ID WATCH
by Ed Septimus, MD

Editor's Choice

1

Catheter-associated urinary tract infections (CAUTIs) and non-CAUTI hospital-onset urinary tract infections: Relative burden, cost, outcomes and related hospital-onset bacteremia and fungemia infections

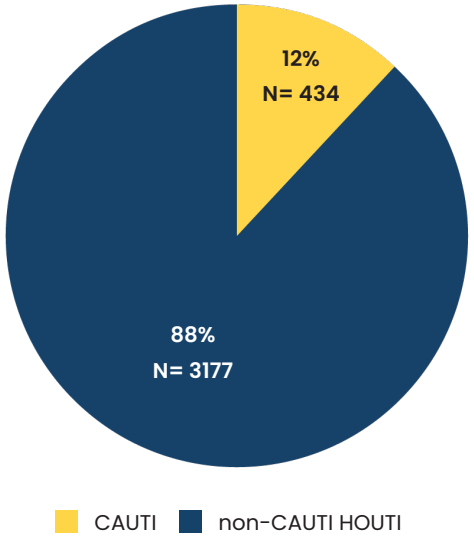
Infect Control Hosp Epidemiol published online February 27, 2024
doi: 10.1017/ice.2024.26

This was a retrospective observational study of patients from 43 acute-care hospitals. CAUTI cases were defined as those reported to the NHSN. Non-CAUTI (health care onset) HOUTI was defined as a positive, non-contaminated, non-commensal culture collected on day 3 or later. All HOUTIs were required to have a new antimicrobial prescribed within 2 days of the first positive urine culture. Outcomes included secondary hospital-onset bacteremia and fungemia (HOB), total hospital costs, length of stay (LOS), readmission risk, and mortality. Understanding how non-CAUTI HOUTIs are associated with secondary bloodstream infections may be important considering the new, proposed HAI metric for hospital-onset bacteremia and fungemia (HOB) that has been endorsed.

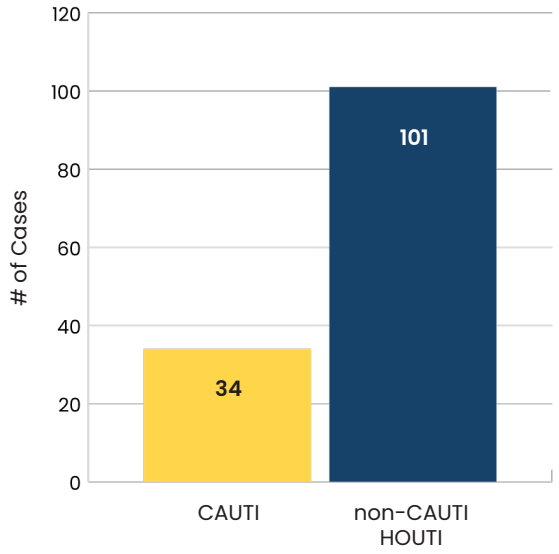
Of 549,433 admissions, 434 CAUTIs and 3,177 non-CAUTI HOUTIs were observed. The overall rate of HOB likely secondary to HOUTI was 3.7%. Total numbers of secondary HOB were higher in non-CAUTI HOUTIs compared to CAUTI (101 vs 34). HOB secondary to non-CAUTI HOUTI was more likely to originate outside the

ICU compared to CAUTI (69.3% vs 44.1%). CAUTI was associated with adjusted incremental total hospital cost and LOS of $9,807 (P < .0001) and 3.01 days (P < .0001) while non-CAUTI HOUTI was associated with adjusted incremental total hospital cost and LOS of $6,874 (P < .0001) and 2.97 days (P < .0001).

Distribution of HOUTI (Prevalence Cohort - Cohort 1)



Case of Likely Secondary HOB in Patients with HOUTI (Prevalence Cohort - Cohort 1)



Dr. Septimus's Annotations

UTIs were the most common HAI in 2002, accounting for 36% of all HAIs. However, in a 2015 point-prevalence analysis catheter-associated urinary tract infections CAUTIs dropped to the fifth most common HAI. [N Engl J Med 2018;379:1732–1744] The decline in HOUTIs may be attributed in part to preventability of CAUTI and the availability and adoption of guidelines for reducing CAUTIs. In addition, changes to the definition of CAUTI in 2009 and 2015 also likely contributed to the decline in prevalence. The first definition modification removed asymptomatic bacteriuria, and the second excluded both urine cultures that were positive for non-bacterial pathogens and those with colony counts below 100,000 colony forming units per milliliter (CFU/mL). The CAUTI definition updates appear primarily responsible for the decline in CAUTI rates, forming units per milliliter (CFU/mL). [HSN CAUTI Definition & Rebaseline, last reviewed June 14, 2023. https://www.cdc.gov/nhsn/pdfs/rebaseline/faqcauti-rebaseline.pdf. Published 2015]

"This analysis...suggests a clinical opportunity for infection prevention efforts to focus on the more serious clinical outcomes of HOB via all-cause HOUTIs irrespective of indwelling urinary catheter use or limitations of pathogen levels and species."

In the current study, CAUTI and non-CAUTI HOUTI were associated with adverse outcomes. In the general hospital population of adults, the proportion of non CAUTI HOUTI was over 7-fold greater compared to CAUTI. The attributable risk of increased LOS and total hospital cost of both CAUTI and non-CAUTI HOUTI were significantly higher compared to controls. Though the risk of likely secondary HOB was higher in patients with CAUTI vs non-CAUTI HOUTI, the volume of HOB was three times greater in non-CAUTI HOUTI. This analysis highlights the importance of both types of HOUTI and associated

patient outcomes and suggests a clinical opportunity for infection prevention efforts to focus on the more serious clinical outcomes of HOB via all-cause HOUTIs irrespective of indwelling urinary catheter use or limitations of pathogen levels and species.

The analyzed hospitals were limited to those where total cost of care per admission and NHSN HAI reporting were both readily available. The urine culture stewardship practices of the individual hospitals were unknown. Residual confounding may still be possible as with all observational studies.

BOTTOM LINE

Non-CAUTI HOUTI occurred more often and was associated with a higher facility aggregate volume of HOB than CAUTI Patients at risk for UTIs in the hospital represent a vulnerable population who may benefit from surveillance and prevention efforts, particularly in the non-ICU setting.

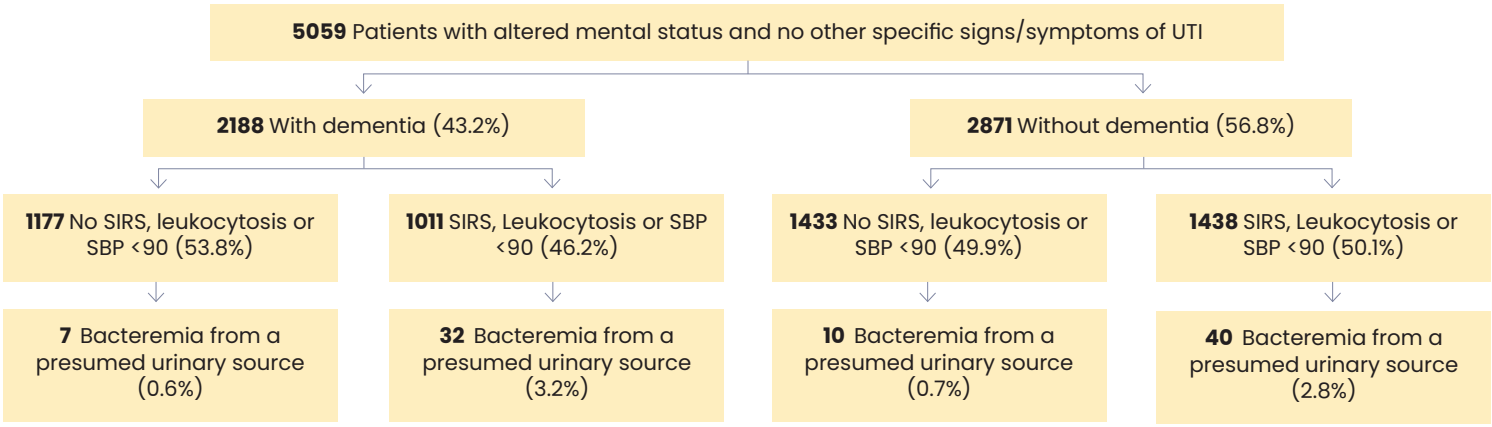
Bacteremia From a Presumed Urinary Source in Hospitalized Adults With Asymptomatic Bacteriuria

JAMA Network Open. 2024;7(3): e242283
doi:10.1001/jamanetworkopen.2024.2283

Despite IDSA guideline recommendations against antibiotics for asymptomatic bacteriuria [Clin Infect Dis 2019; 68: e83], antibiotic treatment for patients with ASB and nonspecific symptoms remains common. This study was a retrospective study estimating the prevalence of bacteremia from a urinary source (i.e., isolation of identical organisms from blood and urine cultures collected within 3 days of each other) among 11,600 hospitalized noncritically ill adults with ASB at 68 hospitals in Michigan; data were obtained by standardized review of individual charts and not simply administrative data. Patients with specific signs or symptoms of UTI and patients who received antibiotics for UTI before blood culture collection were excluded.

Among all patients with ASB (median age, 78; 75% women; 15% with indwelling urinary catheters), 72% received antibiotics, whereas only 1.4% developed bacteremia. Among the 44% of patients with ASB who also had altered mental status (AMS), rates of bacteremia were similarly low (1.8%). Male sex, hypotension, ≥2 systemic inflammatory response syndrome (SIRS) criteria, urinary retention, fatigue, leukocytosis, and pyuria (>25 white blood cells per high-power field) were all associated with bacteremia, although none identified risk for bacteremia exceeding 2%. Older age, AMS, dementia, and change in urine color or odor were not associated with bacteremia.

Bacteremia From a Presumed Urinary Source Among Hospitalized Patients With Bacteriuria and Altered Mental Status With or Without Dementia



SBP indicated systolic blood pressure; SIRS systemic inflammatory response syndrome; UTI, unrinaty tract infection

Dr. Septimus's Annotations

The IDSA guideline suggests a strategy of watchful waiting in patients with AMS and no systemic signs of infection while recommending empiric antibiotic therapy in patients with systemic signs of infection. This study should reassure clinicians that bacteremia is extremely uncommon among patients with ASB who lack systemic symptoms. Their data provide assurance that the history of dementia or altered mental status alone is not a risk factor for bacteremia. Therefore, for patients who have either have altered mentation or have dementia and cannot attest to having specific signs or symptoms of UTI, clinicians should assess for SIRS, leukocytosis, and pyuria when deciding who may possibly benefit from empiric antibiotic treatment. If the patient with ASB does not have systemic signs of infection, they have a very low risk of bacteremia from a urinary source.

This was an observational study dependent on presence of positive urine culture and documentation of signs and symptoms in the medical record. This study only captures bacteremia in patients with blood and urine cultures growing the same organism within the 3-day infection window, so it may miss patients for whom blood or urine cultures were not obtained or were drawn after antibiotic initiation. Lastly, severely immunocompromised patients and those in intensive care units were excluded.

BOTTOM LINE

These findings suggest that bacteremia from a presumed urinary source was rare in patients with ASB, even those presenting with altered mental status supporting current guidelines.

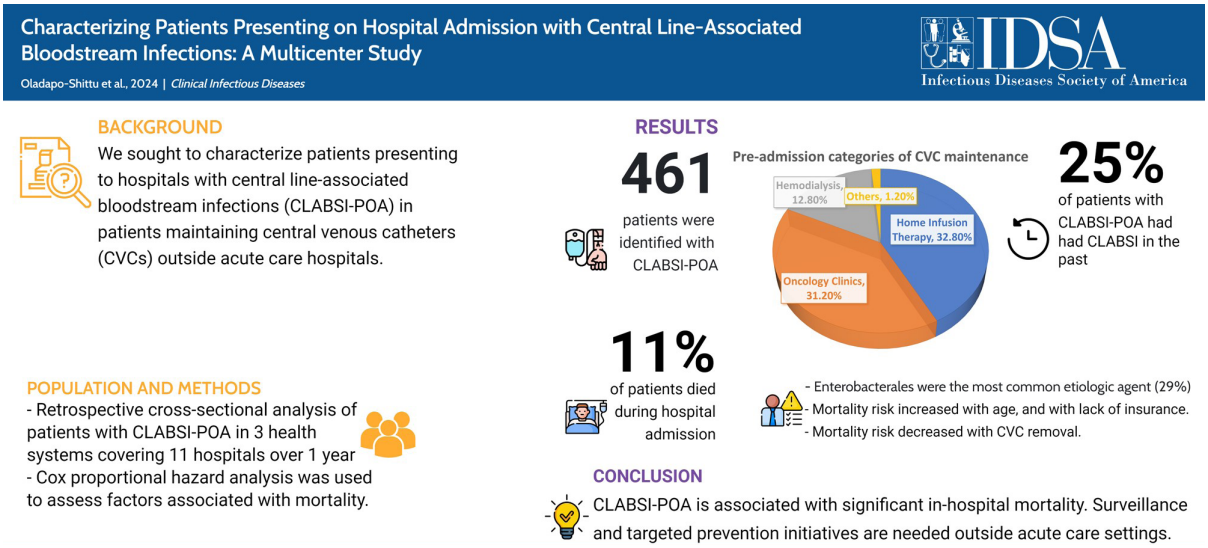
3

Characterizing Patients Presenting on Hospital Admission with Central Line-Associated Bloodstream Infections: A Multicenter Study

Clin Infect Dis published online March 11, 2024
DOI: 10.1093/cid/ciae144

This was a retrospective cross-sectional analysis of patients with CLABSI-POA [present on admission] in three health systems covering eleven hospitals across Maryland, Washington DC, and Missouri from November 2020 to October 2021. CLABSI-POA was defined using an adaptation of the acute care CLABSI definition. Patient demographics, clinical characteristics, and outcomes were collected via chart review. Cox proportional hazard analysis was used to assess factors associated with all-cause mortality within 30 days.

461 patients were identified as having CLABSI-POA. CVCs were most maintained in home infusion therapy (32.8%) or oncology clinics (31.2%). Enterobacterales were the most common etiologic agent (29.2%). Recurrent CLABSIs occurred in a quarter of patients (25%). Eleven percent of patients died during the hospital admission. Among CLABSI-POA patients, mortality risk increased with age (versus ages<20) ages 20-44 years: HR: 11.21, 95% CI: 1.46-86.22; ages 45-64: HR: 20.88, 95% CI: 2.84-153.58; at least 65 years of age: HR: 22.50, 95% CI: 2.98-169.93), and lack of insurance (HR: 2.46; 95% CI: 1.08-5.59), and decreased with CVC removal (HR: 0.57, 95% CI: 0.39-0.84).



Dr. Septimus's Annotations

National estimates of CLABSIs have focused on acute care hospitals, which underestimates the total CLABSI burden in healthcare. CVCs are increasingly maintained outside the hospital, such as in skilled nursing facilities (SNF), long-term acute care facilities (LTACH), hemodialysis (HD) facilities, outpatient infusion centers/oncology, ambulatory surgical centers, and homes. HD facilities report dialysis events to NHSN as a quality metric but only 11% of dialysis events are reported. [Infect Control Hosp Epidemiol 2016; 37:205-7] The investigators believe that measuring CLABSI-POA may help estimate the burden of CLABSI in the community, capturing the different locations where CLABSI may occur, and allowing for targeting of prevention efforts.

BOTTOM LINE

CLABSI-POA is associated with significant in-hospital mortality. Better surveillance is required to understand the burden of CLABSI in the community and to identify targets for CLABSI prevention initiatives outside acute care settings.

4

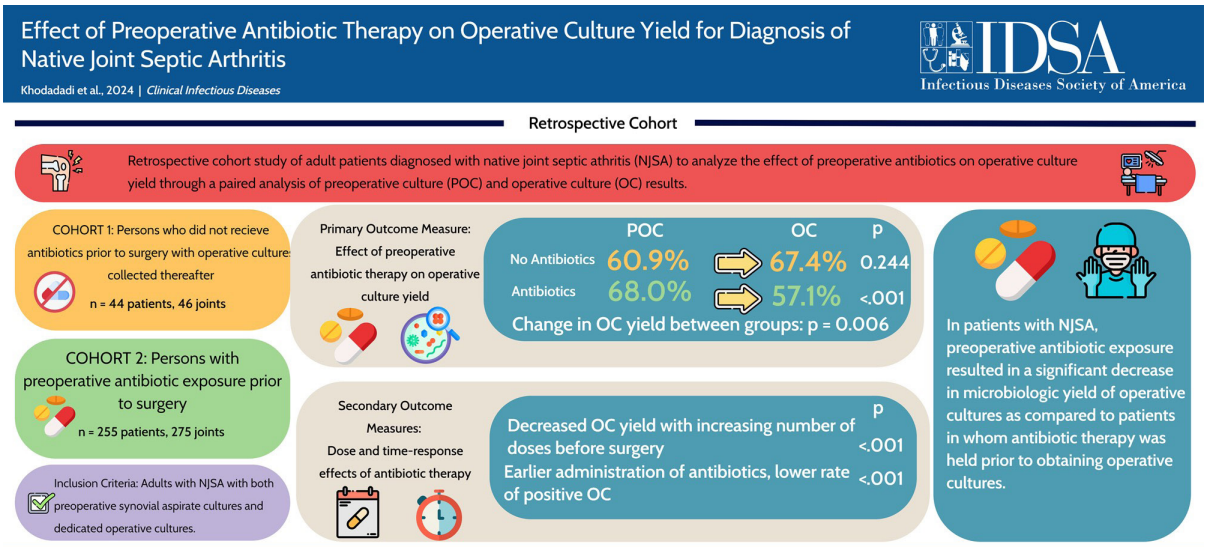
Effect of Preoperative Antibiotic Therapy on Operative Culture Yield for Diagnosis of Native Joint Septic Arthritis

Clin Infect Dis published online March 11, 2024
10.1093/cid/ciae136

The investigators retrospectively reviewed adult cases of native joint septic arthritis (NJSA) who underwent surgery at Mayo Clinic facilities from 2012 to 2021 to analyze the effect of preoperative antibiotics on operative culture yield through a paired analysis of preoperative culture (POC) and operative culture (OC) results using logistic regression and generalized estimating equations.

Two hundred ninety-nine patients with NJSA affecting 321 joints were included. Among those receiving preoperative antibiotics, yield significantly decreased from 68.0% at POC to 57.1% at OC ($P < .001$). In contrast, for patients without preoperative antibiotics there was a non-significant increase in yield from 60.9% at POC to 67.4% at OC ($P = .244$). In a logistic regression model for paired data, preoperative antibiotic exposure was more likely to decrease OC yield compared

to non-exposure (odds ratio [OR] = 2.12; 95% confidence interval [CI] = 1.24–3.64; P = .006). Within the preoperative antibiotic group, additional antibiotic doses and earlier antibiotic initiation were associated with lower OC yield. Furthermore, both the duration of preceding antibiotic therapy and number of antibiotic doses were associated with a lower probability of positive operative cultures in a dose-response manner.



Dr. Septimus's Annotations

Preoperative antibiotics are known to alter synovial fluid cell count, Gram stain, and culture results and are typically postponed until after arthrocentesis to optimize diagnostic accuracy. However, data on the impact of preoperative antibiotics on operative culture yield for NJSA diagnosis are limited. Based on the findings in this article, given the decrease in microbiological yield of OC in patients given preoperative antibiotics they recommend obtaining blood cultures and performing an arthrocentesis prior to starting antibiotics. This was a nonrandomized trial. The nature of patient selection and the limited number of patients who did not receive preoperative antibiotic therapy in their cohort may have impacted their analysis. Further, their ability to elucidate timing and doses of pre-hospital antibiotic therapy individuals received outside of a Mayo Clinic facility was limited. Advanced diagnostics, such as molecular-based techniques for rapid pathogen detection to supplement conventional culture in such instances were only available for recent samples.

"Based on the findings in this article... they recommend obtaining blood cultures and performing an arthrocentesis prior to starting antibiotics."

Beyond NJSA and orthopedic-related infections, the effect of antibiotics on the diagnostic yield of microbiologic studies has been examined in other conditions. Most importantly, in studies focused on evaluating impact of

antibiotics administered prior to blood culture collection in patients presenting with concern for sepsis, prior research consistently demonstrates a significant reduction in the sensitivity of blood cultures to identify a causative pathogen, emphasizing importance of obtaining peripheral blood cultures before initiating empiric antibiotic therapy. [Clin Microbiol Infect 2019; 25:326–31]

BOTTOM LINE

In patients with NJSA, preoperative antibiotic exposure resulted in a significant decrease in microbiologic yield of operative cultures as compared to patients in whom antibiotic therapy was held prior to obtaining operative cultures, therefore, whenever possible obtain blood cultures and arthrocentesis prior to starting antibiotics. Once blood and preoperative synovial fluid cultures are obtained, I recommend administration of empiric preoperative antibiotics and joint evacuation.

5 Aztreonam-avibactam

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended the granting of marketing authorization for Emblaveo (aztreonam-avibactam) for treating adults with complicated intra-abdominal infections, hospital-acquired pneumonia (including ventilator-associated pneumonia), complicated urinary tract infections (including pyelonephritis), and infections caused by aerobic gram-negative organisms with limited treatment options.

Aztreonam-avibactam combines an old beta-lactam antibiotic (aztreonam) with a newer beta-lactamase inhibitor (avibactam). The combination aims to restore aztreonam's activity against gram-negative bacteria that carry two resistant mechanisms—metallo-beta-lactamase (MBL) enzymes and other beta-lactamase enzymes—that confer resistance to nearly all currently available antibiotics. While aztreonam can evade degradation by MBLs on its own, the addition of avibactam helps restore its activity against other beta-lactamases.

Aztreonam-avibactam offers hope to adult patients with life-threatening Gram-negative bacterial infections that currently have limited treatment options.

6 FDA Approves Ceftobiprole

April 3, 2024

The FDA approved the injectable drug ceftobiprole medocaril sodium (Zevtera) to treat adults with Staphylococcus aureus bacteremia (SAB). The antibiotic prodrug is indicated for people with right-sided infective endocarditis, those with acute bacterial skin and skin structure infections (ABSSSI), and adult and pediatric patients 3 months to less than 18 years old with community-acquired bacterial pneumonia (CABP). Ceftobiprole, a pyrrolidinone cephalosporin antibiotic, is the active moiety of the prodrug ceftobiprole medocaril.

Ceftobiprole is an advanced-generation cephalosporin with activity against gram-positive pathogens--including methicillin-resistant S. aureus (MRSA)--and gram-negative pathogens.

Common side effects for those receiving the antibiotic for each of the three indications included nausea, vomiting, and diarrhea. Some participants with SAB experienced additional side effects including hypertension, leukopenia, fungal infection, headache, and dyspnea. For pediatric patients with CABP, the most common side effects of ceftobiprole medocaril included vomiting, headache, increased levels of hepatic enzymes, diarrhea, infusion site reaction, phlebitis, and fever.

Dr. Septimus's Annotations

Last year ID Watch reviewed "Ceftobiprole for Treatment of Complicated Staphylococcus aureus Bacteremia." [N Engl J Med 2023; 389:1390-1401] In that publication Ceftobiprole was found to be noninferior to daptomycin with respect to overall treatment success in patients with complicated S. aureus bacteremia.

BOTTOM LINE

Ceftobiprole may be a useful treatment option for patients with complicated S. aureus bacteremia, including right sided infective endocarditis caused by either MSSA or MRSA.

7

Dalbavancin Sequential Therapy for Gram-Positive Bloodstream Infection: A Multicenter Observational Study

Infect Dis Ther (2024) 13:565–579
doi.org/10.1007/s40121-024-00933-2

This was a retrospective cohort study performed to provide further multicenter real-world evidence on dalbavancin use as a sequential therapy for Gram-positive BSI. One hundred fifteen patients received dalbavancin with Gram-positive BSI, defined as any positive blood culture or diagnosed with infective endocarditis, from 13 centers geographically spread across the US between July 2015 and July 2021.

Patients had a mean (SD) age of 48.5 (17.5) years, the majority were male (54%), with many who injected drugs (40%). The most common infection sources (non-exclusive) were primary BSI (89%), skin and soft tissue infection (SSTI) (25%), infective endocarditis (19%), and bone and joint infection (17%). S aureus accounted for 72% of index cultures, coagulase-negative Staphylococcus accounted for 18%, and Streptococcus species in 16%. Dalbavancin started a median (Q1–Q3) of 10 (6–19) days after index culture collection. The most common regimen administered was dalbavancin 1500 mg as one dose for 50% of cases. Patients with complicated BSI started receiving dalbavancin at a median of 15 days post-index culture, compared to 8 days post-index culture among patients with uncomplicated infections. The primary outcome of composite clinical failure occurred at 12.2%, with 90-day mortality at 7.0% and 90-day BSI recurrence at 3.5%.

Dr. Septimus's Annotations

Dalbavancin has recently become more accepted as an option for step-down therapy for BSI. Patients were more frequently IV drug users (40%) who received dalbavancin for BSI in this study compared to other recent single center US studies examining dalbavancin for osteomyelitis, deep-seated infections, or Staphylococcus BSI. [Pharmacy. 2022;10(1):1; Open Forum Inf Dis. 2022. https://doi. org/10.1093/ofid/ofac335] In fact dalbavancin was used in the IV drug user population due to difficulties in discharge, placement, and the tendency to avoid central lines. The pathogens targeted by dalbavancin were similar to European real-world studies, with S aureus being the most common. Dalbavancin administration may have saved upwards of a median 5 inpatient days for uncomplicated BSI and a median 15 inpatient days for complicated BSI. Administration was timed primarily on the day of discharge (45%). This was a retrospective study that captured data mostly from large academic centers, which may not be applicable to smaller community hospitals, especially given the high cost of dalbavancin. In addition, there was no comparator group.

BOTTOM LINE

Dalbavancin may serve as a useful tool in facilitating hospital discharge in patients with Gram-positive BSIs. The challenge is making sure patients return for evaluation and/or repeat dosing. Randomized controlled trials are needed to validate dalbavancin as an alternative to current treatment standards.

Reducing Hospitalizations and Multidrug-Resistant Organisms via Regional Decolonization in Hospitals and Nursing Homes

JAMA published online April 1, 2024
doi:10.1001/jama.2024.2759

The intervention was the second stage of a CDC-funded two-part public health endeavor called SHIELD-OC (the Shared Healthcare Intervention to Eliminate Life-Threatening Dissemination of MDROs in Orange County), which aimed to identify a high-yield strategy for reducing MDROs and the complications they can cause in a network of hospitals, nursing homes, and LTACHs in the nation's sixth-largest county. While the prevalence of MDROs is roughly 10% to 15%, research has shown that it's as high as 65% in nursing homes and 80% in LTACHs.

In the first part, a simulation model identified decolonization as the most effective strategy. Thea investigators then did a networking analysis to find the hospitals, nursing homes, and LTACHs that share the most patients. Coordination among these facilities was crucial because the pathogens don't remain within the walls of a single facility. Rather, the frequent movement of MDRO-colonized patients between facilities fuels the spread of resistant pathogens that can infect other patients.

In the trial to evaluate the impact of the intervention, the investigators assessed MDRO carriage prevalence in all participating facilities at the end of the intervention compared with a baseline period (February 2015 through February 2017). Additional outcomes included incident MDRO clinical cultures (i.e., cultures sent to the lab to identify an infection) in participating versus non-participating facilities, and infection-related hospitalizations, associated costs, and deaths among residents in participating versus nonparticipating nursing homes.

The intervention involved twice-daily application of an intranasal iodophor for 5 days every other week combined with routine bathing using a CHG-containing product. All residents of participating LTCFs were exposed to the decolonization intervention while its application in hospitals was limited to patients undergoing contact precautions (CP). The intervention involved universal decolonization in NHs and LTACHs using 2% leave-on chlorhexidine-impregnated cloths for bed bathing and 4% rinse-off chlorhexidine liquid for showering on admission and routinely thereafter. Additionally, all residents (from NHs) or patients (from LTACHs) received twice-daily nasal iodophor (10% povidone-iodine) for 5 days on admission and then Monday through Friday, every other week. Both participating and nonparticipating facilities maintained their usual bathing frequency. In both groups, residents in NHs generally received a bath or shower 3 times per week, while patients in LTACHs or hospitals were generally offered a daily bath or shower. Nurses received standardized training to collect bilateral nares swabs for MRSA, as well as skin (bilateral axilla and groin) and perirectal swabs, which were processed for MRSA, VRE, ESBL, and CRE.

Decolonization Intervention	
Intranasal iodophor	Twice-daily application for 5 days every other week
Bathing with a CHG-containing product	On admission and routinely thereafter

The biggest impact on MDRO colonization was seen in the nursing homes and LTACHs, where MDRO prevalence fell from 63.9% to 49.9% (a 21.9% relative decrease) and 80% to 53.3% (a 33% relative decrease), respectively. In hospitalized patients, MDRO prevalence fell 64.1% to 55.4% (a 13.6% relative decrease). Adjusted analyses showed significant declines in the prevalence of MRSA, VRE, and ESBL–producing bacteria, while hospitals saw significant declines in VRE and ESBLs.

The effect on incident MDRO clinical cultures was similar. In adjusted models, there was a 30.4% reduction in MDRO-positive clinical cultures at participating nursing homes compared with nonparticipating nursing homes, while LTACHs (all of which participated) saw a 22.5% reduction. Compared with nonparticipating hospitals, the hospitals that implemented the decolonization strategy saw a 12.9% reduction in MDRO-positive clinical cultures.

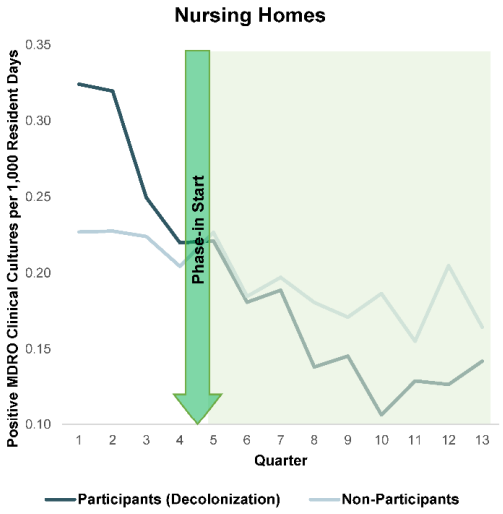
In participating nursing homes, the rate of infection-related hospitalizations per 1,000 resident-days fell 26.7%, associated hospitalization costs fell 26.8%, and deaths from infection-related hospitalizations declined 23.7% compared with nonparticipating nursing homes.

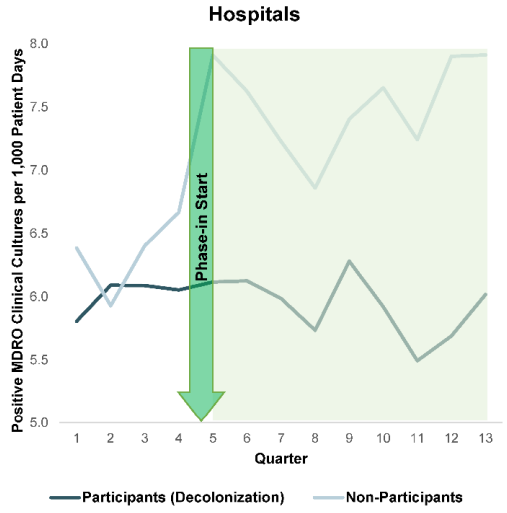
Among participating NHs, mean CHG adherence was 86.3% and povidone-iodine adherence, 69.5%. In LTACHs, mean CHG adherence was 94.0% and povidone-iodine adherence, 83.9% . Among hospitalized patients in CP, mean CHG adherence was 79.3% and povidone-iodine adherence, 69.6%.

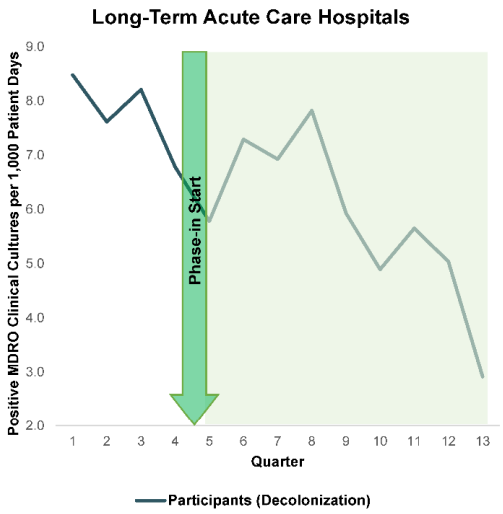
Using these products to decolonize patients isn't a new strategy. Both products have been shown to reduce colonization with MRSA and are widely used in healthcare facilities to protect patients from infections, particularly those in ICUs. Subsequent research has found that chlorhexidine is also effective against several resistant pathogens that can cause healthcare-associated infections, such VRE and ESBL–producing bacteria.

Their findings of a 23% to 30% reduction in MDRO-positive clinical cultures in NHs and LTACHs are consistent with those from randomized clinical trials of universal decolonization in hospital ICUs, non-ICUs, and post discharge settings. Universal decolonization reduced MRSA-positive clinical cultures by 37% in ICUs [N Engl J Med 2013; 368:2255-2265] reduced MRSA/VRE-positive clinical cultures by 37% in non-ICU inpatients with medical devices [Lancet 2019; 393:1205-1215] and reduced the incidence of MRSA infection by 30% among MRSA carriers after hospital discharge. [N Engl J Med 2019; 380:638-650] The 27% reduction in infection-related hospitalizations among NH residents was similar to the 31% reduction seen in the Protect Trial, a randomized clinical trial of universal chlorhexidine and nasal iodophor in NHs. [N Engl J Med 2023; 389:1766-1777]

Quarterly Multidrug-Resistant Organism (MDRO)-Positive Clinical (Non-Screening) Cultures per 1,000 Patient Days among Participating (Decolonization) versus Non-Participating Healthcare Facilities







This was a quasi-experimental nonrandomized design trial. Participating facilities were selected based on their high degree of shared patients, and thus, were more interconnected and tended to be larger than nonparticipating facilities. Data on hand hygiene, contact/barrier precautions, or antibiotic stewardship were not available and may have confounded results. Recruitment of interconnected facilities was a strength of SHIELD-OC but other regions may not be able to recruit facilities in this manner.

BOTTOM LINE

A regional collaborative involving universal decolonization in long-term care facilities and targeted decolonization among hospital patients in CP was associated with lower MDRO carriage, infections, hospitalizations, costs, and deaths. This proves that to adequately address MDROs, we need regional efforts across the continuum of care.

9

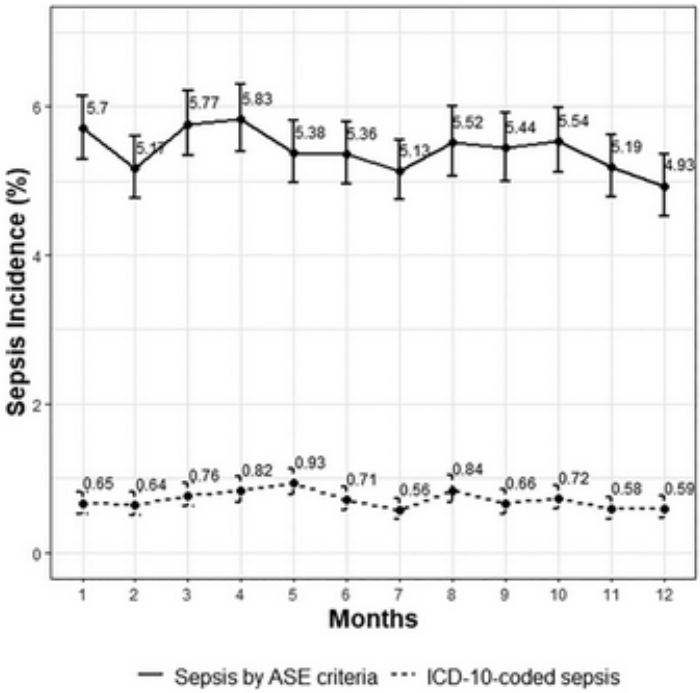
Validation of Adult Sepsis Event and Epidemiologic Analysis of Sepsis Prevalence and Mortality Using Adult Sepsis Event's Electronic Health Records-Based Sequential Organ Failure Assessment Criteria: A Single-Center Study in South Korea

Crit Care Med published online March 24, 2024
DOI: 10.1097/CCM.0000000000006270

In 2018, the CDC introduced the Adult Sepsis Event (ASE) definition based on the study published in 2017. [JAMA 2017; 318:1241–1249] In this retrospective cohort study the investigators aimed to validate the diagnostic accuracy of the ASE definition and to assess the prevalence and mortality of sepsis using ASE. Adult patients who were hospitalized or visiting the ED between November 5 and November 11, 2019, were included. They used multiple criteria to diagnose sepsis, including Sepsis-3 definition [JAMA 2016; 315:801–810], the ASE, and the ICD-10 codes for sepsis.

In phase I they validated the diagnostic accuracy of the ASE criteria compared with the Sepsis-3 criteria. In this phase, a total of 6186 patients were included and two study personnel thoroughly reviewed the complete medical records of all patients and identified cases of sepsis using the Sepsis-3 criteria. Concurrently, they identified ASE cases for the same period. They evaluated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of ASE in comparison to the Sepsis-3 definition and identified the factors contributing to both false positives and false negatives in ASE. They also identified cases of sepsis coded using ICD-10 during the same period.

In phase II, they assessed the prevalence and mortality of sepsis cases diagnosed using ASE criteria. A total of 126,988 patients were included in this period, among whom cases that met the ASE criteria or ICD-10-coded sepsis were extracted. They assessed the monthly prevalence and mortality of sepsis using the ASE criteria and compared them with ICD-10-coded sepsis cases. Additionally, they explored factors linked to hospital mortality in ASE cases.



ASE had a sensitivity of 91.6%, a specificity of 98.3%, a positive predictive value (PPV) of 57.4%, and a negative predictive value of 99.8% when compared with the Sepsis-3 definition. Of 126,998 adult patient hospitalizations in 2020, 6,872 cases were diagnosed with sepsis based on the ASE (5.4% per year), and 893 patients were identified as having sepsis according to the ICD 10th Edition (0.7% per

year). Hospital mortality rates were 16.6% (ASE) and 23.5% (ICD-10-coded sepsis). Monthly sepsis prevalence and hospital mortality exhibited less variation when diagnosed using ASE compared with ICD-10 coding (coefficient of variation [CV] for sepsis prevalence: 0.051 vs. 0.163, Miller test p < 0.001; CV for hospital mortality: 0.087 vs. 0.261, p = 0.001)

Dr. Septimus's Annotations

ASE demonstrated high sensitivity and a moderate PPV compared with the Sepsis-3 criteria in this population. The prevalence of sepsis, as defined by ASE, was 5.4% per year and was similar to US estimates. The prevalence of sepsis by ASE was eight times higher compared with that based on the ICD-10 code. The hospital mortality rate for ICD- 10-coded sepsis was higher than that of ASE. This disparity suggests that many cases of sepsis went undetected by ICD-10 coding. The underreporting could be due to several reasons: physicians might not have recognized sepsis, but more likely they could have been unaware of the revised sepsis diagnostic criteria. Furthermore, sepsis that developed during hospital stays often went unrecorded, especially if the initial reasons for admission were not related to sepsis. Physicians in this study typically enter diagnosis codes at admission or discharge, not during the hospitalization. Therefore, the more severe cases of sepsis were identified with the ICD-10 sepsis code. As other studies have shown patients exhibiting failures across all six organs had a 36.6% mortality rate, whereas those with only one organ failure faced a 12.3% mortality rate. This study is notable as few studies have validated the ASE using in-depth reviews of medical records. This center treats a particularly large group of patients with hematologic oncological conditions, solid organ transplantations, and multiple comorbidities. Therefore, the observed severity and mortality rates of sepsis might be higher compared with a general hospital setting. Although examining hospital mortality, they did not account for variations in patients' performance or comorbidities within the ASE group. ICD-10-coded sepsis in Korea was only 0.7%, which is significantly lower than the US claim-based sepsis prevalence reported by Rhee et al [N Engl J Med 2014; 370:1673–1676]. In the US, the implementation of Severe Sepsis and Septic Shock Early Management Bundle (SEP-1) and the introduction of financial incentives, such as enhanced reimbursement rates, have motivated clinicians and hospitals to be more meticulous in documenting sepsis codes.

"The hospital mortality rate for ICD-10-coded sepsis was higher than that of ASE. This disparity suggests that many cases of sepsis went undetected by ICD-10 coding."

BOTTOM LINE

Compared with ICD-10-coded sepsis, sepsis according to ASE criteria appears approximately eight times more frequent, more objective and exhibits lower mortality in part due to the higher denominator.

10

Antibiotic Receipt for Pediatric Telemedicine Visits With Primary Care vs Direct-to-Consumer Vendors

JAMA Network Open. 2024;7(3): e242359.
doi:10.1001/jamanetworkopen.2024.2359

Using a database of medical and pharmacy claims from commercially insured children ages 17 and younger, the researchers compared antibiotic management for pediatric acute respiratory tract infections during telemedicine visits with primary care practitioners (PCPs) versus commercial direct-to-consumer (DTC) telemedicine companies in 2022. Direct-to-consumer telemedicine is virtual-only care staffed by clinicians not part of the patient's primary care practice, offering care on demand to address common acute concerns, such as acute respiratory tract infections (ARTIs). Prior research showed substantially higher antibiotic prescribing to children during DTC telemedicine visits compared with

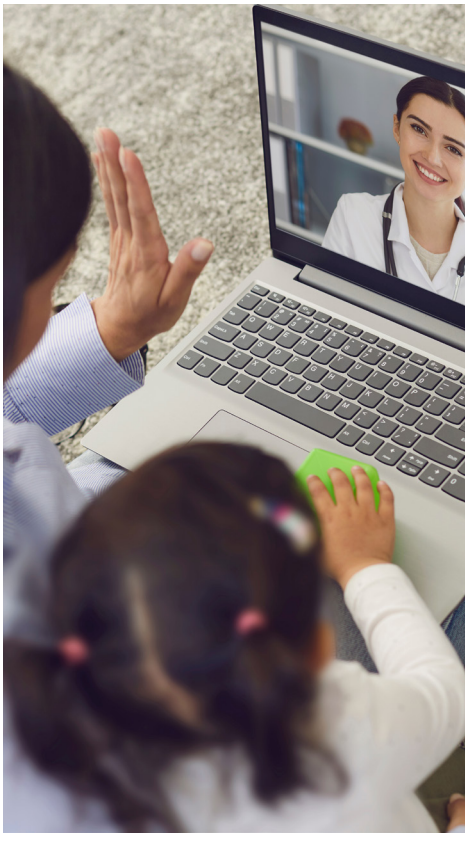
in-person visits provided by primary care practitioners (PCPs). [Pediatrics. 2019;143:e20182491]

Providers that had a total of more than 10,000 total visits in 2022, of which more than 97% were classified as telemedicine, were categorized as DTC telemedicine. Visits were matched based on patient's sex, age-group, medical complexity status, state of residence, and urban-rural status. Data from 27,686 children (mean age, 8.9 years; 48.9% female) were included in the study, and a total of 14,202 PCP telemedicine visits were matched with 14,627 DTC telemedicine visits. The primary outcome was the percentage of index visits that resulted in the filling of an antibiotic prescription. Secondary outcomes were the percentages of visits with diagnoses for which prescription of an antibiotic was potentially appropriate, guideline-concordant antibiotic management, and follow-up acute respiratory tract infection (ARTI) visits within the ensuing 1 to 2 days and 3 to 14 days.

Overall, PCP telemedicine visits were less likely to result in receipt of antibiotics than DTC telemedicine visits (28.9% vs 37.2%; relative risk [RR], 0.78; 95% confidence interval [CI], 0.74 to 0.81) and less likely to result in a diagnosis in which antibiotics may be appropriate (19.0% vs 28.4%; RR, 0.67; 95% CI, 0.63 to 0.71). Specifically, PCP telemedicine visits were less likely than DTC telemedicine visits to receive a diagnosis of sinusitis (9.9% vs 15.5%; RR, 0.64; 95% CI, 0.59 to 0.69) or acute otitis media (ear infection; 4.0% vs 6.9%; RR, 0.59; 95% CI, 0.51 to 0.59). In addition, fewer PCP telemedicine visits involved a follow-up visit within 1 to 2 days (5.0% vs 8.0%; RR, 0.63; 95% CI, 0.56 to 0.71), and PCP telemedicine had lower receipt of antibiotics associated with an ARTI revisit than did DTC telemedicine (1.7% vs 3.2%; RR, 0.53; 95% CI, 0.56 to 0.75). When accounting for diagnosis, rates of nonguideline-concordant antibiotic management were similar for PCP and DTC telemedicine visits (20.2% vs 20.1%; RR, 1.01; 95% CI, 0.95 to 1.07). Among PCP telemedicine visits, nonguideline-concordance was lower for visits completed by pediatricians than for visits completed by family practitioners (13.6% vs 25.4%); a breakdown by individual practitioner specialty was not available for the DTC telemedicine visits.

Dr. Septimus's Annotations

The investigators conclude the differences they observed in antibiotic management indicate the issue is less about the modality of care (telemedicine vs in-person) than who is providing the care. PCP telemedicine providers caring for children may be more likely to be pediatricians or family care providers who are trained in pediatric care and have existing relationships with the patients and access to their history and medical records. They can also coordinate in-person follow-up with patients. DTC telemedicine providers, on the other hand, may have limited pediatric experience, have no prior relationships with patients, have limited ability to follow up, and may be more motivated by patient-satisfaction scores. These differences, they suggest, could make DTC telemedicine providers more likely to prescribe antibiotics. As this was an observational analysis of claims data, they lacked clinical information to confirm diagnoses, and therefore performed their primary analysis agnostic to diagnoses and sensitivity analysis specific to diagnoses. Patient race, ethnicity, and language information were not available. Lastly, since this was an observational study, the use of PCP telemedicine and DTC telemedicine was not randomized.



BOTTOM LINE

These findings suggest that ARTI antibiotic management via telemedicine differed by context of telemedicine use such that telemedicine policy should account for different models and quality of telemedicine care and support integration of telemedicine within pediatric primary care.

11

Inappropriate Diagnosis of Pneumonia Among Hospitalized Adults

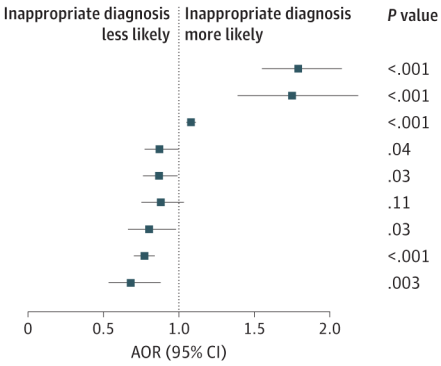
JAMA Intern Med. Published online March 25, 2024
doi:10.1001/jamainternmed.2024.0077

This was a prospective cohort study, which included medical record review and patient telephone calls across 48 Michigan hospitals. Trained abstractors retrospectively assessed hospitalized patients treated for CAP between July 1, 2017, and March 31, 2020. Patients were eligible for inclusion if they were adults admitted to general care with a discharge diagnostic code of pneumonia who received antibiotics on day 1 or 2 of hospitalization. Data were analyzed from February to December 2023. Inappropriate diagnosis of CAP was defined using a National Quality Forum–endorsed metric as CAP-directed antibiotic therapy in patients with fewer than 2 signs or symptoms of CAP or negative chest imaging.[Clin Infect Dis. 2024;ciae044] Risk factors for inappropriate diagnosis were assessed and, for those inappropriately diagnosed, 30-day composite outcomes (mortality, readmission, emergency department visit, C difficile infection, and antibiotic-associated adverse events) were documented and stratified by full course (>3 days) vs brief (≤3 days) antibiotic treatment using generalized estimating equation models adjusting for confounders and propensity for treatment. Patients who had documentation of treatment for an additional infection unrelated to pneumonia, were severely immunocompromised, were pregnant, were admitted for comfort measures, or who left against medical advice were ineligible.

Of the 17,290 hospitalized patients treated for CAP, 2079 (12.0%) met criteria for inappropriate diagnosis (median [IQR] age, 71.8 [60.1-82.8] years; 1045 [50.3%] female), of whom 1821 (87.6%) received full antibiotic courses. Compared with patients with CAP, patients inappropriately diagnosed were older (adjusted odds ratio [AOR], 1.08; 95% CI, 1.05-1.11 per decade) and more likely to have dementia (AOR, 1.79; 95% CI, 1.55-2.08) or altered mental status on presentation (AOR, 1.75; 95% CI, 1.39-2.19). Among those inappropriately diagnosed, 30-day composite outcomes for full vs brief treatment did not differ (25.8% vs 25.6%; AOR, 0.98; 95% CI, 0.79-1.23). However, full vs brief duration of antibiotic treatment among patients was associated with greater antibiotic-associated adverse events (31 of 1821 [2.1%] vs 1 of 258 [0.4%]; P = .03).

Multivariable Model of Characteristics Associated With Inappropriate vs Appropriate Diagnosis of Community-Acquired Pneumonia

Measure	AOR (95% CI)	*P* value
Dementia	1.79 (1.55-2.08)	<.001
Altered mental status, no dementia	1.75 (1.39-2.19)	<.001
Age, per 10 y	1.08 (1.05-1.11)	<.001
Home oxygen	0.87 (0.77-1.00)	.04
Chronic kidney disease	0.87 (0.76-0.99)	.03
Respiratory viral panel negative	0.88 (0.75-1.03)	.11
Respiratory viral panel positive	0.80 (0.66-0.98)	.03
≥2 SIRS criteria plus end organ dysfunction	0.77 (0.70-0.84)	<.001
History of pulmonary cancer	0.68 (0.53-0.88)	.003



Dr. Septimus's Annotations

The investigators state "Inappropriate diagnosis of CAP may harm patients through delayed recognition and treatment of acute (e.g., exacerbations of congestive heart failure), chronic (e.g., pulmonary cancer), or novel diagnoses (e.g., pulmonary cancer) and may lead to unnecessary antibiotic use, adverse effects, and antibiotic resistance." While brief empiric antibiotic treatment in older patients at risk of poor outcomes from CAP may be reasonable, the guidelines recommend reconsidering, de-escalating, or stopping antibiotics within 48 to 72 hours once infection has been ruled out. Yet the study found that the majority of patients with presumed CAP received a full antibiotic course, which in turn was linked with increased adverse events.

CAP symptoms are nonspecific and may overlap with other cardiopulmonary diseases (e.g., congestive heart failure, exacerbation of COPD), making diagnosis difficult. Given poor outcomes associated with CAP, in the setting of uncertainty, physicians favor overtreatment rather than potentially missing a CAP diagnosis. Historical quality metrics imposed by organizations such as The Joint Commission (e.g., requiring antibiotics within 4-6 hours of presentation) may have unintentionally led to more inappropriate diagnoses of CAP. Bias from unmeasured confounders may exist. They were unable to assess outcomes related to missed or delayed diagnosis or capture alternative diagnoses for those inappropriately diagnosed.

BOTTOM LINE

Inappropriate diagnosis of pneumonia among hospitalized adults is common, particularly among older adults with geriatric syndromes, and may be harmful.

Anaerobic Antibiotic Coverage in Aspiration Pneumonia and the Associated Benefits and Harms A Retrospective Cohort Study

Chest published online February 20, 2024
doi.org/10.1016/j.chest.2024.02.025

Investigators conducted a retrospective cohort study involving almost 4000 patients with aspiration pneumonia treated in 18 Canadian hospitals between 2015 and 2022. Patients were included if the physician diagnosed aspiration pneumonia and prescribed guideline concordant first-line community-acquired pneumonia parenteral antibiotic therapy to the patient within 48 h of admission.

Median treatment duration was 5 days for limited anaerobic coverage (LAC; monotherapy with ceftriaxone, cefotaxime, or levofloxacin) in 2683 patients and 7 days for extended anaerobic coverage (EAC; aminopenicillin/beta-lactamase inhibitors, moxifloxacin, or a combination of clindamycin or metronidazole and ceftriaxone, cefotaxime, or levofloxacin) in 1316 patients.

Primary and Secondary Outcomes

Variable	Limited Anaerobic Coverage (n = 2,683)	Extended Anaerobic Coverage (n = 1,316)	Extended Anaerobic Coverage vs Limited Anaerobic Coverage
Primary outcome			
In-hospital mortality	814 (30.3%)	422 (32.1%)	RD, 1.7% (95% CI, −1.3% to 4.8%) aRD, 1.6% (95% CI, −1.7% to 4.9%)
Secondary outcomes			
Transfer to ICU	66 (2.5%)	35 (2.7%)	RD, 0.2% (95% CI, −0.8% to 1.3%) aRD, 0.5% (95% CI, −0.6% to 1.7%)
C difficile colitis	≤ 5 (≤ 0.2%)	11-15 (0.8%-1.1%)	RD, 0.8% (95% CI, 0.3%-1.4%) aRD, 1.0% (95% CI, 0.3%-1.7%)
Exploratory outcome			
30-d attributable mortality[a]	781 (29.1%)	394 (29.9%)	RD, 0.8% (95% CI, −2.2% to 3.9%) aRD, 0.9% (95% CI, −2.3% to 4.2%)

Dr. Septimus's Annotations

Up to 15% of community-acquired pneumonias occur secondarily to aspiration of oropharyngeal or gastric secretions, with an associated mortality of about 30%. Extended anaerobic coverage with aminopenicillin/beta-lactamase–inhibitor combinations (or moxifloxacin, or metronidazole or clindamycin with cephalosporins) has long been standard of care. However, smaller studies recently have questioned the need for regimens with extended anaerobic spectra. A recent systematic review found three relevant studies (two observational studies and one randomized controlled trial). [J Clin Med. 2023; 12:1992] All three studies did not show a significant difference in mortality or clinical cure rate with extended anaerobic coverage. The results of this study support the 2019 ATS/IDSA CAP guidelines that state that extended anaerobic coverage for aspiration pneumonia is unnecessary. [Am J Respir Crit Care Med 2019; 200: e45-e67] As is the case for any observational study, residual confounding may still be present. It is plausible that clinicians' empiric antibiotic choice depended on illness severity, where sicker patients were more likely to receive additional anaerobic coverage. A bacterial pathogen was not identified in the majority of study patients.

BOTTOM LINE

Extended anaerobic coverage likely is unnecessary in aspiration pneumonia because it is associated with no additional mortality benefit, only an increased risk of C difficile colitis. It is reasonable to treat these patients with a first-line antibiotic therapy for CAP such as ceftriaxone without adding clindamycin or metronidazole.

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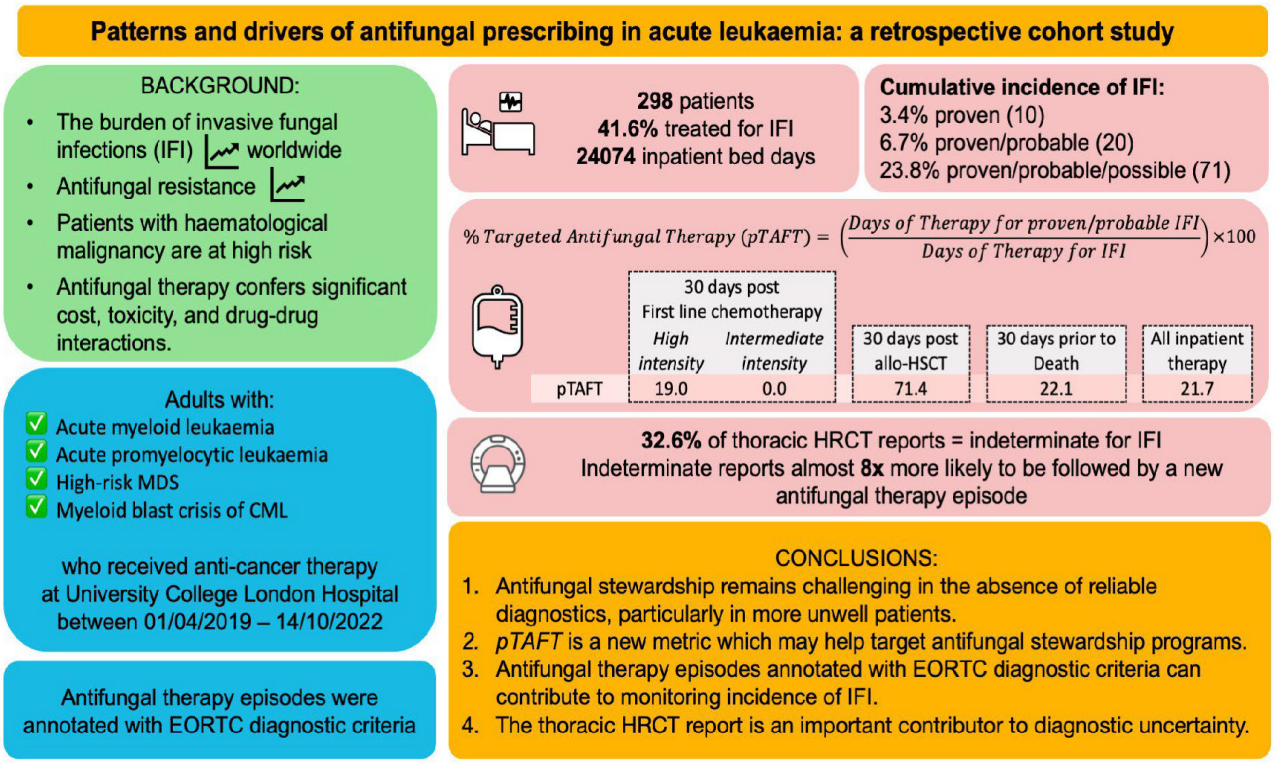
Patterns and drivers of antifungal prescribing in acute leukaemia: a retrospective cohort study

OFID published online March 1, 2024
DOI: 10.1093/ofid/ofae094

Patients receive prophylactic antifungals which are frequently escalated to treatment despite diagnostic uncertainty. Investigators in London queried electronic records to capture treatment courses and categorize the strength of indications among 298 patients who had undergone chemotherapy or hematopoietic stem cell transplantation (HSCT) in 2019–2022.

Among 298 patients accruing 24,074 inpatient days, 95% received mold-active antifungal prophylaxis. Consensus diagnostic guidelines, published by European Organization for Research and Treatment of Cancer and the Mycoses Study Group (EORTC/MSG), categorize 'probable' and 'possible' IFI based on a combination of host, mycological and clinical criteria.[Clin Infect Dis. 2020;71:1367-76] In all, 288 treatment episodes were recorded, including antifungal therapy for invasive fungal infection that was proven or probable (71 patients), possible (102 patients), or did not meet diagnostic criteria (115 patients). A reading of "indeterminate" for invasive fungal infection on thoracic computed tomography contributed to the initiation of antifungal therapy in patients who otherwise did not meet consensus criteria for invasive fungal infections. High-resolution computed tomography (HRCT) was performed for new suspicion of IFI. 31/383 (8.0%) reports were suggestive of IFI, 126/383 (32.6%) were indeterminate and 227/383 (59.3%) were negative for IFI. Overall, therapeutic antifungals were started within 48 hours after 76/383 (19.8%) of the HRCT studies. An HRCT with an indeterminate report was almost 8 times more likely to be followed by a new antifungal therapy episode within 48 hours than a negative scan (32.0% c.f. 4.4%). Galactomannan and beta-D glucan contributed to diagnosis of probable IFI in 6 and 3 patients respectively. Test positivity for galactomannan was 14/502 (2.8%) and beta-D glucan was 33/463 (7.1%). Less than half of the positive biomarker results were obtained from patients not already receiving antifungal therapy. There was variation in therapeutic antifungal strategy between prescribers.



Dr. Septimus's Annotations

This study raises the challenge concerning the uncertainty of fungal infections as well as the catastrophic outcomes in patients where therapy is started late. Achieving the right balance is difficult in the absence of reliable diagnostics. From the stewardship perspective the majority of antifungal use was given for prophylaxis which has been shown to lower the risk of invasive fungal infections. The next step should be to increase the reliability of diagnostic testing.

BOTTOM LINE

Antifungal stewardship remains challenging in the absence of reliable diagnostics, particularly in ill patients. The thoracic HRCT report is an important contributor to diagnostic uncertainty.

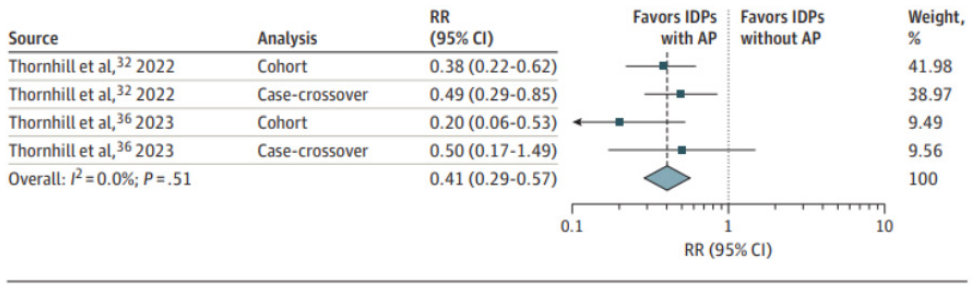
Antibiotic Prophylaxis and Infective Endocarditis Incidence Following Invasive Dental Procedures A Systematic Review and Meta-Analysis

JAMA Cardiol. Published online April 6, 2024
doi:10.1001/jamacardio.2024.0873

This publication was a systematic review and analysis reviewing existing evidence on the association between antibiotic prophylaxis and infective endocarditis following invasive dental procedures. PubMed, Cochrane-CENTRAL, Scopus, Web of Science, Proquest, Embase, Dentistry and Oral Sciences Source, and ClinicalTrials.gov were systematically searched from inception to May 2023. Studies on the association between antibiotic prophylaxis and infective endocarditis following invasive dental procedures or time-trend analyses of infective endocarditis incidence before and after current antibiotic prophylaxis guidelines were included. Data were extracted by independent observers. A pooled relative risk (RR)

of developing infective endocarditis following invasive dental procedures in individuals who were receiving antibiotic prophylaxis vs those who were not was computed by random-effects meta-analysis. The outcome of interest was the incidence of infective endocarditis following invasive dental procedures in relation to antibiotic prophylaxis.

Figure. Risk of Infective Endocarditis After Invasive Dental Procedures (IDPs) in Individuals at High Risk Who Received Antibiotic Prophylaxis (AP) vs Those Who Did Not



Related risks (RRs) and 95% CIs are shown for each study using black blue squares and bars, respectively. The diamond represents the pooled RR and 95% CI.

Of 11,217 records identified, 30 were included (1,152,345 infective endocarditis cases). Of them, 8 (including 12 substudies) were either case-control/crossover or cohort studies or self-controlled case series, while 22 were time-trend studies; all were considered good quality. Eight of the 12 substudies with case-control/crossover, cohort, or self-controlled case series designs performed a formal statistical analysis; 5 supported a protective role of antibiotic prophylaxis, especially among individuals at high risk, while 3 did not. By meta-analysis, antibiotic prophylaxis was associated with a significantly lower risk of infective endocarditis after invasive dental procedures in individuals at high risk (pooled RR, 0.41; 95% CI, 0.29-0.57; P for heterogeneity = .51; I2, 0%). Nineteen of the 22 time-trend studies performed a formal pre-post statistical analysis; 9 found no significant changes in infective endocarditis incidence, 7 demonstrated a significant increase for the overall population or subpopulations (individuals at high and moderate risk, streptococcus-infective endocarditis, and viridans group streptococci–infective endocarditis), whereas 3 found a significant decrease for the overall population and among oral streptococcus-infective endocarditis.

Dr. Septimus's Annotations

Between 2007 and 2009, the AHA, the European Society of Cardiology (ESC), and the National Institute for Health and Care Excellence (NICE) recommended restrictions on antibiotic prophylaxis to different degrees. The AHA and ESC recommended antibiotic prophylaxis to be considered only in individuals at the highest risk (i.e., those with a previous history of infective endocarditis, prosthetic heart valves or prosthetic material used in cardiac valve repair, unrepaired cyanotic congenital heart disease, congenital heart disease with prosthetic materials or devices placed in the previous 6 months or with residual defects and those undergoing surgical or interventional procedures) who undergo an invasive dental procedure, defined as procedures that involve manipulation of the gingival tissue, periapical region of teeth, or perforation of the oral mucosa. [Eur Heart J. 2009; 30:2369-2413] Conversely, antibiotic prophylaxis was no longer recommended for individuals at moderate risk, such as those with acquired valvular heart disease, hypertrophic cardiomyopathy, and most other congenital heart diseases. This message was later reinforced in updated statements. [Circulation. 2021;143(20): e963-e978] The effectiveness of antibiotic prophylaxis to prevent infective endocarditis following invasive dental procedures has been hampered by the lack of robust data and absence of randomized clinical trials.

"...investigators found that individuals at high risk who received antibiotic prophylaxis before invasive dental procedures were 59% less likely to develop infective endocarditis..."

In this meta-analysis, the investigators found that individuals at high risk who received antibiotic prophylaxis before invasive dental procedures were 59% (95% CI, 43-71) less likely to develop infective endocarditis compared to those who did not receive antibiotic prophylaxis, thereby supporting current AHA and ESC recommendations. This association was not proven for individuals at moderate or low/unknown risk. The absence of randomized clinical

trials addressing the association between antibiotic prophylaxis and the incidence of infective endocarditis remains a limitation. However, this meta-analysis brings together the most recent data—including 2 large case-crossover/ cohort studies—allowing for control group comparison and group stratification, providing stronger, although still limited, evidence to support the role of antibiotic prophylaxis in preventing infective endocarditis after invasive dental procedures in individuals at high risk. There are also ethical concerns that exist around withholding antibiotic prophylaxis measures from at-risk populations. Data on guideline adherence were limited, and assumptions were made on antibiotic prophylaxis prescription and administration.

BOTTOM LINE

These findings support the use of antibiotic prophylaxis for individuals at high risk undergoing invasive dental procedures, supporting current American Heart Association and European Society of Cardiology guidelines.

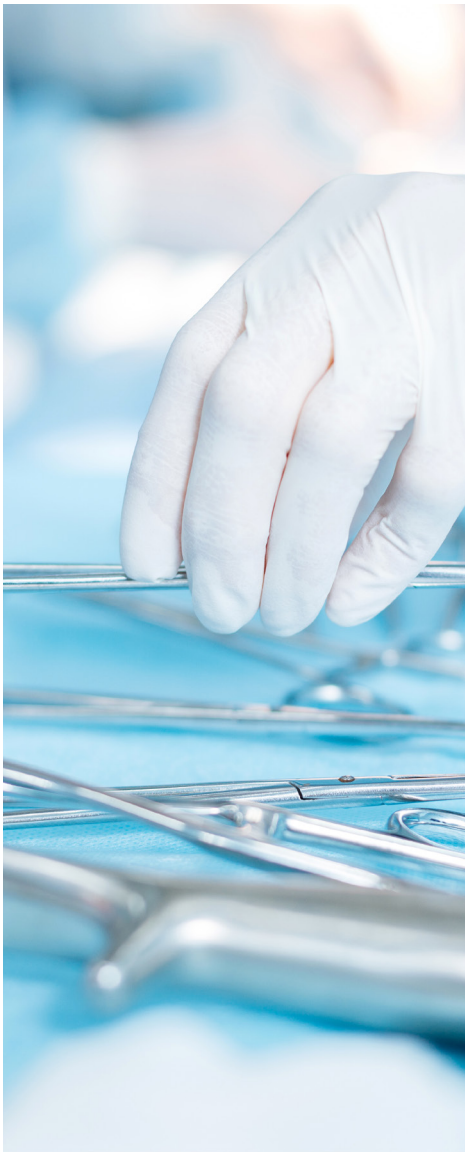
Contribution of the patient microbiome to surgical site infection and antibiotic prophylaxis failure in spine surgery

Sci. Transl. Med. 16, eadk8222 (2024)
DOI: 10.1126/scitranslmed.adk8222

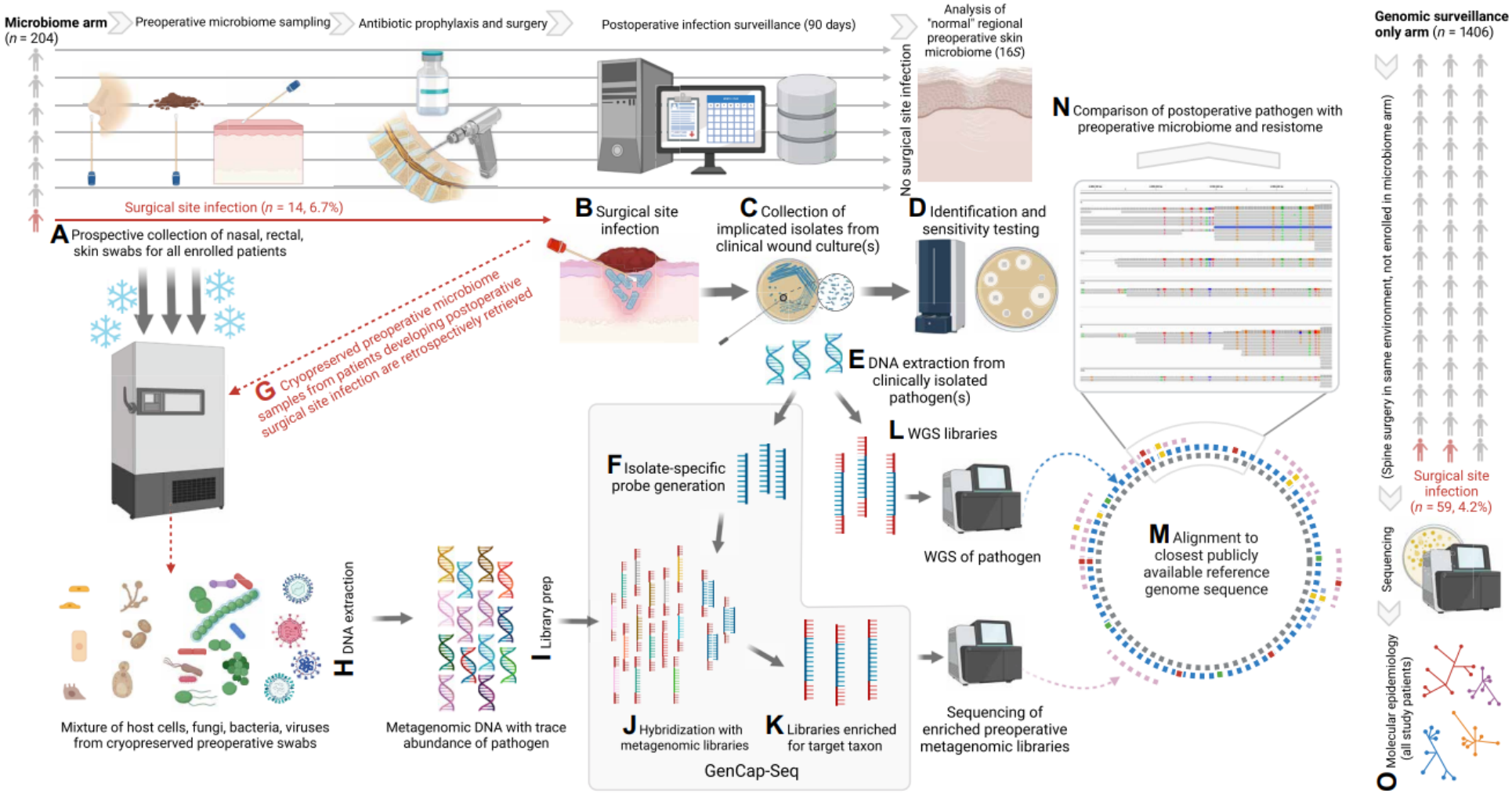
The objectives of this prospective study were to characterize the contributions of the preoperative patient microbiome and resistome to SSI after instrumented spine surgery. Using multiple forms of genomic analysis, including techniques for species-targeted whole-genome enrichment of metagenomic sequencing libraries [genome capture sequencing (GenCap-Seq)], they sought to determine

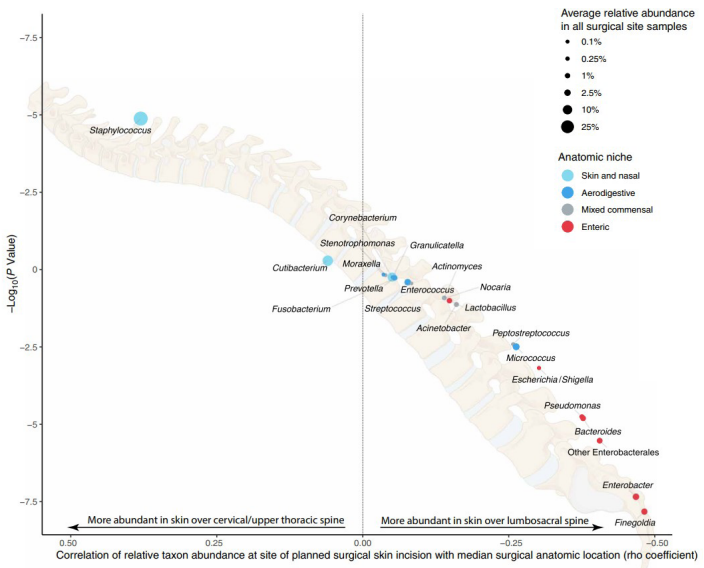
i. whether anatomic differences in the organisms causing SSI at various surgical anatomic locations correlate with differences in the preoperative skin microbiome,
ii. whether the causative SSI strain(s) identified by clinical wound culture are present in the patient's preoperative microbiota, and
iii. whether the preoperative resistome is related to the development of prophylaxis resistant infection.

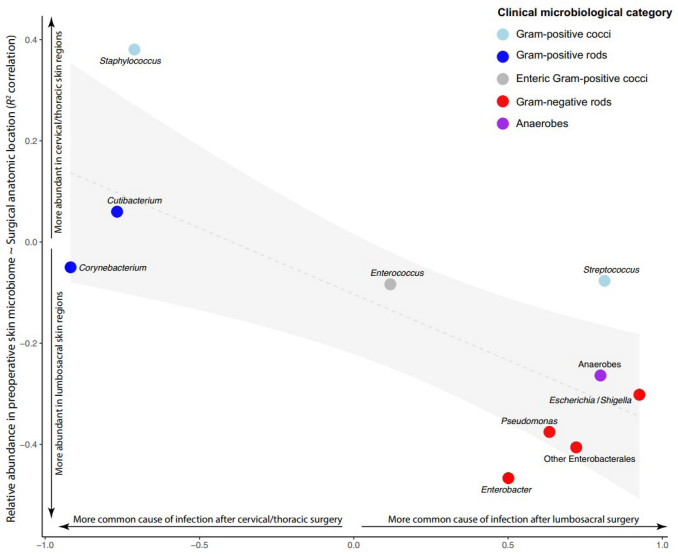
Infections after these procedures also occur at a predictable rate (3 to 5%) [Spine 2021; 46:143-151] involving a wide range of pathogens.



Using instrumented spine surgery as a model of clean (class I) skin incision, the investigators prospectively sampled preoperative microbiomes and postoperative SSI isolates in a cohort of 204 patients. Spine surgery represented an ideal choice since there is no entry into alimentary, respiratory, or urogenital tracts or breach in sterile procedure. Combining multiple forms of genomic analysis, they correlated the identity, anatomic distribution, and antimicrobial resistance profiles of SSI pathogens with those of preoperative strains obtained from the patient skin microbiome. To assess anatomic differences in the composition of the preoperative skin microbiome along the length of the back, they collected skin swabs on the day of surgery (immediately before topical antiseptic application) from the region directly overlying the planned incision and characterized the microbiome by 16S ribosomal RNA (rRNA) amplicon sequencing. For this analysis, they used a subset of samples from 124 cases with procedures focused within cervical (18.5%), thoracic (12.9%), or lumbosacral (68.5%) operative regions.


Microbiome arm
(n = 204)
Preoperative microbiome sampling
Antibiotic prophylaxis and surgery
Postoperative infection surveillance (90 days)
Analysis of "normal" regional preoperative skin microbiome (16S)
No surgical site infection
Surgical site infection (n = 14, 6.7%)
A Prospective collection of nasal, rectal, skin swabs for all enrolled patients
B Surgical site infection
C Collection of implicated isolates from clinical wound culture(s)
D Identification and sensitivity testing
N Comparison of postoperative pathogen with preoperative microbiome and resistome
G Cryopreserved preoperative microbiome samples from patients developing postoperative surgical site infection are retrospectively retrieved
E DNA extraction from clinically isolated pathogen(s)
L WGS libraries
WGS of pathogen
F Isolate-specific probe generation
M Alignment to closest publicly available reference genome sequence
H DNA extraction
I Library prep
Mixture of host cells, fungi, bacteria, viruses from cryopreserved preoperative swabs
Metagenomic DNA with trace abundance of pathogen
J Hybridization with metagenomic libraries
K Libraries enriched for target taxon
GenCap-Seq
Sequencing of enriched preoperative metagenomic libraries
Genomic surveillance only arm (n = 1406)
(Spine surgery in same environment, not enrolled in microbiome arm)
Surgical site infection (n = 59, 4.2%)
Sequencing
O Molecular epidemiology (all study patients)





They found that 86% of SSIs, comprising a broad range of bacterial species, originated endogenously from preoperative strains, with no evidence of common source infection among a superset of 1610 patients. Most SSI isolates (59%) were resistant to the prophylactic antibiotic administered during surgery, and their resistance phenotypes correlated with the patient's preoperative resistome (P = 0.0002). The relative abundance of pathogenic Gram-positive organisms (for example, Staphylococcus and Cutibacterium sp. was greater in cervical and thoracic skin regions, whereas Gram-negative and anaerobic organisms (such as Escherichia, Enterobacter, and Bacteroides sp.) were overrepresented in lumbosacral skin regions. Even within spinal anatomic regions, a high degree of interpatient variability in the relative abundance of potentially pathogenic skin microbiota was observed.

They ascertained the epidemiological relationship between individual SSI isolates and strains present in a patient's preoperative microbiome. Previous studies have used 16S rRNA polymerase chain reaction (PCR) amplicon sequencing to assess changes in the microbiome during the perioperative period and their relationship with infection [Front Microbiol. 2015; 5: 787]; however, such methods do not provide strain-level resolution, limiting inference about the dynamics of infection. In contrast, metagenomic sequencing provides the ability to distinguish individual bacterial strains and interrogate the complement of relevant AMR and virulence genes outside the 16S region.

Among the superset of 1610 patients undergoing spine surgery in the same operative environment during the study period, no cases of SSI were caused by a bacterial strain that was shared among patients This finding indicates that spine SSIs in our population were not caused by exogenous strains.

Dr. Septimus's Annotations

They observed a strong correlation between the preoperative patient microbiome and both the microbiology and antibiotic resistance phenotypes of subsequent infection. conclude that endogenous routes of infection, rather than introduction of exogenous strains originating from the hospital environment, are responsible for most such infections. They found that 86% of SSI pathogens, spanning a diverse range of Gram-positive, Gram-negative, anaerobic, and atypical organisms, matched strains carried by the same patient before surgery. This value closely corresponds with rates of endogenous infection reported in studies of S. aureus SSI (60 to 85%). [N. Engl. J. Med. 2002; 346: 1871–1877] AMR genetic complement, accessory virulence factors may also play important roles in SSI pathogenesis. Virulence factors were not analyzed in this study because of species- and procedure-specific considerations but could be evaluated

in future work using similar designs. Although present in the patient microbiome immediately before the start of the procedure, it remains possible that endogenous translocation of these strains occurred after the time of surgery (for example, fecal wound contamination during the early recovery period) In the resulting conceptual model, most SSIs—not only those caused by S. aureus—originate from resident microbiota preexisting in the patient before the time of surgery, and resistance to surgical antibiotic prophylaxis similarly results from bacterial genetic reservoirs already established in the host. If these findings are replicated in other cohorts, this model of SSI pathogenesis could drive important shifts in infection prevention strategy and enable more individualized and patient centered approaches.

In an article shared by Bob Weinstein, they published an article back in 1987 which concluded that Enterobacter part of the patients' endogenous flora can become an important pathogen when amplified by prophylactic antibiotics in cardiac surgery. [J Infect Dis 1987; 156:363-368] He later termed this the "fecal patina."

BOTTOM LINE

In this study the investigators provide compelling data to demonstrate that many pathogens causing SSIs in patients undergoing instrumented spine surgery originate from endogenous rather than from exogenous source meaning from the patients' own microbiomes. These findings indicate the need for SSI prevention strategies tailored to the preoperative microbiome and resistome present in individual patients.

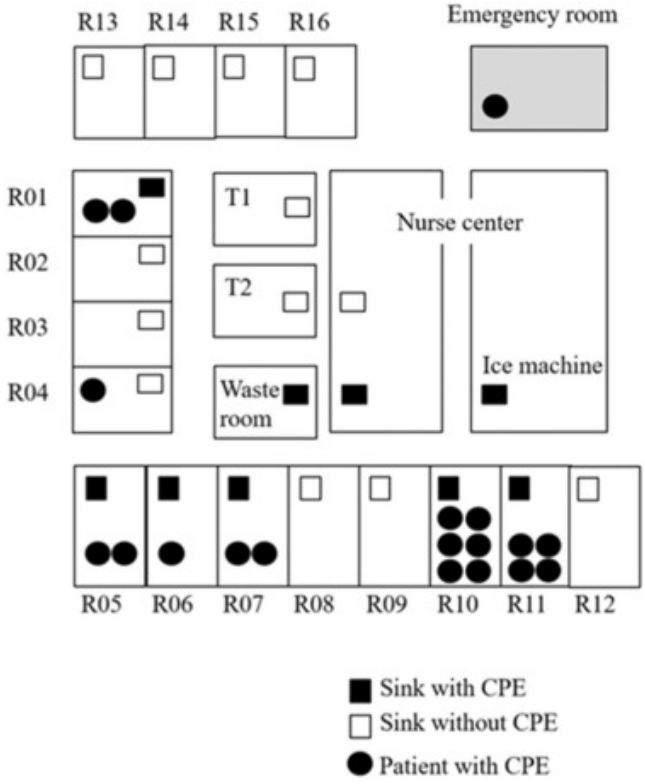
16

The outbreak of multispecies carbapenemase-producing Enterobacterales associated with pediatric ward sinks: IncM1 plasmids act as vehicles for cross-species transmission

Am J Infect Control published online April 10, 2024
doi.org/10.1016/j.ajic.2024.02.013

This publication is from an academic medical center in Tokyo which details the detection of carbapenemase-producing Enterobacterales (CPE) in a single patient in June 2016, which appears to have triggered an outbreak starting in March 2017 and ending in October 2017. The outbreak involved a total of 19 pediatric patients. The infection prevention team sampled microbes from patients and the environment of the pediatric ward to better understand how the outbreak was spreading. This sampling identified nine sinks contaminated with CPE, including six in hospital rooms and three more in a nurse center, a waste room, and an ice machine. The CPE-positive sinks were all found in rooms where CPE-positive patients had been treated. In rooms with CPE-negative patients, no sink contamination was detected.

As part of the outbreak control process, genome analysis was performed to identify the specific resistance mechanisms found in the bacterial strains, which included Klebsiella variicola, Klebsiella quasipneumoniae, and E coli, among others. Identical DNA sequences from all samples but one support the idea that the resistance mechanism could have been passed from one bacterial species to



another within the hospital. All CPE strains analyzed using draft-whole-genome sequencing harbored blaIMP-1, except for one harboring blaIMP-11; these strains harbored identical bla_{IMP-1}-carrying IncM1 plasmids.

To help control the outbreak, all sinks in the pediatric ward were replaced with new ones in June 2017, and the new sinks were thoroughly disinfected with hydrogen peroxide. However, CPE contamination continued even after that step. The discovery of the same bacterial species in sinks in adjoining rooms indicates that pathogen transmission may be possible from one sink to another via the drains and connected plumbing.

Other measures implemented by the infection prevention team — composed of doctors, nurses, pharmacists, and microbiologists — included recommending hand disinfection after using sinks, introducing disposable tools for cleaning sinks, prohibiting mouth-washing with sink water, enacting disinfection and drying procedures to any items exposed to sink water, and more. Finally, after October 2017, no further CPE contamination was identified in patient samples or environmental surveillance.

Dr. Septimus's Annotations

In this study, the investigators described an outbreak caused by multispecies CPE associated with pediatric ward sinks. In the outbreak investigation, they used WGS to analyze the relatedness of the CPE, which revealed a bla IMP-1-carrying IncM1 plasmid-borne multispecies CPE outbreak. The main plasmid-conjugated transfer fields could be sinks in each patient room, nurse center, waste room, and ice machine room. Water-related structures and areas, especially sinks, are important for CPE transmission and are the key to suppressing and controlling CPE outbreaks. [J Hosp Infect. 2020; 104:492–496; Antimicrob Resist Infect Control. 2017; 6:1–6 24] In addition, once CPE colonized children's intestinal tracts, it can persist for more than 2 years in 20% of individuals. [Clin Microbiol Infect. 2013;19: E190–E196] Despite this analysis, the origin of bla IMP-11-carrying IncM1 plasmid remains unknown.

BOTTOM LINE

Multiple bacterial species can become CPE via blaIMP-1-carrying IncM1 plasmids of the same origin and spread through sinks in a hospital unit. Thorough infection-control measures implemented as a bundle is critical to control these outbreaks.

17

CDC's Hospital-Onset Clostridioides difficile Prevention Framework in a Regional Hospital Network

JAMA Network Open. 2024;7(3): e243846
doi:10.1001/jamanetworkopen.2024.3846

This quality improvement study was performed within the Duke Infection Control Outreach Network from July 1, 2019, through March 31, 2022. In all, 20 hospitals in the network participated in an implementation study of the Framework recommendations, and 26 hospitals did not participate and served as controls. The Framework has 39 discrete intervention categories organized into 5 focal areas for CDI prevention:

1. isolation and contact precautions,
2. CDI confirmation,
3. environmental cleaning,
4. infrastructure development, and
5. antimicrobial stewardship engagement.

Primary outcomes were HO-CDI incidence trends at participating hospitals compared with controls and postintervention HO-CDI incidence at intervention sites compared with rates during the 24 months before the intervention. They define

HO-CDI cases as those occurring after hospital day 3. Cases of HO-CDI and patient-days present were electronically collected and submitted by infection preventionists at each participating hospital. Incidence rates of HO-CDI were calculated monthly per 10,000 patient-days.

The study sample included a total of 2184 HO-CDI cases and 7,269,429 patient-days. In the intervention cohort of 20 participating hospitals, there were 1403 HO-CDI cases and 3,513,755 patient-days, with a median (IQR) HO-CDI incidence of 2.8 (2.0-4.3) cases per 10 000 patient-days. The first analysis included an additional 3,755,674 patient-days and 781 HO-CDI cases among the 26 controls, with a median (IQR) HO-CDI incidence of 1.1 (0.7-2.7) case per 10 000 patient-days. The second analysis included an additional 2,538,874 patient-days and 1751 HO-CDI cases, with a median (IQR) HO-CDI incidence of 5.9 (2.7-8.9) cases per 10 000 patient-days, from participating hospitals 24 months before the intervention. In the first analysis, intervention sites had a steeper decline in HO-CDI incidence over time relative to controls (yearly incidence rate ratio [IRR], 0.79 [95% CI, 0.67- 0.94]; P = .01), but the decline was not temporally associated with study participation. In the second analysis, HO-CDI incidence was declining in participating hospitals before the intervention, and the rate of decline did not change during the intervention. The degree to which hospitals implemented the Framework was associated with steeper declines in HO-CDI incidence (yearly IRR, 0.95 [95% CI, 0.90-0.99]; P = .03).

Dr. Septimus's Annotations

In this quality improvement study of a regional hospital network, implementation of the Framework was not associated with declining HO-CDI incidence. HO-CDI incidence was already falling across intervention sites prior to study onset. Regression toward the mean may have contributed to the steeper decline in HO-CDI incidence observed among intervention sites. Alternatively, sites with higher HO-CDI incidence rates may already have been enacting C difficile control measures prior to study onset that were not captured. As with any observational study, unmeasured confounders may remain. In addition, this study did not capture measures of adherence to Framework measures over time, so it is possible that such changes might also have affected HO-CDI incidence trends.

BOTTOM LINE

Findings of this study suggest that benefits from implementation of the Framework warrant further study. External validation of the effectiveness of a multimodal prevention measure, such as the Framework, for controlling HO-CDI could be useful for future research merging insights from implementation science with clinical studies.

18

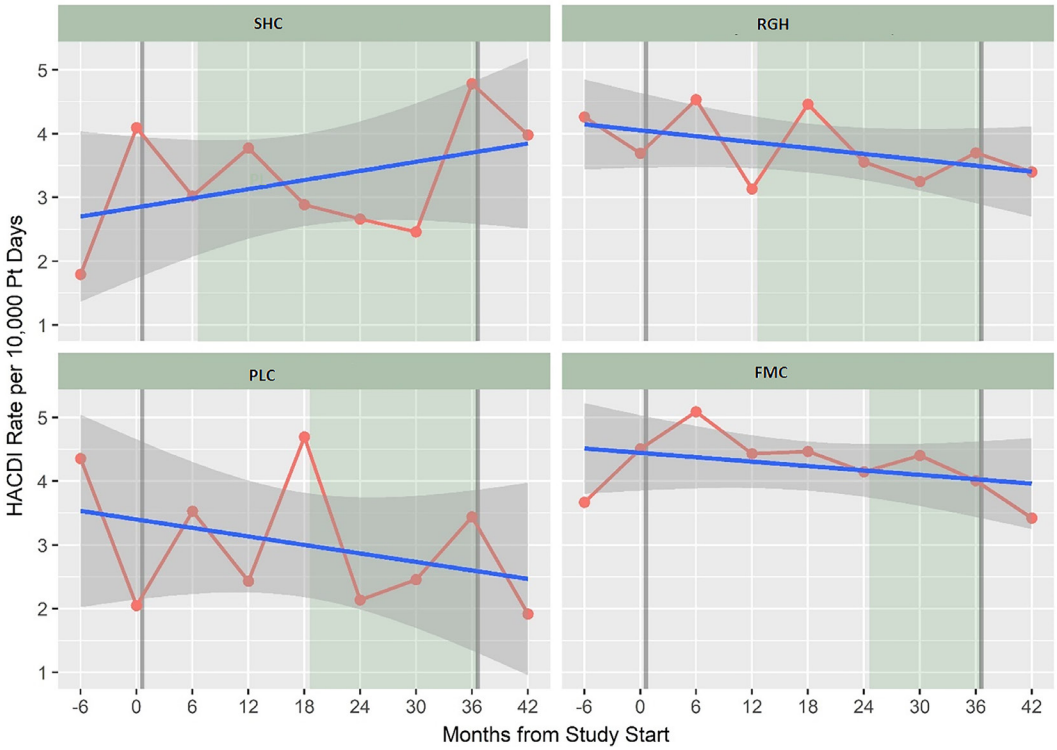
Effectiveness of Bio-K+ for the prevention of Clostridioides difficile infection: Stepped-wedge cluster-randomized controlled trial

Infect Control Hosp Epidemiol 2024, 45:443–451
doi:10.1017/ice.2023.169

This was a quasi-experimental, stepped-wedge, cluster randomized trial (SW-CRT) conducted at the 4 integrated Alberta Health Services acute-care hospitals in Calgary between September 1, 2016, and August 31, 2019. Adult patients were given 2 probiotic capsules daily (Bio-K+), containing 50 billion colony-forming units of Lactobacillus acidophilus CL1285, L. casei LBC80R, and L. rhamnosus CLR2. They measured hospital-acquired CDI (HA-CDI) and the number of positive C. difficile tests per 10,000 patient days as well as adherence to administration of Bio-K+ within 48 and 72 hours of antibiotic administration. Mixed effects generalized linear models, adjusted for influenza admissions and facility characteristics, were used to evaluate the impact of the intervention on outcomes. During the study period, there were no new IPC interventions; hand hygiene monitoring, antimicrobial stewardship and laboratory testing remained unchanged, limiting confounding of our findings.

Overall adherence of Bio-K+ administration ranged from 76.9% to 84.6% when stratified by facility and periods. Rates of adherence to administration within 48 and 72 hours of antibiotic treatment were 60.2% –71.4% and 66.7%–75.8%, respectively. In the adjusted analysis, there was no change in HA-CDI (incidence rate ratio [IRR], 0.92; 95% confidence interval [CI], 0.68–1.23) or C. difficile positivity rate (IRR, 1.05; 95% CI, 0.89–1.24). Discharged patients may not have received a complete course of Bio-K+. Their hospitals had a low baseline incidence of HA-CDI. Patients who did not receive Bio-K+ may have differential risks of acquiring CDI, introducing selection bias.

HA-CDI rate per 10,000 patient days by facility and 6-month period between March 1, 2015 to February 29, 2020



Dr. Septimus's Annotations

A 13% reduction of HA-CDI and 25% reduction in C. difficile test positivity rates per 10,000 patient days was observed in the unadjusted analysis. However, the adjusted analysis accounting for period and cluster effects, did not show a statistically significant reduction in the primary outcome of HA-CDI. A Cochrane systematic review and meta-analysis on probiotics for the primary prevention of CDI found no difference when the baseline risks of developing CDI were 0–2% and 3%–5%. [Cochrane Database Syst Rev 2017;12:CD006095] During the planning of this study rates of HA-CDI were >4.0 per 10,000 days, but when this study was actually initiated, they found a declining baseline rate of 4.0 per 10,000 patient days (0.25 per 100 admissions), below which it would be harder to detect a reduction in outcome. Maziade et al conducted a 7- and 10-year prospective cohort study in a community hospital in Montreal Canada, whereby all adult patients on antibiotics were prescribed Bio-K+. They

"There was high adherence with the intervention...However, adherence was lower than expected within 48 and 72 hours which may have reduced the effects of Bio-K+."

demonstrated a 73% reduction in HA-CDI and 76.4% reduction of severe cases. [Clin Infect Dis 2015;60 suppl 2: S144–S147] The decision to introduce the use of Bio-K+ in this hospital occurred during an outbreak when their peak incidence rate was 18.0 cases per 10,000 patient days. Trick et al conducted a before-and-after quasi-experimental study using segmented regression to evaluate Bio-K+ for the primary prevention of hospital-onset CDI compared to a 12-month baseline period. The incidence rate was similar during baseline and intervention periods, but they noted a significant decrease in HA-CDI during the final 6 months compared to the first 6 months of the intervention (IRR, 0.6; 95% CI, 0.4–0.9; P = .009) despite poor adherence to the protocol. [Infect Control Hosp Epidemiol 2018; 39:765–770]

There was high adherence with the intervention in this study. However, adherence was lower than expected within 48 and 72 hours which may have reduced the effects of Bio-K+. Shen et al found that probiotics were more effective if they were provided closer to the first antibiotic dose, with decrements in efficacy for every day of delay in starting probiotics. [Gastroenterology 2017; 152:1889–19009] Therefore, the results may have been due to low baseline HA-CDI incidence and/or delayed initial Bio-K+ administration to patients. Lastly, admission screening for C. difficile intestinal carriage was not performed in their hospitals.

BOTTOM LINE

Hospitals considering probiotics as a primary prevention strategy should consider the baseline incidence of HA-CDI in their population and timing of probiotics relative to the start of antimicrobial administration.

19

The Strain and the Clinical Outcome of Clostridioides difficile Infection: A Meta-analysis

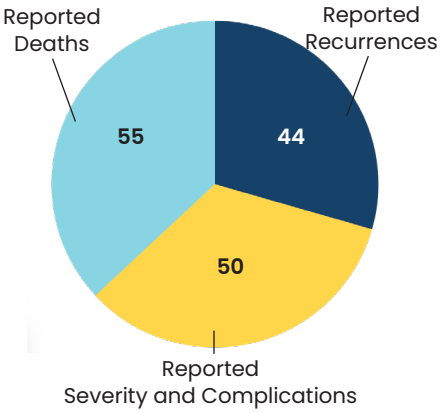
OFID 2024; 11: ofae085
doi.org/10.1093/ofid/ofae085

The investigators conducted a systematic review and meta-analyses to assess the impact of different C difficile strains. Five electronic databases were used to identify studies reporting CDI severity, complications, recurrence, or mortality according to strain type from inception to June 2022. Random effect meta-analyses were conducted to assess outcome proportions and risk ratios (RRs).

A total of 93 studies were included: 44 reported recurrences, 50 reported severity or complications, and 55 reported deaths. Pooled proportions of complications were statistically comparable between NAP1/BI/R027 and R001, R078, and R106. Pooled attributable mortality was 4.8% with a gradation in patients infected with R014/20 (1.7%), R001 (3.8%), R078 (5.3%), and R027 (10.2%). Higher 30-day all-cause mortality was observed in patients infected with R001, R002, R027, and R106 (range, 20%–25%).

NAP1/BI/R027 was associated with several unfavorable outcomes: recurrence 30 days after the end of treatment (pooled RR, 1.98; 95% CI, 1.02–3.84); admission to ICU, colectomy, or CDI-associated death (1.88; 1.09–3.25); and 30-day attributable mortality (1.96; 1.23–3.13). The association between harboring the binary toxin gene and 30-day all-cause mortality did not reach significance (RR, 1.6 [0.9–2.9]; 7 studies).

Impact of Different C. difficile Strains Across 93 Studies



30-day Attributed Mortality (4.8% of Reported Deaths)	
R027	10.2%
R078	5.3%
R001	3.8%
R014/020	1.7%

Dr. Septimus's Annotations

The investigators claim this is the first review to assess the association between C difficile strains, disease severity, and unfavorable clinical outcomes via a meta-analysis. In contrast, previous reviews employed narrative approaches. [Clin Infect Dis 2013; 56:1601–3]. This review included a large number of studies (n = 93) overall and for each outcome. Major limitations include the lack of a standard definition for the severity of CDI disease, the associated events that were considered complications, and the delay of occurrence of mortality. Studies on recurrence also had discrepancies in the index date, as well as in the criteria to consider a separate recurrent episode vs persistence of previous symptoms. They could not conduct meta-regressions because several important factors were infrequently reported, such as follow-up duration for prospective studies, delay in the occurrence of outcomes, patient age, underlying diseases, and treatments. Stratifying the analyses by typing techniques was even more challenging.

Despite some of the shortcomings, NAP1/BI/R027, the most frequently reported and assessed strain, was associated with unfavorable outcomes. NAP1/BI/R027 was associated with an 88% increased risk of complicated CDI (cCDI), including the need for ICU admission, colectomy, and CDI-associated death in studies of ≥1000 patients. Regardless of the study design, period of data collection, region, types of patients, and sample size, recurrent CDI (rCDI) occurred 30 days after the end of treatment in 1 out of every 4 cases of NAP1/R027 infection. However, there was not sufficient data to reach significant conclusions on other strains. They showed that the proportions of outcomes were statistically comparable between this strain and other strains, such as R001, R078, and R106. However, few studies were included in the meta-analysis of other strains. In addition, a study analyzing a sample of 939 isolates in the US between 2011 and 2016 showed a decline in R027 (35% to 13%), with R106 becoming the most common strain in 2016. [Anaerobe 2020; 63:102185]

BOTTOM LINE

NAP1/BI/R027 was the most frequently reported and assessed strain, and it was associated with a higher proportion of unfavorable clinical outcomes; however, the incidence of NAP1/BI/R027 is declining.

20

Sustained Human Outbreak of a New MPXV Clade I Lineage in Eastern Democratic Republic of the Congo

medRxiv posted April 15, 2024
doi.org/10.1101/2024.04.12.24305195

Monkeypox virus (MPXV) got attention in 2022 during a widespread outbreak linked primarily to sexual contact. Clade I MPXV was prevalent in Central Africa and characterized by severe disease and high mortality, while Clade II was confined to West Africa and associated with milder illness. A Clade IIb MPXV emerged in Nigeria in 2017, with protracted human-to-human transmission a forerunner of the global Clade II B.1 lineage outbreak in 2022. In October 2023, a large mpox outbreak emerged in the Kamituga (Eastern region) mining region of the Democratic Republic of the Congo (DRC). The investigators conducted an outbreak investigation.

Surveillance data and hospital records were collected between October 2023 and January 2024. Blood samples and skin/oropharyngeal swabs were obtained for molecular diagnosis at the National Institute of Biomedical Research, Kinshasa. MPXV genomes were sequenced and analyzed using Illumina NextSeq 2000 and bioinformatic tools.

The Kamituga mpox outbreak involved 241 suspected cases reported within 5 months of the first reported case. Of 108 confirmed cases, 29% were sex workers, highlighting sexual contact as a key mode of infection. Genomic analysis revealed a distinct MPXV Clade Ib lineage, divergent from previously sequenced Clade I strains in DRC. Predominance of APOBEC3-type mutations and estimated time of emergence around mid-September 2023 suggest recent human-to-human transmission. So far, no cases involving the new lineage have been reported outside of the DRC.

Dr. Septimus's Annotations

This report describes a novel Clade I MPXV lineage associated with sustained human-to-human transmission in an ongoing outbreak in eastern DRC. Identification of APOBEC3-related mutations – the hallmark of efficient MPXV spread via human-to-human transmission – bolstered this assertion. Due to the distinct geographical location and divergent phylogenetic relationship, the investigators propose to name this new Clade Ib, with the previously described Clade I renamed Clade Ia. Their data suggest that transmission in this outbreak was primarily linked to sexual contact. Most affected individuals were adolescents and young adults, contrasting with previous mpox outbreaks in the DRC, where children under 15 years were most affected, and second, professional sex workers were disproportionately affected and third the hospital records indicate that most suspected cases presented virus-compatible genital lesions.

BOTTOM LINE

Urgent measures, including reinforced, expanded surveillance, contact tracing, case management support, and targeted vaccination are needed to contain this new pandemic potential Clade Ib outbreak.

21

CDC ventilation guidance

March 22, 2024

CDC details steps that people can take to reduce the number of respiratory particles that circulate in indoor air.

The guidance emphasizes the importance of bringing in fresh outdoor air and ensuring that air conditioning and heating systems are operating properly, preferably with filters rated MERV-13 or higher. It also describes other steps that can be added, including air circulation, proper exhaust venting, air cleaners, and ultraviolet air treatment.

- CDC recommends setting ventilation systems to circulate more air when people are in the building. They say this can be done by setting the thermostat's fan control to the "ON" position instead of "AUTO." This will make the fan operate continuously without having to adjust the temperature. This can increase fan energy use, so limit use to when needed, like shortly before, during, and after gathering of people or if someone in your home is sick with a respiratory virus.
- UV air treatment systems can be used to kill germs in the air. They can also provide a high level of effective air changes per hour while using little energy.
- Check that the exhaust fans in kitchens and bathrooms work and vent outside your home or building. These fans help remove stale air and bring fresh air into your living spaces. You can also keep exhaust fans turned on when visitors are in your home and leave them on for an hour after they leave.
- If possible, move activities outdoors, to lower the risk of virus transmission.

Dr. Septimus's Annotations

Steps for improving ventilation are useful year-round but are especially helpful when virus levels are high in the community, when people are exposed, sick, or recovering, or when people have risk factors for severe illness.

22

Global technical consultation report on proposed terminology for pathogens that transmit through the air

WHO report April 2024

Before the pandemic, the WHO and other agencies typically recognized a few ways diseases could spread. One was by "contact transmission," in which someone picked up a pathogen either by touching an infected person directly or through contact with a contaminated surface. "Droplet transmission" involved the short-range spread of diseases when people coughed or sneezed droplets larger than 5 microns (five millionths of a meter), which then landed directly on a victim's mouth, eyes, or nose. "Airborne transmission" referred to just a handful of diseases that spread in droplets smaller than 5 microns, floating for long distances until someone inhaled them.

The new proposal:

- Pathogens, contained within a particle (known as 'infectious particles'), that travel through the air, when these infectious particles are carried by expired airflow (they are known as 'infectious respiratory particles or IRPs), and which enter the human respiratory tract (or are deposited on the mucosa of the mouth, nose or eye of another person) and;
- Pathogens from any source (including human, animal, environment), that cause predominantly respiratory infections (e.g.,TB, influenza, SARS, MERS), but as well as those causing infections involving the respiratory and other organ systems (e.g. COVID-19, measles)
- The descriptor 'transmission through the air' can be used to describe the mode of transmission of IRPs through the air. Under the umbrella of the 'through the air', two descriptors can be used:
- Airborne transmission/inhalation
  - Occurs when IRPs expelled into the air as described above and enter, through inhalation, the respiratory tract of another person and may potentially cause infection. This form of transmission can occur when the IRPs have travelled either short or long distances from the infectious person. The portal of entry of an IRP with respiratory tract tissue during airborne transmission can theoretically occur at any point along the human respiratory tract, but preferred sites of entry may be pathogen specific. It should be noted that the distance travelled depends on multiple factors including particle size, mode of expulsion and environmental conditions (such as airflow, humidity, temperature, setting, ventilation).
- Direct deposition
  - Occurs when IRPs expelled into the air following a short-range semi-ballistic trajectory, then directly deposited on the exposed facial mucosal surfaces (mouth, nose or eyes) of another person, thus, enter the human respiratory tract via these portals and potentially cause infection.

Pathogens that can be transmitted to another human via contact transmission (direct contact) and not via transmission through the air (e.g. via hands) or indirectly via touching secondary objects (fomites e.g. tabletops), or that enter the human body via routes (e.g. open wounds, sharps or needle-stick injuries) or pathogens with an environmental reservoir with a predilection for lungs (e.g., Legionella and melioidosis) are not covered by the included descriptors but are referenced for completeness.

Dr. Septimus's Annotations

Traditionally, hospital guidelines for controlling airborne diseases have called for expensive measures such as isolation rooms with negative air pressure, as well as N95 respirators and other protective gear to avoid inhaling fine droplets. But

it is not clear which diseases warrant that kind of control, or what efforts should be taken outside of hospitals. Evidence is still limited for many diseases. Scientists are still debating, for instance, the extent that influenza spreads by air. The CDC is currently revising isolation guidelines and one of the issues stimulating conversation is the section on prevention of respiratory agents in healthcare.

BOTTOM LINE

The WHO's previous stance was that only a handful of pathogens — those that travel in small droplets and spread across long distances, like tuberculosis — could be considered airborne. But the new report suggests broader categories that do not rely on droplet size or distance spread.

23

The association between influenza vaccination uptake and influenza and pneumonia-associated deaths in the United States

Vaccine 2024; 42: 2044–2050
doi.org/10.1016/j.vaccine.2024.01.089

Using publicly available data the investigators examined the association between state-level influenza vaccination and all-age pneumonia and influenza(P&I) associated deaths in the US from the 2013–2014 influenza season to the 2018–2019 season. In the main model, they evaluated influenza vaccine uptake in all those age 6 months and older. They used a mixed-effects regression analysis with generalized least squares estimation to account for within state correlation in P&I mortality.

From 2013–2014 through 2018–2019, the total number of all-age P&I related deaths during the influenza seasons was 480,111. The mean overall cumulative influenza vaccine uptake (age 6 months and older) across the states and years considered was 46.7%, with higher uptake (64.8%) observed in those aged ≥ 65 years. They found that overall influenza vaccine uptake (6 months and older) had a statistically significant protective association with the P&I death rate. This translated to a 0.33 (95% CI: 0.20, 0.47) per 100,000 population reduction in P&I deaths in the influenza season per 1% increase in overall influenza vaccine uptake.

Association of influenza vaccine uptake with the per 100,000 population rate of pneumonia and influenza (P&I) deaths rate per 100,000 population (from December to March) controlling for other variables, from 2013–2014 through 2018–2019, United States.

Parameter	M1		M2	
	Coefficient (95% CI)	**p-value**	**Coefficient (95% CI)**	**p-value**
Overall vaccine uptake (%), 6 months and older	−0.33 (−0.47, −0.20)*	<0.001	–	–
Vaccine uptake in 6 month-17-year-olds (%)	–	–	−0.04 (−0.16, 0.07)	0.462
Vaccine uptake in the > 65-year-olds (%)	–	–	−0.17 (−0.27, −0.08) *	0.001
Vaccine effectiveness (%)	−0.18 (−0.22, −0.14) *	<0.001	−0.17 (−0.21, −0.13) *	0.000
Temperature (°F)	−0.02 (−0.10, 0.07)	0.705	−0.01 (−0.09, 0.07)	0.794
Poverty rate (%)	0.76 (0.35, 1.17) *	<0.001	0.86 (0.45, 1.28) *	<0.001
Proportion of persons aged 65 + years	105.90 (44.68, 167.11) *	0.001	105.22 (44.65, 165.78) *	0.001
Year	−0.62 (−1.07, −0.17) *	0.006	−0.56 (−1.00, −0.11) *	0.014
Hispanic population proportion	−22.31 (−34.15, −10.46) *	<0.001	−21.81 (−33.63, −9.98) *	<0.001
Black population proportion	−19.67 (−32.21, −7.14) *	0.002	−19.84 (−32.57, −7.11) *	0.002

Notes:
M1, Overall vaccine uptake (age 6 months and older) as the main independent variable (IV) in the model.
M2, Both vaccine uptakes in 6 months-17-year-olds and ≥ 65-year-olds as main independent variables in the model.
CI, confidence interval.
* Statistically significant at 0.05.

Dr. Septimus's Annotations

These results using a population-level statistical approach provide additional support for the overall effectiveness of the US influenza vaccination program. This reassurance is critical given the importance of ensuring confidence in this life saving program.

24

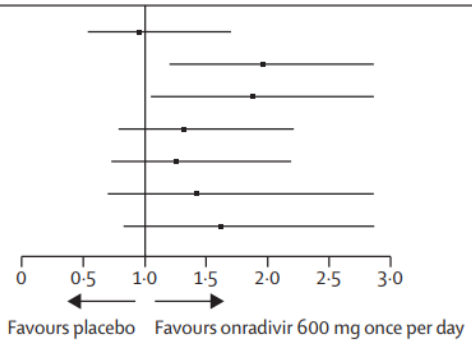
Safety and efficacy of onradivir in adults with acute uncomplicated influenza A infection: a multicentre, double-blind, randomised, placebo-controlled, phase 2 trial

Lancet Infect Dis published online February 5, 2024
doi.org/10.1016/S1473-3099(23)00743-0

Onradivir is a novel drug that targets the RNA polymerase basic protein-2 (PB2) subunit of influenza virus. Preclinical studies show that onradivir can inhibit influenza A viruses H1N1 and H3N2 replication and increase the survival rate of infected animals. In-vitro studies have shown that onradivir is effective against human influenza A and avian influenza A(H7N9) viruses, including baloxavir resistant and oseltamivir-resistant strains. [Pharmaceuticals 2023; 16: 365.] The investigators did a multicenter, double-blind, randomized, placebo-controlled, phase 2 trial at 20 clinical sites in China. Eligible participants were adults (18–65 years) with an influenza-like illness screened by rapid antigen testing at the first clinical visit, had the presence of a fever (axillary temperature ≥38·0°C), and had the presence of at least one moderate systemic and one respiratory symptom within 48 hr of symptom onset. Patients were excluded if they were pregnant, allergic to onradivir, or had received any influenza antiviral medication within 7 days before enrollment. Participants were randomly assigned (1:1:1:1) into four groups by an interactive web response system: onradivir 200 mg twice per day group, onradivir 400 mg twice per day group, onradivir 600 mg once per day group, and a matching placebo group. A 5-day oral treatment course was initiated within 48 h after symptoms onset. The primary outcome was the time to alleviate influenza symptoms in the modified intention-to-treat population. Safety was a secondary outcome. They evaluated the patients' self-assessed severity of seven influenza symptoms on a 4-point ordinal scale, and the treatment-emergent adverse events in all patients. The participants on day 1 (before taking the first drug dose) and later on days 2, 4, 6, and 21 were provided with standardized detection tools, which included pharyngeal swabs and transport medium. The specimens were sent to the same third-party independent medical laboratory for viral testing on days 1 (before treatment initiation), 2, 4, and 6 using reverse transcriptase quantitative PCR (RT-qPCR), and virus isolation.

Between Dec 7, 2019, and May 18, 2020, a total of 205 patients were screened; of whom, 172 (84%) were randomly assigned to receive onradivir (n=43 in the 200 mg twice per day group; n=43 in the 400 mg twice per day group; and n=43 in the 600 mg once per day group), or placebo (n=42). The median age was 22 years (IQR 20–26). All three onradivir groups showed decreased median time to alleviate influenza symptoms (46.92 h [IQR 24·00–81.38] in the 200 mg twice per day group, 54·87 h [23.67–110.62] in the 400 mg twice per day group, and 40.05 h [17.70–65.82] in the 600 mg once per day) compared with the placebo group (62.87 h [36.40–113.25]). The median difference between the onradivir 600 mg once per day group and the placebo group was −22.82 h (p=0.0330). The most frequently reported treatment-emergent adverse event was diarrhea (71 [42%] of 171), ranging from 33–65% of the patients in onradivir treated groups compared with 10% in the placebo group; no serious adverse events were observed. The mean virus load AUC measured with RT-qPCR from the baseline to day 6 was significantly lower for the onradivir treatment groups than the placebo group (p=0.0226).

	Median recovery time (onradivir 600 mg once per day group)	Median recovery time (placebo group)	HR (95% CI)	p value
Headache	15·29	13·50	0·96 (0·54–1·70)	0·889
Fever or chills	14·22	18·12	1·96 (1·20–3·19)	0·007
Muscle or joint pain	19·90	27·85	1·88 (1·05–3·36)	0·034
Fatigue	12·23	14·77	1·32 (0·79–2·21)	0·288
Cough	20·17	28·42	1·26 (0·73–2·19)	0·412
Sore throat	33·26	16·77	1·42 (0·70–2·87)	0·332
Nasal congestion	17·70	38·83	1·62 (0·83–3·16)	0·154



Dr. Septimus's Annotations

Their findings showed that patients given onradivir reported symptom improvement more quickly, especially resolution of fever, and faster reduction in viral replication than those given placebo. This study had a small sample size because of unavoidable factors that limited the recruitment process, and the participants had a median age of 22 years. Only 172 (43%) of the 400 planned sample size enrolled in this trial. They stopped recruitment ahead of schedule because the incidence of influenza markedly declined due to the strict zero Covid-19 policy execution in China. Since the study was stopped early, this lead to reduced statistical power, which made it difficult to detect true positives even in the presence of large effects. They observed more treatment-emergent adverse events in the onradivir groups than in the placebo group, especially diarrhea; but these "adverse events were well tolerated."

"...[T]he available evidence of this study shows promising antiviral and clinical benefits of onradivir..."

BOTTOM LINE

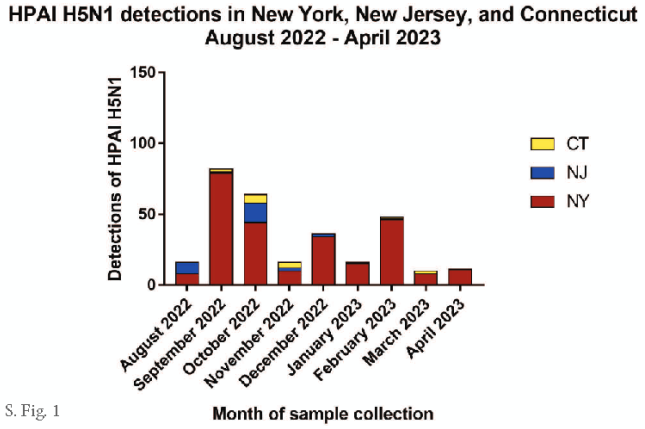
All the available evidence of this study shows promising antiviral and clinical benefits of onradivir for treating adult patients with uncomplicated influenza A infection with a good safety profile. Although this study was a small-to-moderate-size trial, the clinical outcomes of onradivir treatment have illustrated its safety and efficacy in patients with uncomplicated influenza infection compared with the placebo group.

25

Detection of clade 2.3.4.4b highly pathogenic H5N1 influenza virus in New York City

bioRxiv posted April 4, 2024
doi.org/10.1101/2024.04.04.588061

The investigators conducted surveillance of avian species in the urban environment in New York City. They detected highly pathogenic H5N1 viruses in six samples from four different bird species and performed full genome sequencing. Sequence analysis showed the presence of multiple different genotypes. Among the roughly 1,900 samples from the animals, they found versions of H5N1 in six, in four species: Canada geese in the Bronx and Queens; a red-tailed hawk near a major highway in Queens; a Canada goose and a peregrine falcon in Brooklyn; and a chicken in Upper Manhattan.



S. Fig. 1

Dr. Septimus's Annotations

Highly pathogenic avian influenza viruses of the H5N1 clade 2.3.4.4b arrived in North America in the winter of 2021/2022. These viruses have spread across the Americas causing morbidity and mortality in both wild and domestic birds as well as some mammalian species, including cattle. Many surveillance programs in wildlife as well as commercial poultry operations have detected these viruses. While surveillance for avian influenza viruses is often focused on migratory routes and their associated migratory locations, or commercial poultry operations, many bird species – including migratory birds – frequent or live in urban green spaces and wetlands. This brings them in proximity in populated are of humans and pets providing an urban animal human interface in which the general public may have little awareness of circulating infectious diseases. In the last few weeks North Carolina Department of Agriculture & Consumer Services (NCDAC) announced that tests have confirmed highly pathogenic avian influenza (HPAI) in one of the state's dairy herds, raising the number of affected states to seven.

The CDC warned health care providers to watch for signs of bird flu infection. So far, only two Americans have been reported as infected with H5N1, one in 2022 and the other in early April 2024. The patient reported conjunctivitis with no other symptoms, was not hospitalized, and has recovered. CDC has sequenced the influenza virus genome identified in a specimen collected from the patient and compared it with HPAI A(H5N1) sequences from cattle, wild birds, and poultry. While minor changes were identified in the virus sequence from the patient specimen compared to the viral sequences from cattle, both cattle and human sequences lack changes that would make them better adapted to infect mammals. In addition, there were no markers known to be associated with influenza antiviral drug resistance found in the virus sequences from the patient's specimen, and the virus is closely related to two existing HPAI A(H5N1) candidate vaccine viruses that are already available to manufacturers, and which could be used to make vaccine if needed.

The virus has caused large outbreaks in mink and foxes, and wiped-out thousands of marine mammals, especially in South America. Scientists have tracked the virus along migratory routes and stopovers, among wild birds in rural areas and commercial poultry operations and, most recently, among cattle on dairy farms.

Recommendations for Clinicians

1. Clinicians should consider the possibility of HPAI A(H5N1) virus infection in people showing signs or symptoms of acute respiratory illness or conjunctivitis and who have relevant exposure history. (persons who have had contact with potentially infected sick or dead birds, livestock, or other animals within the week before symptom onset (e.g., handling, slaughtering, defeathering, butchering, culling, preparing for consumption or consuming uncooked or undercooked food or related uncooked food products, including unpasteurized (raw) milk or other unpasteurized dairy products), direct contact with water or surfaces contaminated with feces, unpasteurized (raw) milk or unpasteurized dairy products, or parts (carcasses, internal organs, etc.) of potentially infected animals; and persons who have had prolonged exposure to potentially infected birds or other animals in a confined space)
    - Mild illness: (e.g., cough, sore throat, eye redness or eye discharge such as conjunctivitis, fever or feeling feverish, rhinorrhea, fatigue, myalgia, arthralgia, and headache)
    - Moderate to severe illness: (e.g., shortness of breath or difficulty breathing, altered mental status, and seizures)
    - Complications: (e.g., pneumonia, respiratory failure, acute respiratory distress syndrome, multi-organ failure (respiratory and kidney failure), sepsis, and meningoencephalitis)
2. If signs and symptoms compatible with avian influenza A(H5N1) virus infection are present:
    - Isolate patient and follow infection control recommendations, including using PPE.

- Initiate empiric antiviral treatment as soon as possible. Do not delay treatment while awaiting laboratory results.
- Notify the state and local health department to arrange testing for influenza A(H5N1) virus.
- Collect respiratory specimens from the patient to test for influenza A(H5N1) virus at the state health department. If the exposed person has conjunctivitis, with or without respiratory symptoms, both a conjunctival swab and a nasopharyngeal swab should be collected for testing.
- Encourage patients to isolate themselves at home away from their household members and not go to work or school until it is determined they do not have avian influenza A(H5N1) virus infection.

3. Starting empiric antiviral treatment with oral or enterically administered oseltamivir (twice daily for five days) is recommended regardless of time since onset of symptoms.

BOTTOM LINE

Their work highlights that the interface between animals and humans that may give rise to zoonotic infections or even pandemics is not limited to rural environments and commercial poultry operations but may extend into urban centers. There is no reason to panic at this point since human sequences lack changes that would make them better adapted to infect mammals and there is no evidence of antiviral resistance.

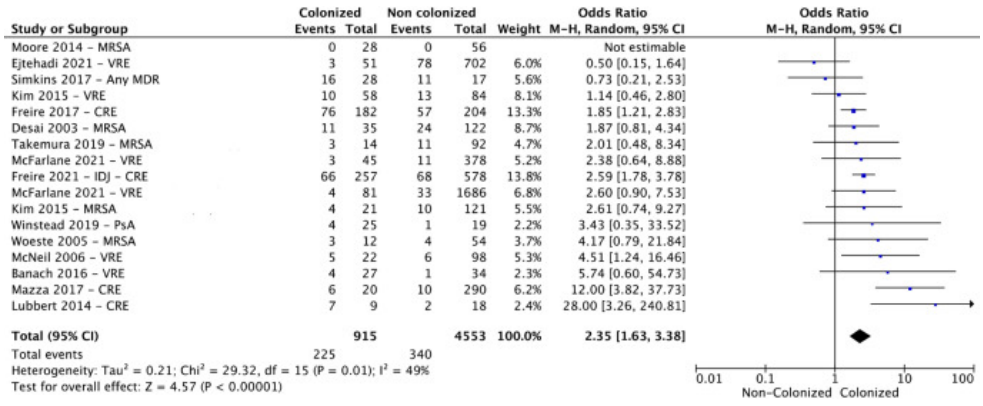
26

The Impact of Colonization by Multi Drug Resistant Bacteria on Graft Survival, Risk of Infection, and Mortality in Recipients of Solid Organ Transplant: Systematic Review and Meta-analysis

Clin Microbiol Infect published online April 9, 2024
doi.org/10.1016/j.cmi.2024.03.036

Cohorts and case-control studies that reported on adult solid organ transplant recipients (SOTR) colonized by Methicillin-resistant Staphylococcus-aureus (MRSA), Vancomycin-resistant Enterococci (VRE), Extended-spectrum beta-lactamase (ESBL) or carbapenem-resistant Enterobacteriaceae (CRE), or MDR-Pseudomonas, and compared to non-colonized, were included. Two reviewers assessed eligibility, conducted risk of bias evaluation using the Newcastle-Ottawa scale, and rated certainty of evidence using the GRADE approach.

Death Within One-year Post-Transplant Among MDR Colonized Solid Organ Transplant Recipients



15,202 SOTR (33 cohort, 6 case-control studies) were included, where Liver transplant and VRE colonization (25 and 14 studies) were predominant. MDR colonization significantly increased post-transplant one-year mortality (OR= 2.35, 95%CI 1.63-3.38) and mixed-infections (OR=10.74, 95%CI 7.56-12.26) across transplant types (p<0.001 and I2 =58%) but no detected impact on graft-loss (p=0.41, I2= 0%) Subgroup analysis indicated a higher association between CRE or ESBL colonization with outcomes (CRE: death OR=3.94, mixed-infections OR=24.8; ESBL: mixed-infections OR=10.3, no mortality data) compared to MRSA (Death: OR=2.25; Mixed infection: OR=7.75) or VRE colonization (Death: p=0.20, Mixed-infections: OR=5.71).

Dr. Septimus's Annotations

Bacterial infections are the leading infections after solid organ transplant (SOT). [N Engl J Med 2007; 357:2601–14] In the past decade, there has been a significant global increase in infections by multidrug-resistant bacteria (MDR). MDR colonization is particularly prevalent in SOT candidates leading to post-transplant infections. Antibiotic exposure, acute care facility stays, indwelling devises, and immunosuppression are the main risk factors present in SOT candidates and recipients that can contribute to this high prevalence. Aside from the increased risk of infection, MDR bacterial colonization in SOT recipients can affect graft function. In a recent meta-analysis that included conventional ward or ICU hospitalized patients (including SOT and cancer), infection risk was 19%, 8%, and 8% in patients colonized with CRE, third-generation cephalosporin-resistant Enterobacteriaceae and VRE, respectively. [Lancet Infect Dis 2023; 23:719-731] Another meta-analysis found that MDR colonization was associated with increased mortality in ICU patients, with a pooled relative risk for overall mortality among ESBL colonized patients of 1.57.[Crit Care Med J 2017;45:705–14]

"In this systematic review and meta-analysis...MDR colonization was associated with increased risk of all-cause mortality, infection-related mortality, mixed infections, and BSIs but not graft loss or re-transplant. "

In this systematic review and meta-analysis of observational studies that included 4077 MDR colonized SOT recipients, MDR colonization was associated with increased risk of all-cause mortality, infection-related mortality, mixed infections, and BSIs but not graft loss or re-transplant. SOT recipients colonized with CRE exhibited the highest risk of infection and mortality.

The authors postulate the increased risk of death seen in MDR colonized SOT could have several explanations. First harboring an MDR could serve as a surrogate for sicker candidates and recipients with prolonged hospitalization, prolonged antibiotic exposure, and increased complications. Second, the use of antibiotics, which is common in SOT, causes disruption of microbiota diversity (dysbiosis) which has been associated with increased death in non-SOT patients. [Am J Infect Control 2016; 44:539– 43; Clin Infect Dis 2017;64:1753–1759] Gut dysbiosis might affect the host immunity and hemostasis, contributing to the increased death. [Transpl Infect Dis 2022,24]

There was a larger representation of liver transplant in this study, similar to previous systematic review. [Am J Transplant 2014; 14:1887–94] Various mechanisms predispose cirrhotic candidates and liver transplant recipients to increased colonization and infection with MDR bacteria and these include impairment of immune function, increased gastrointestinal permeability, bacterial translocation, and prolonged hospitalization. In addition, infections are more likely to occur with abdominal transplants, especially liver and intestinal transplants where integrity of the bowel is compromised [J Antimicrob Chemother 2021;76: i27–39] They could not evaluate the impact of broad-spectrum perioperative antibiotic prophylaxis and infection control strategies and its association with MDR colonization or infection. The studies were conducted in different periods of time and countries in which antimicrobial availability could differ. An example they gave-the mortality from CRE in an era where only colistin was available has changed as more novel beta lactam/b-lactamase inhibitors have become available. Lastly, the certainty of the evidence of this meta-analysis in assessing the role of MDR colonization in SOT on infection, death and graft failure was judged as low and very low.

BOTTOM LINE

This study highlights the burden of MDR colonization in SOT and can aid in stratifying the recipient's risk of infection and mortality according to type of MDR colonization. Whether decolonization strategies may improve the prognosis of SOT patients should be evaluated in prospective studies. FMTs have been suggested as a strategy.

27

Prospective observational pilot study of the T2Resistance panel in the T2Dx system for detection of resistance genes in bacterial bloodstream infections

J Clin Microbiol 62: e01296-23
doi.org/10.1128/jcm.01296-23

The investigators conducted a prospective pilot study of the T2R Panel in two major medical centers, one in Italy, and the other in Athens, Greece, over 5 months. The objective of this study was to evaluate the sensitivity and time of identification of the T2R Panel, for the detection of resistance genes in patients with resistant BSIs in comparison to those of BCs and conventional clinical microbiological methods. Patients with a clinical suspicion of sepsis or septic shock, in which the attending physician requested BCs, were eligible for enrollment into the study. At the same time as the blood cultures were collected, three additional 4 mL EDTA tubes were collected for study. The first tube was T2Bacteria Panel (T2B) analysis and performed immediately upon receipt. The second sample (Tube 2) was indicated for the T2R Panel, classified as Research Use Only, and run sequentially after T2Bacteria. The third tube was frozen for further studies. Whole blood collection was performed from the same peripheral vein/anatomic site as those from BCs.

The T2R Panel is performed using a 4 mL EDTA blood sample. The T2R Panel runs on the T2Dx instrument that qualitatively detects the 13 resistance genes. See below

Genetic biomarker groups	Specific genes detected
bla_{KPC}	bla_{KPC}
bla_{CTX-M}	$bla_{CTX-M\ 14/15}$
Metallo-β-lactamase	$bla_{NDM}/bla_{VIM}/bla_{IMP}$
bla_{OXA-48}	bla_{OXA-48} *group*
van	*vanA/vanB*
mec	*mecA/mecC*
AmpC	*AmpC* (bla_{CMY}/bla_{DHA})

For each patient, the following data were collected: site of infection, results of BC, susceptibility phenotype or genotype, empirical antimicrobial therapy being administered during T2 collection and directed therapy changes performed after T2 result date and time of sample collection for BC and T2, and date and time for susceptibility phenotype. Interventions related to results from T2 reports, pathogens recovered from blood, and other sites before or after T2 was performed, for a time interval of 2 weeks were also documented.

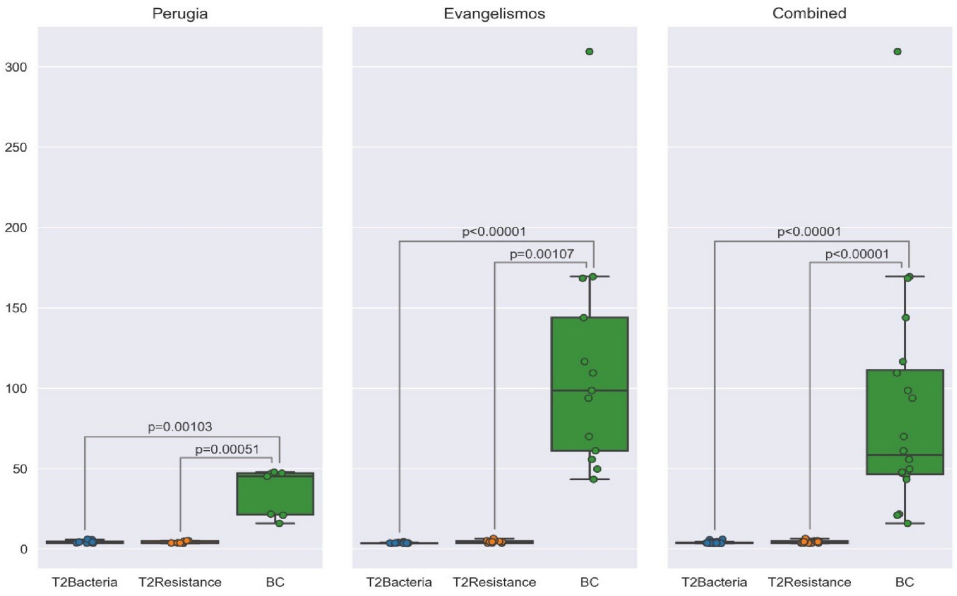
In all a total of 59 patients were enrolled from October 2019 to February 2020. Among the 26 patients enrolled at PGH(Italy), 15 were males and 11 were females with a mean age of 57.7 years ± 25.27 (SD), a median of 63.5 years [interquartile range (IQR): 25%–75%], and range of 53–76 years. Among the 33 patients enrolled at EGH(Greece), 19 were males with a mean age of 59.9 years ± 17.98 (SD), a median of 63 years (IQR: 25%–75%), and range of 17–87 years. Concomitant conditions assessed by the patient's care team included septic shock, sepsis, fever and hematological malignancy, ARDS, pneumonia, intraabdominal infection and/or peritonitis, meningitis, and trauma.

T2Bacteria results were positive in 42.4% (25 of 59) of patients, with identification of 33 bacteria. Overall, pathogens identified by T2B, included: S. aureus (n = 3), K. pneumoniae (n = 14), A. baumannii (n = 11), P. aeruginosa (n = 2), and E. coli (n = 3). No E. faecium targets were identified. The T2B panel covered 86% of bacterial pathogens causing BSIs in this patient population. BCs and T2B results (T2B+/BC+, T2B-/BC-) were concordant in 74.6% (50/67) of results. Among the T2B+/BC- cases, a probable BSI was confirmed in 12/16 (75%) of cases through analysis of additional microbiological evidence including BCs and cultures obtained from other infected sites within 15 days of the original T2B blood draw. Four additional possible BSIs were confirmed through clinical and microbiological assessment. BC failed to identify 14 organisms identified by T2B. The per-assay sensitivity and specificity of T2B for proven BSIs were 94% (95% CI, 72.7%–99.9%) and 95% (95% CI, 92.4%–97.3%), respectively. The median time to species identification by T2B for all patients (n = 25) was 3.63 hours (IQR: 3.6–3.93 hours) versus time to final species identification with BCs at 58.34 hours (IQR: 45.51–

111.2 hours; P < 0.00001 [Fig. 1]). The median time for negative T2B results was 4 ± 0.6 hours compared with a median time to final negative BCs of 154.9 ± 67.9 hours.

The performance of T2R in diagnosing BSIs caused by resistant pathogens: In all, 25 resistance genes in 19 patients were identified by T2R: blaKPC (n = 10), blaNDM/blaIMP/blaVIM (n = 5), blaCTXM-14/15 (n = 4), blaAmpC (n = 2), and mecA/mecC (n = 4). No vanA, vanB, or blaOXA genes were detected. The mean time to positive T2R in PGH was 4.2h ± 0.7 hours, while the mean time to positive BCs with species identification was 34.7 ± 14.4 hours (P = 0.001). The mean time to positive T2R in EGH was 4.6 ± 0.9 hours in comparison to that for final reporting of positive BCs with AST of 94.3 ± 47.0 hours (P < 0.001).

Comparative times to identification from T2Bacteria and T2Resistance versus blood cultures and phenotypic assay and/or molecular assay for both centers and combined



Moreover, the mean time to a positive result from standard molecular resistance assay (GeneXpert® System) following BCs in 5 patients was 33.7 ± 5.3 hours (P = 0.001), from immunochromatographic assay for CTXM in four patients was 27.6 ± 6.9 hours (P = 0.008), and from AST in five patients was 53.8 ± 5.8 hours (P = 0.004). When monitored for the impact of significant changes in antimicrobial therapy resulting from T2B and T2R results, there were a total of 49 drug¬ specific antimicrobial interventions in 24 patients, including 17 events of antibiotic additions, and 32 discontinuations. At EGH, there were seven antibiotic additions and 23 events of discontinuation of unnecessary antimicrobial agents in 17 patients. At PGH, there were 19 specific interventions among 7 patients, which consisted of 10 antibiotic additions of antimicrobial agents, and 9 discontinuations.

Dr. Septimus's Annotations

Early treatment of resistant bacterial BSIs improves outcomes. [Crit Care Med 2006 34:1589–1596] The therapeutic implications of the rapid turnaround time of BC independent molecular tests like T2B and T2R for clinicians caring for septic patients are important and potentially lifesaving. There is a critical need for rapid diagnostics for patients suffering from sepsis, particularly in the setting of antimicrobial resistance. [Front Med 2021; (Lausanne) 8:635831] In the current study, clinicians were able to intervene in 42% (24/57) of patient cases to optimize therapy immediately after receiving T2R results. In 36% (16/44), T2R facilitated therapeutic antibiotic additions indicating that even broad empiric therapy may miss some potential resistant pathogens.

This study has several limitations. First, the number of patients enrolled and centers participating are relatively small in comparison to those of the large definitive study of T2B. [Ann Intern Med 2019; 170:845–852] Second, time to test result availability for T2R was limited due to preliminary software that did not permit simultaneous testing with both T2B and T2R.

BOTTOM LINE

This pilot study demonstrates proof of concept that the T2R Panel can detect commonly encountered bacterial genes encoding resistance mechanisms in patients with BSIs and sepsis at significantly more rapid turnaround times than those of conventional culture-based phenotypic and genotypic methods and culture dependent molecular tests.

28 BioMerieux receives FDA clearance for rapid respiratory/sore throat test- Spotfire

The panel, Biofire Spotfire, is a multiplex polymerase chain reaction (PCR) test capable of detecting and identifying nucleic acids from up to 15 of the most common bacteria, viruses, and viral subtypes that cause respiratory or sore throat infections in about 15 minutes. The test uses samples taken from nasopharyngeal and throat swabs. The company also received a Clinical Laboratory Improvement Amendments(CLIA) waiver for the test, which allows it to be used by non-lab professionals and in any setting where patients seek care.

Viruses:

- Adenovirus,
- Coronavirus (seasonal),
- SARS-CoV-2,
- Human metapneumovirus,
- Human rhinovirus/enterovirus,
- Influenza A,
- Influenza A subtype H3,
- Influenza A subtype H1-2009,
- Influenza B virus,
- Parainfluenza virus, and
- RSV.

Bacteria:

- *Bordetella pertussis*,
- *Bordetella parapertussis*,
- *Chlamydia pneumoniae*, and
- *Mycoplasma pneumoniae*.

There is also a mini panel which is not available yet which detects 5 of the most common respiratory pathogens.

Viruses:

- Human rhinovirus,
- Influenza A virus,
- Influenza B virus,
- RSV, and
- SARS-CoV-2.

Bacteria [Sore Throat only]:

- Group A Strep

Dr. Septimus's Annotations

I do not know the cost of the panel. Theoretically the panel should allow clinicians to test for multiple pathogens with overlapping signs and symptoms, allowing better diagnostic certainty and supporting diagnostic and antimicrobial stewardship; however, studies with other respiratory diagnostics has not always resulted in better care.

BOTTOM LINE

In order for these panels to impact care be cost effective, diagnostic stewaredship much be linked to antimicrobial stewardship.

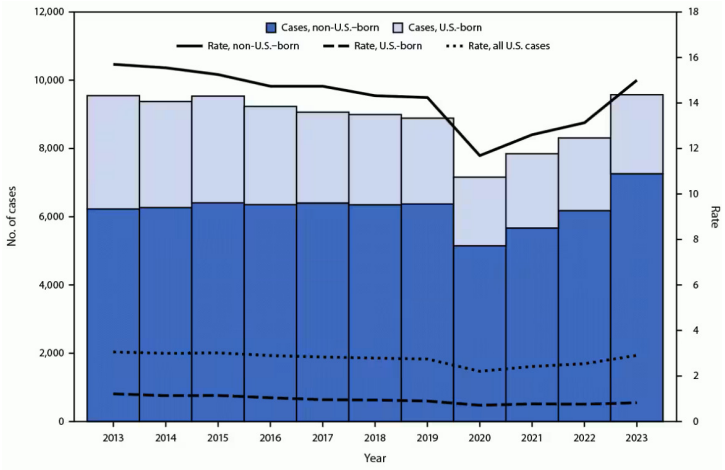
29

Tuberculosis — United States, 2023

MMWR 2024; 73:265-270

Provisional national surveillance data show that TB case counts and rates have increased since the Covid-19 pandemic, returning to the number of cases last observed in 2013. Increases occurred in every age group and all except 10 US states. Case counts increased among both US-born and non-US–born persons, with the most substantial increase, 18%, among non-US–born persons (1,082 cases). The US has one of the lowest TB rates in the world and most US residents are at minimal risk for TB (2,4). The overall epidemiology of TB continues to reflect persistent disparities by birth origin, and race and ethnicity in the United States. TB rates in 2023 were highest among non-U.S.–born persons which is consistent with prepandemic trends. Among US-born persons, rates remained.

Annual number and rate of cases of tuberculosis disease, by birth origin — United States, 2013–2023



9,615 TB cases were reported in the US in 2023, a 16% increase from 2022 and the highest number reported since 2013. The TB incidence rate of 2.9 cases per 100,000 persons represented a 15% increase from 2022. TB incidence increased in every age-group, with the largest increase seen in children ages 5 to 14 years. Most reported TB cases in 2023 (76%) occurred in non–US-born residents. But case counts rose among both US-born and non–US-born residents, who saw increases of 9% and 18%, respectively. Among US-born persons with TB, 33% were Black, 27% Hispanic, 26% White, 6% Asian, 5% American Indian or Native Alaskan, and 3% Native Hawaiian or other Pacific Islander. CDC reported that roughly 85% of US TB cases are attributed to reactivation of latent TB infection rather than recent transmission.

Dr. Septimus's Annotations

Despite the rise in cases and incidence, the US still has one of the lowest TB rates in the world, and most US residents are at minimal risk of infection. The CDC says the increase may be related to Covid-19 pandemic–related disruptions to TB services. In contrast the number of people who received a new TB diagnosis has also risen globally. In 2022, the WHO reported a second consecutive year of increasing TB case counts, with the global estimate of TB cases equaling that of 2016. Influenza and measles have also experienced postpandemic surges.

Renewed progress toward TB elimination will require strengthened capacity of public health programs to carry out critical TB control and prevention strategies and engagement of providers and affected communities in TB elimination efforts. In addition, because most TB cases in the US occur among non-US–born persons, collaboration of public health in the US with international partners is important to reduce TB morbidity globally.

BOTTOM LINE

Continued progress toward TB elimination will require strong public health systems that can maintain essential disease prevention and control activities and prepared to withstand the next pandemic or other large-scale crisis.

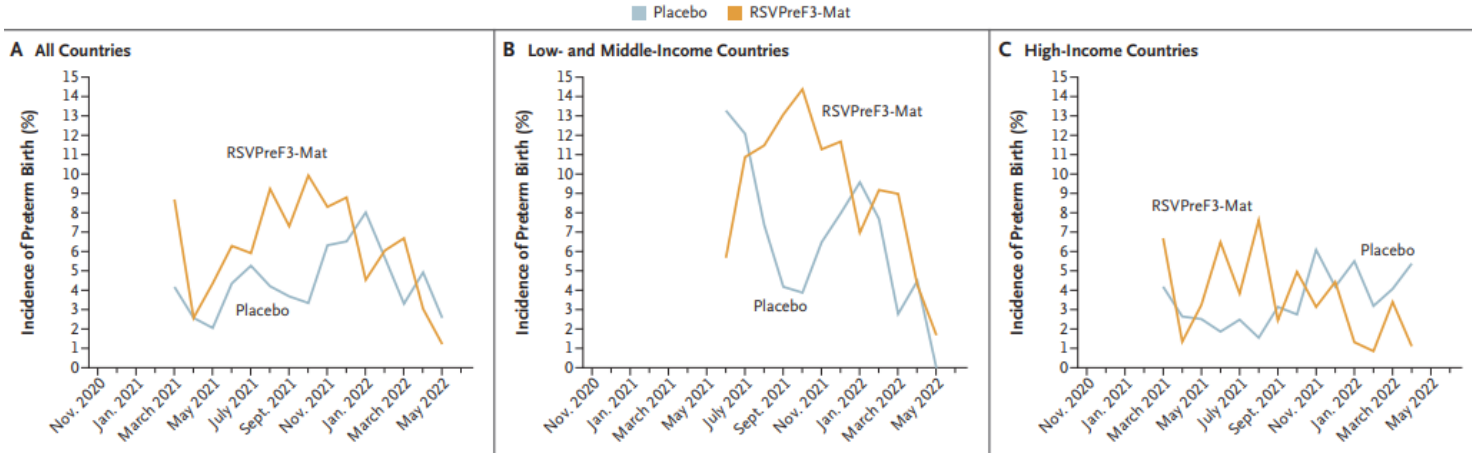
30

RSV Prefusion F Protein–Based Maternal Vaccine — Preterm Birth and Other Outcomes

N Engl J Med 2024; 390:1009-21.
DOI: 10.1056/NEJMoa2305478

To test the efficacy of a prefusion-stabilized F protein–based vaccine in pregnant women for preventing medically attended RSV-associated lower respiratory tract disease in their infants, investigators planned to enroll 10,000 pregnant women in a multinational, industry-funded study. After 5328 participants were enrolled, they were randomized to receive vaccine (3551 women) or placebo (1771 women); however, the study was halted early due to an imbalance of preterm births between groups.

In the vaccine and placebo groups, maternal gestation at vaccination was 24–28 weeks in 41% of participants and 29–34 weeks in 58%; about half resided in LMIC. Incidence of preterm birth was higher in the vaccine group (6.8% vs. 4.9%; relative risk, 1.37; P=0.01). Among the 7 neonatal deaths in preterm infants, all were in the vaccine group. Preterm births occurred predominantly in LMIC, and a temporal association with the COVID-19 delta wave was observed. However, no between-group imbalances in SARS-CoV-2 infections by history or serology were seen. Vaccine efficacy at preventing medically attended RSV-associated lower respiratory tract disease in infants was 65.5%.



Dr. Septimus's Annotations

The results of this trial, in which enrollment was stopped early because of safety concerns, suggest that the risks of any and severe medically assessed RSV-associated lower respiratory tract disease among infants were lower with the candidate maternal RSV vaccine than with placebo but that the risk of preterm birth was higher with the candidate vaccine. The mechanism by which RSVPreF3-Mat may have led to an increased risk of preterm birth as compared with placebo is unknown. Although inflammatory processes have been associated with premature birth [Lancet 2008; 371:75-84] post hoc analyses in the current trial showed no association between cytokine levels in maternal participants. However, blood samples were not obtained soon enough after vaccination to reliably detect vaccine-related increases in cytokine levels. The increased risk of preterm birth in the vaccine group was largely seen in low- and middle-income countries. In trials leading to licensure of another perfusion-stabilized F protein-based maternal vaccine an insignificant increase in preterm births were seen among vaccinees. An increased number (non-significant) risk of preterm births prior to 32 weeks gestation led ACIP to recommend its use for persons at 32-36 weeks gestation. Post-marketing vaccine surveillance is underway. The trial was conducted during the Covid-19

pandemic, and the peak imbalance occurred when the delta variant was dominant. SARS-CoV-2 infection during pregnancy — particularly during waves of infection with the delta variant — has been associated with an increased risk of preterm birth. [Semin Fetal Neonatal Med 2023; 28:101428] This trial included use of post hoc analysis to assess safety of preterm birth.

BOTTOM LINE

The results of this trial, in which enrollment was stopped early because of safety concerns, suggest that the risks of any medically assessed RSV-associated lower respiratory tract disease and severe medically assessed RSV-associated lower respiratory tract disease among infants were lower with RSVPreF3-Mat than with placebo but that the risk of preterm birth was higher with RSVPreF3-Mat.

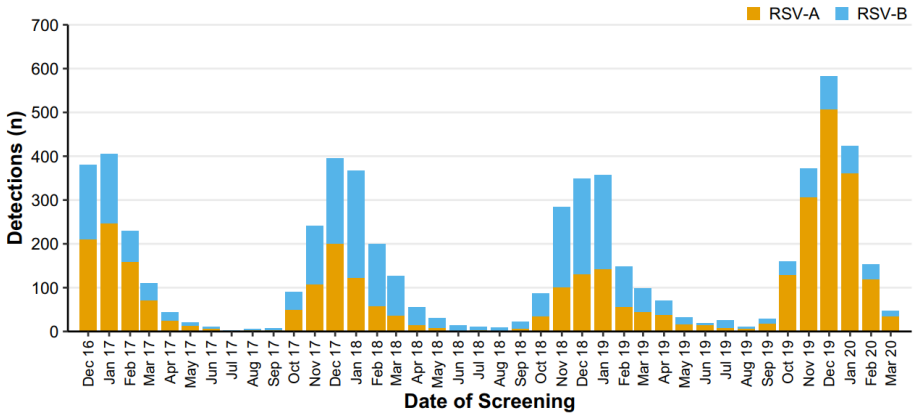
31

Seasonality, Clinical Characteristics, and Outcomes of Respiratory Syncytial Virus Disease by Subtype Among Children Aged < 5 Years

Clin Infect Dis published online February 15, 2024
doi.org/10.1093/cid/ciae085

During 2016–2020, children aged <5 years were enrolled in prospective surveillance in the emergency department or inpatient settings at 7 US pediatric medical centers. Surveillance data collection included parent/guardian interviews, chart reviews, and collection of midturbinate nasal plus/minus throat swabs for RSV (RSV-A, RSV-B, and untyped) using rPCR.

Distribution of signs and symptoms among RSV-positive children aged <5 years in inpatient or emergency department settings stratified by RSV subtype, New Vaccine Surveillance Network, 2016–2020



Among 6398 RSV-positive children aged < 5 years, 3424 (54%) had subtype RSV-A infections, 2602 (41%) had subtype RSV-B infections, and 272 (5%) were not typed, inconclusive, or mixed infections. In both adjusted and unadjusted analyses, RSV A–positive children were more likely to be hospitalized, as well as when restricted to < 1 year. By season, RSV-A and RSV-B cocirculated in varying levels, with 1 subtype dominating proportionally. They found that RSV-A and RSV-B frequently cocirculate during the RSV season, with the predominant subtype varying by location and year.

Dr. Septimus's Annotations

Findings indicate that RSV-A and RSV-B may only be marginally clinically distinguishable, but both subtypes are associated with medically attended illness in children aged < 5 years. Furthermore, circulation of RSV subtypes varies substantially each year, seasonally and geographically. Since most children are infected with RSV in the first 2 years of life, heterogeneous backgrounds of existing natural immunity in this study population could obscure detection of some subtype-specific clinical features of RSV infection.

BOTTOM LINE

These findings have important implications for public health policies and the rollout of RSV prevention strategies such as nirsevimab and maternal vaccination. Furthermore, with the availability of new RSV prevention products, this highlights the importance of continued monitoring of RSV-A and RSV-B subtypes.

32

Joint analysis of vaccination effectiveness and antiviral drug effectiveness for COVID-19: a causal inference approach

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This study was conducted in Hong Kong in 2022. During the study period, Omicron BA.2 and BA.5 subvariants were dominant. They analyzed an unselected cohort of hospitalized patients with confirmed SARS CoV 2 infection. An IPW Andersen-Gill model was applied to estimate the causal effects of Covid-19 vaccinations (i.e., CoronaVac and Comirnaty) and oral antivirals (i.e., molnupiravir and nirmatrelvir-ritonavir) in prevention against development into severe Covid-19 and all-cause mortality. The primary outcome was all-cause 28-day mortality from a confirmed Covid-19 infection. A secondary outcome was the development of severe illness, defined as requiring intubation, intensive care unit admission, extracorporeal membrane oxygenation, shock, or oxygen supplement of at least three liters per minute.

The investigators assessed 61,105 hospitalized adult patients who had confirmed SARS-CoV-2 infection. A total of 16,068 (26.3%) of patients were treated with molnupiravir, and 18,113 (29.6%) were treated with nirmatrelvir-ritonavir (Paxlovid). About 44% of patients did not receive antiviral treatments. The molnupiravir users, nirmatrelvir-ritonavir users, and controls had cumulative fatal incidences of 1,404, 245, and 2,732, respectively, and severe case incidences of 1,766, 794, and 2,848, respectively.

Nirmatrelvir-ritonavir use within 5 days of confirmed infection for those 18 to 59 years was associated with a significantly lower risk of all-cause mortality (hazard ratio [HR], 0.48; 95% confidence interval, 0.25 to 0.92). Molnupiravir was also associated with significantly lower risks of all-cause mortality and progression to severe Covid-19 for patients aged 60 to 79 years (mortality and severe case HRs of 0.65 and 0.69, respectively). There was also a benefit for people 80 and older if given within 5 days. There was no significant benefit for oral antivirals prescribed beyond 5 days of confirmed infection. There was no significant difference between CoronaVac (made by Sinovac Biotech) and Comirnaty (Pfizer-BioNTech) vaccines in the effectiveness of reducing all-cause mortality and progression to severe Covid-19.

Dr. Septimus's Annotations

Antivirals given within five days of confirmed infection reduce all-cause mortality. The use of nirmatrelvir-ritonavir was associated significantly lower risks of all-cause mortality and progression to severe Covid-19 than those of molnupiravir, although molnupiravir was also associated with significantly lower risks of all-cause mortality and progression to severe Covid-19 compared to no treatment. Both Comirnaty and CoronaVac were found to be equally effective in preventing severe outcomes, in all age-groups. The investigators claim this is the first study to evaluate the causal effects of oral antivirals and vaccinations in an integrative setting with both types of treatments (i.e., antivirals and vaccinations) considered as intervention factors. In the current study, different propensity models were constructed for the treatment assignments of oral antivirals and vaccinations, and inverse probability weighting was applied to the Breslow partial likelihood of the Andersen-Gill model so that the causal effects of antivirals and vaccinations can be estimated in an integrative model with a large sample size. However, the causal estimates were based upon the assumption that the

propensity models for treatment assignments were properly specified and there was no unobserved confounding factor missing from the models. Second, the effects of vaccinations were evaluated in a discrete manner, and the time-varying effects of vaccinations were not considered. Lastly, regarding the target variable of all-cause mortality, they were not able to differentiate deaths from all causes and identify those directly related to SARS-CoV-2 infection.

BOTTOM LINE

This study demonstrated that, if prescribed within 5 days of confirmed infection, nirmatrelvir-ritonavir is more effective in protecting against all-cause mortality and severe Covid-19 in adults than is molnupiravir and vaccines were effective in preventing severe outcomes.

Nirmatrelvir for Vaccinated or Unvaccinated Adult Outpatients with Covid-19

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DOI: 10.1056/NEJMoa2309003

In this phase 2–3 trial, the investigators randomly assigned adults who had confirmed Covid-19 with symptom onset within the past 5 days in a 1:1 ratio to receive nirmatrelvir– ritonavir or placebo every 12 hours for 5 days. Patients who were fully vaccinated against Covid-19 and who had at least one risk factor for severe disease, as well as patients without such risk factors who had never been vaccinated against Covid-19 or had not been vaccinated within the previous year, were eligible for participation. Participants logged the presence and severity of prespecified Covid-19 signs and symptoms daily from day 1 through day 28. The primary end point was the time to sustained alleviation of all targeted Covid-19 signs and symptoms. Covid-19–related hospitalization and death from any cause were also assessed through day 28.

Among the 1296 participants who underwent randomization and were included in the full analysis population, 1288 received at least one dose of nirmatrelvir–ritonavir (654 participants) or placebo (634 participants) and had at least one postbaseline visit. More than half the participants were women (54.0%), and the median age at enrollment was 42 years. Only 5% were over age 65 and < 50% had any risk factors for progression. The median time to sustained alleviation of all targeted signs and symptoms of Covid-19 was 12 days in the nirmatrelvir–ritonavir group and 13 days in the placebo group (P=0.60). Five participants (0.8%) in the nirmatrelvir–ritonavir group and 10 (1.6%) in the placebo group were hospitalized for Covid-19 or died from any cause (difference, −0.8 percentage points; 95% confidence interval, −2.0 to 0.4). The percentages of participants with adverse events were similar in the two groups (25.8% with nirmatrelvir–ritonavir and 24.1% with placebo). In the nirmatrelvir–ritonavir group, the most commonly reported treatment-related adverse events were dysgeusia (5.8% of the participants) and diarrhea (2.1%). By day 14, viral load rebound had occurred in 4.3% of the participants in the nirmatrelvir– ritonavir group and 4.1% of those in the placebo group; symptom rebound occurred in 11.4% and 16.1%, respectively, and symptom and viral load rebound together occurred in 1.2% and 0.5%, respectively.

Dr. Septimus's Annotations

The NIH guidelines currently recommend nirmatrelvir-ritonavir as first-line therapy for outpatients with Covid-19 who are at high risk for progressing to severe disease. This recommendation was based on the initial randomized trial of nirmatrelvir-ritonavir which showed that the drug lowered risk for hospitalization and death among high-risk, unvaccinated adults. [N Engl J Med 2022; 386:1397] In subsequent observational trials, benefits have varied, depending on the patient population included. In this trial the time to sustained alleviation of all signs and symptoms of Covid-19 did not differ significantly between participants who received nirmatrelvir–ritonavir and those who received placebo. An important point-the study participants were young with few comorbidities.

BOTTOM LINE

Since the study participants were younger without significant comorbidities, I would still suggest prescribing nirmatrelvir-ritonavir for older patients, immunosuppressed patients, and patients with serious comorbidities.

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One-Year Recovery Among Survivors of Prolonged Severe COVID-19: A National Multicenter Cohort

Crit Care Med published online April 10, 2024
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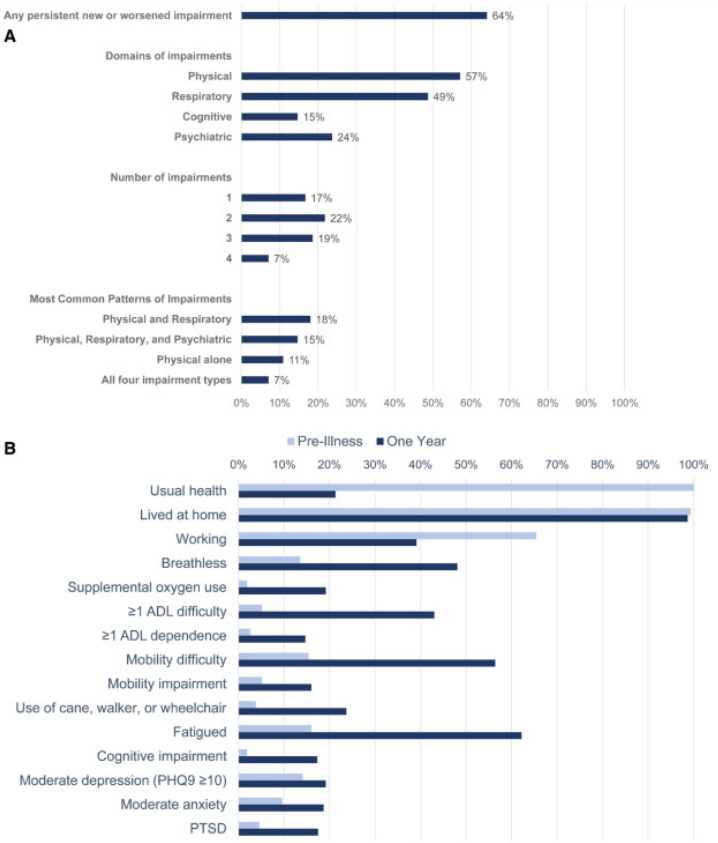
The Recovery After Transfer to an LTACH for COVID-19 (RAFT COVID) study was a national, multicenter, prospective longitudinal cohort study. They included hospitalized English-speaking adults transferred to one of nine LTACHs in the US between March 2020 and February 2021 and completed a survey.

Among 282 potentially eligible participants who provided permission to be contacted, 156 (55.3%) participated (median age, 65; 38.5% female; 61.3% in good prior health; median length of stay of 57 d; 77% mechanically ventilated for a median of 26 d; 42% had a tracheostomy). Approximately two-thirds (64%) had a persistent impairment, including physical (57%), respiratory (49%; 19% on supplemental oxygen), psychiatric (24%), and cognitive impairments (15%). Nearly half (47%) had two or more impairment types. Participants also experienced persistent debility from hospital-acquired complications, including mononeuropathies and pressure ulcers. Participants described protracted recovery, attributing improvements to exercise/ rehabilitation, support, and time. While considered life-altering with 78.7% not returning to their usual health, participants expressed gratitude for recovering; 99% returned home and 60% of previously employed individuals returned to work.



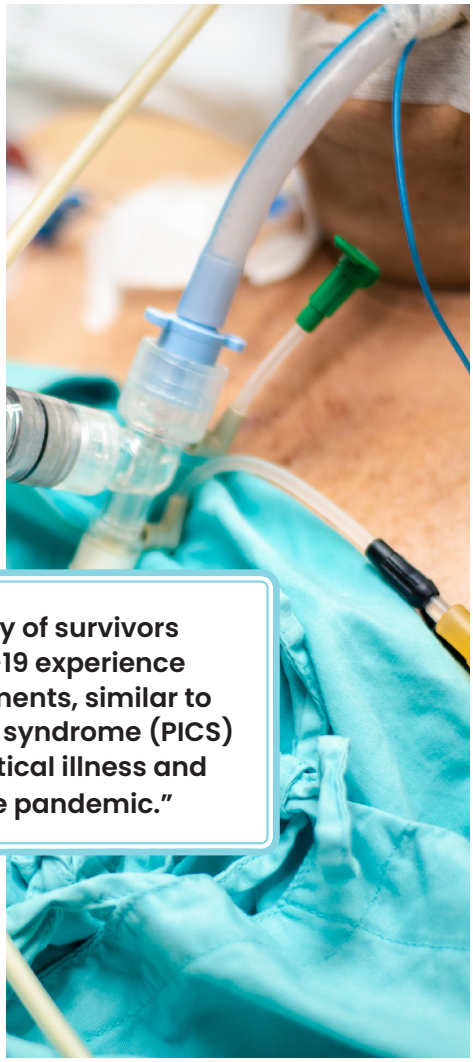
Dr. Septimus's Annotations

This study adds to the evolving evidence that the majority of survivors of severe Covid-19 experience persistent impairments, similar to post-intensive care syndrome (PICS) observed after critical illness and ARDS before the pandemic. They similarly found that physical and respiratory impairments were most common, including difficulties with self-care, trouble walking, fatigue, and breathlessness, and that these impairments improved over time. They also found that nearly half of survivors had two or more domains impaired highlighting the need for interdisciplinary care to enhance recovery, ideally with multidisciplinary services co-located within an outpatient clinic or rehabilitation environment.

Their findings also highlight two unique observations about PICS after Covid-19 critical illness. First, nearly one

in five survivors remained on supplemental oxygen at 1 year, which was much higher than other studies of Covid-19–related ARDS, where long-term oxygen use ranged from 0% to 5%. [Thorax 2022; 77:300–303] The investigators say this may be because their study included patients with very prolonged respiratory failure, and thus may have had more advanced pulmonary fibrosis with reduced lung function. Second, their findings suggest cognitive impairment may be a distinct phenotype of PICS after Covid-19. While all other domains improved over time, cognition did not. They also observed there were additional acquired physical impairments during the hospitalization, which limited long-term function and recovery, including peripheral mononeuropathies, pressure ulcers, and tracheostomy related complications not typical of PICS. These impairments have not been well described among critical illness survivors before the pandemic.

This study did not capture more granular details about the hospitalization and subsequent treatment were unavailable, such as the use of sedation or post discharge rehabilitation. This study did not have a control group, so they could distinguish the impairments of SARS-CoV-2 (long COVID) from critical illness (PICS), which requires further investigation. Last, although their study is relevant to the millions globally who survived prolonged severe Covid-19, their findings may not generalize beyond the ancestral strain of SARS-CoV-2 or to contemporary populations with immunity.



"...[T]he majority of survivors of severe Covid-19 experience persistent impairments, similar to post-intensive care syndrome (PICS) observed after critical illness and ARDS before the pandemic."

BOTTOM LINE

Persistent impairments were common for survivors of prolonged severe COVID-19 and resembled post-intensive care syndrome after critical illness plus debility from hospital-acquired complications.

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FDA Authorizes New Antibody To Protect Immunocompromised Patients From COVID-19

March 22, 2024

The FDA has authorized a new antibody to protect immunocompromised individuals against Covid-19. The drug, known as Pemgarda and marketed by the biotech Invivyd, is the first such drug to become available since the agency pulled AstraZeneca's Evusheld off the market in January 2023. New Omicron variants had rendered Evusheld ineffective. Pemivibart is a human monoclonal antibody targeting the SARS-CoV-2 receptor binding domain, with a half-life of 44.8 days (vs. 80–90 days for Evusheld). In vitro assays demonstrated activity against currently circulating variants,

Still, it's not clear how many patients will avail themselves of the new treatment. Its initial focus will be on the 485,000 with the most acute need: Stem cell transplant recipients, organ transplant recipients, and blood cancer patients. Pemivibart is given as a single intravenous infusion and is not for use as post-exposure prophylaxis or in people currently infected with SARS-CoV-2. Pemivibart is given as a 4500-mg intravenous infusion over the course of ≥1 hour. Additional doses are recommended at 3-month intervals.

Dr. Septimus's Annotations

Pemivibart may serve as a valuable tool for protecting immunocompromised patients at highest risk of severe Covid-19. As SARS-CoV-2 evolves, testing of pemivibart's activity against emerging variants will be important.