARS-CoV-2. [JAMA 2024; 332:5-6] But defining the true incidence, underlying pathophysiology, full manifestations, and prognosis of long Covid continues to be challenging. Overall, the data showed that the cumulative incidence of long Covid decreased over the course of the pandemic, from a high of 10.42 cases per 100 persons at 1 year after infection during the pre-delta era to a low of 3.50 cases per 100 persons at 1 year among vaccinated persons who had SARS-CoV-2 infection during the omicron era. Still, there were new cases of long Covid among vaccinated persons infected during the omicron era, a finding that suggests that new cases of PASC will probably continue to occur. An additional finding was that although the risk of most sequelae from acute Covid-19 decreased across the eras, the risk of metabolic and gastrointestinal disorders may have increased, particularly among unvaccinated persons. However, Covid symptoms including cardiovascular and kidney problems, decreased. This study provides a snapshot across only the first 2 years of the pandemic (March 2020 through January 2022) and focuses primarily on male US veterans. Second, the use of EHR can miss confounding variables and lead to the misclassification of SARS-CoV-2 infection.

BOTTOM LINE

First vaccinations can prevent many but not all cases of long Covid. Second, viral variants influence the risk of post-acute sequelae of SARS-CoV-2 infection (PASC). Third, the study suggests that new cases of PASC may continue to occur.

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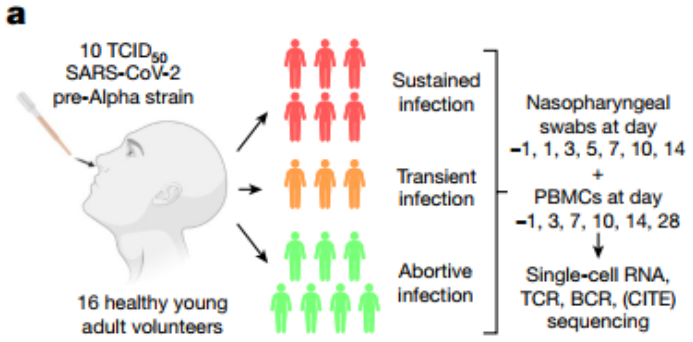
Human SARS-CoV-2 challenge uncovers local and systemic response dynamics

Nature 2024; 631:189-198
DOI: 10.1038/s41586-024-07575-x

An international team experimentally infected 16 healthy young adults with low doses of an early SARS-CoV-2 variant and followed the volunteers closely for 1 month. The participants had not been infected with, nor vaccinated against the virus previously. Immune-system measurements involving cells from both blood and nasal swabs were made both before and after infection. Below is the study design and cohort composition.



They observed that the interferon response in blood preceded the nasopharyngeal response. Moreover, nasopharyngeal immune infiltration occurred early in samples from individuals with only transient infection and later in samples from individuals with sustained infection. High expression of *HLA-DQA2* before inoculation was associated with preventing sustained infection. Ciliated cells showed multiple immune responses and were most permissive for viral replication, whereas nasopharyngeal T cells and macrophages were infected non-productively

Six participants had persistently positive viral tests and mild symptoms. Of the remaining 10 people, 3 had intermittently positive nasal swabs for a few days but no symptoms (transient infection), and 7 had persistently negative viral test results (abortive infection). What most distinguished participants who developed sustained infections — compared with those who had transient or

abortive infections — were lower levels of a type I interferon response in the nose and lower levels of HLA-DQA2 on antigen-presenting cells in both blood and nasal mucosa. These observations are consistent with past reports. [Science 2020; 370: eabd4570]

Dr. Septimus's *Annotations*

These findings may explain why stimulating an interferon response in the nose may be therapeutic in people with Covid-19. This study goes further in suggesting that intervention that amplify two specific elements of the immune response might help prevent and/or treat SARS-CoV-2.

BOTTOM LINE

This study provides a comprehensive and detailed time-resolved description of the course of mild SARS-CoV-2 infection and gives new insights into responses that are associated with resisting a sustained infection and disease.

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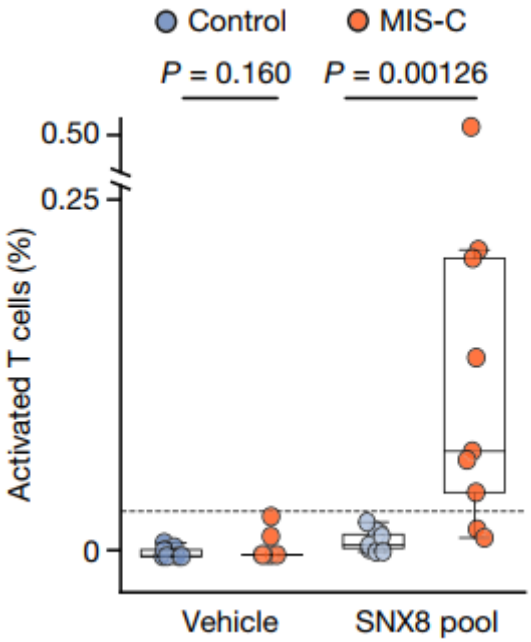
Molecular mimicry in multisystem inflammatory syndrome in children

Nature published online August 7, 2024
DOI: 10.1038/s41586-024-07722-4

The investigators used a large set of samples from patients with MIS-C to identify a distinct set of host proteins targeted by patient autoantibodies including a particular autoreactive epitope within SNX8, a protein involved in regulating an antiviral pathway associated with MIS-C pathogenesis. In parallel, they also probed antibody responses from patients with MIS-C to the complete SARS-CoV-2 proteome and found enriched reactivity against a distinct domain of the SARS-CoV-2 nucleocapsid protein. The immunogenic regions of the viral nucleocapsid and host SNX8 proteins bear remarkable sequence similarity.

Consequently, they found that many children with anti-SNX8 autoantibodies also have cross-reactive T cells engaging both the SNX8 and the SARS-CoV-2 nucleocapsid protein epitopes. SNX8 is a protein that is 456 amino acids and belongs to a family of sorting nexins involved in endocytosis, endosomal sorting and signaling. Publicly available expression data36 show that SNX8 is widely expressed across various tissues including the brain, heart, gastrointestinal tract, kidneys and skin, with the highest expression in undifferentiated cells and immune cells. Previous work has associated SNX8 with host defense against RNA viruses. [Cell. Mol. Immunol. 202017:1126–1135] Together, these findings suggest that patients with MIS-C develop a characteristic immune response to the SARS-CoV-2 nucleocapsid protein that is associated with cross-reactivity to the self-protein SNX8, demonstrating a mechanistic link between the infection and the inflammatory syndrome, with implications for better understanding a range of post-infectious autoinflammatory diseases.



Dr. Septimus's Annotations

To date, at least 34 autoantigen candidates have been reported to be associated with MIS-C. [J. Clin. Invest. 2021 131, e151520] However, the investigators in this study also found that only UBE3A (a ubiquitously expressed ubiquitin protein ligase) was differentially enriched in their MIS-C dataset, whereas the remaining 33 were present in a similar proportion of cases with MIS-C and at-risk controls. This study adds evidence that there is an autoimmune component to MIS-C. They also found that children with MIS-C had an unusual immune response to the coronavirus: They made antibodies to a part of the viral nucleoprotein that the other children who had severe Covid did not. The part of the viral nucleoprotein that the children with MIS-C react to is remarkably similar to a section of SNX8.

BOTTOM LINE

These findings help to connect several important known aspects of MIS-C pathophysiology and draw parallels to other diseases in which exposure to a new antigen leads to autoimmunity.

28 Covid-19 by the Numbers

COVID-19 Update for the United States

Early Indicators

Test Positivity
% Test Positivity
18.1%
Week ending August 10, 2024
Previous week 17.9%
Aug 19, 2023 Aug 10, 2024

Emergency Department Visits
% Diagnosed as COVID-19
2.4%
Week ending August 10, 2024
Previous week 2.5%
Aug 19, 2023 Aug 10, 2024

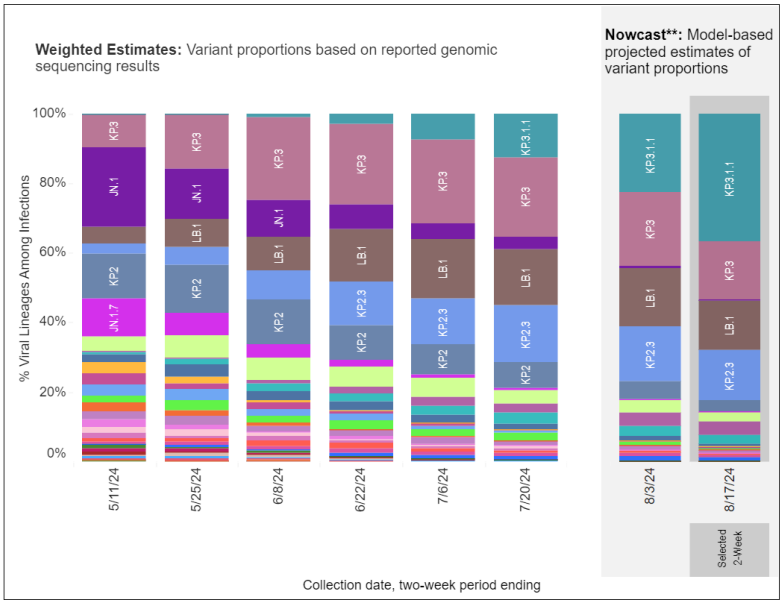
Severity Indicators

Hospitalizations
Rate per 100,000 population
3.3
Week ending July 20, 2024
Previous week 3.2
Jul 29, 2023 Jul 20, 2024

Deaths
% of All Deaths in U.S. Due to COVID-19
1.9%
Week ending August 10, 2024
Previous week 1.6%
Aug 19, 2023 Aug 10, 2024

Weighted and Nowcast Estimates in United States for 2-Week Periods in 4/28/2024 – 8/17/2024

Hover over (or tap in mobile) any lineage of interest to see the amount of uncertainty in that lineage's estimate.



Nowcast Estimates in United States for 8/4/2024 – 8/17/2024

USA

WHO label	Lineage #	%Total	95%PI
Omicron	KP.3.1.1	36.8%	31.1-42.7%
	KP.3	16.8%	14.4-19.6%
	KP.2.3	14.4%	11.7-17.7%
	LB.1	14.1%	11.2-17.5%
	LP.1	4.1%	3.0-5.6%
	KP.2	3.2%	2.7-3.8%
	KP.1.1	2.7%	1.9-3.7%
	KP.1.1.3	2.5%	1.7-3.6%
	KS.1	1.0%	0.6-1.7%
	KP.2.15	0.9%	0.4-2.1%
	LF.3.1	0.9%	0.6-1.4%
	JN.1.16.1	0.8%	0.5-1.1%
	JN.1.18	0.4%	0.3-0.7%
	KP.4.1	0.3%	0.2-0.6%
	JN.1	0.2%	0.1-0.3%
	JN.1.11.1	0.2%	0.1-0.3%
	XDV.1	0.2%	0.1-0.4%
	KW.1.1	0.1%	0.1-0.2%
	JN.1.16	0.1%	0.1-0.1%
	KP.1.2	0.1%	0.0-0.1%
	JN.1.7	0.1%	0.1-0.1%
	KQ.1	0.0%	0.0-0.0%
	JN.1.13.1	0.0%	0.0-0.0%
	JN.1.4.3	0.0%	0.0-0.0%
	JN.1.8.1	0.0%	0.0-0.0%
	XDP	0.0%	0.0-0.0%
	JN.1.32	0.0%	0.0-0.0%

Dr. Septimus's Annotations

A new coronavirus variant named KP.3.1.1 has risen to dominance in the US., almost doubling in prevalence in just two weeks, according to the CDC.

Experts are warning that the new variant—which, as of August 17, accounts for more than 35% of Covid-19 cases—is more challenging to our immune systems compared to previous variants.

The new variant is a sub-lineage of the previously dominant KP.3, which rose to prominence at the end of May. Together, KP.3.1.1 and KP.3 account for more than half of all Covid-19 cases in the US, as the virus continues to spread amid a "summer wave" of infections.

Both KP.3.1.1 and KP.3 belong to a new class of variants nicknamed the "FLiRT" variants. They are named after the mutations in the projections on the virus' surface that allow them to enter our cells. According to early analysis, KP.3.1.1 is significantly more transmissible than previous variants, including KP.3.

BOTTOM LINE

KP.3.1.1 is more transmissible and more immune evasive and is a key factor driving the current summer wave. At this time, we believe treatments and vaccines should continue to be effective.