ID WATCH
by Ed Septimus, MD

Editor's Choice

1

Biomarker Assessment of a High-Risk, Data-Driven Pediatric Sepsis Phenotype Characterized by Persistent Hypoxemia, Encephalopathy, and Shock

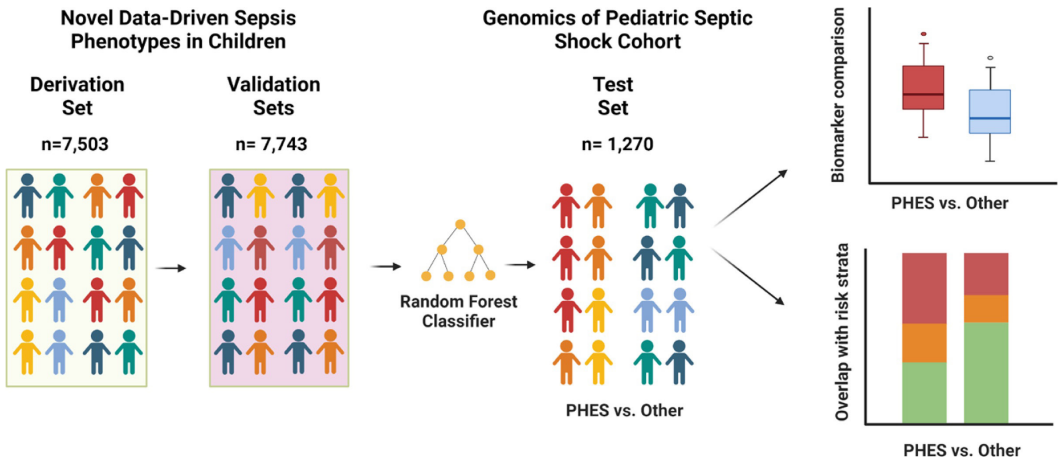
Pediatric Critical Care Medicine 2024; 25:512-517
DOI: 10.1097/PCC.0000000000003499

The investigators recently developed and validated a data-driven phenotype of high-risk sepsis-associated MODS based on organ dysfunction trajectories within the first 72 hours of PICU admission [Pediatr Crit Care Med 2023; 24:795–806] This phenotype, which they called the "persistent hypoxemia, encephalopathy, and shock" (PHES) phenotype based on its clinical characteristics, was independently associated with worse clinical outcomes and demonstrated differential response to common adjuvant therapies. In the current study, they sought to test the reproducibility of this phenotyping approach, test association of phenotypes with serum biomarkers (IL-8, HSP70, CCL3, CCL4, GZMB, and IL-1a) reflective of systemic inflammation and endothelial activation(soluble thrombomodulin, Angpt-2, Angpt-2/Angpt-1, Angpt-2/Tie-2, and ICAM-1) and assess their overlap with established biomarker-based risk strata in a large prospective observational cohort of pediatric septic shock. They set out to validate a random forest classifier using organ dysfunction subscores

in the 2012–2018 electronic health record (EHR) dataset used to derive the PHES phenotype. The original PHES phenotype designation was based on the trajectory of the six pediatric Sequential Organ Failure Assessment (pSOFA) subscores during the first 72 hours after PICU admission. The primary outcome of interest was complicated course, a composite that included patients who had died by or had persistence of greater than or equal to 2 organ dysfunctions on day 7 of septic shock. The secondary outcome was 28-day mortality.

EHR data from 15,246 critically ill patients with sepsis-associated MODS split into derivation and validation sets and 1,270 pediatric septic shock patients in the test set of whom 615 had complete biomarker data. This involved 25 PICUs across the US. The area under the receiver operator characteristic curve of the modified classifier to predict PHES phenotype membership was 0.91 (95% CI, 0.90–0.92) in the EHR validation set. In the test set, PHES phenotype membership was associated with both increased adjusted odds of complicated course (adjusted odds ratio [aOR] 4.1; 95% CI, 3.2–5.4) and 28-day mortality (aOR of 4.8; 95% CI, 3.11–7.25) after controlling for age, severity of illness, and immunocompromised status. Patients belonging to the PHES phenotype were characterized by greater degree of systemic inflammation and endothelial activation and were more likely to be stratified as high risk based on biomarkers predictive of death and persistent MODS.

Overview of study detailing study subjects in derivation, validation, and test cohorts



PHES = persistent hypoxemia, encephalopathy, and shock

Dr. Septimus's Annotations

In this study, the investigators demonstrated reproducibility of the data-driven PHES phenotype in a large prospective cohort of pediatric septic shock patients from 2012 to 2018. They also show in another dataset (2003–2023) that the modified PHES phenotype was associated with a biomarker profile reflective of greater systemic inflammation and endothelial activation—a pattern common among data-driven phenotypes of children and adults with sepsis and acute respiratory distress syndrome. [Lancet Respir Med 2022; 10:289–297] The test set did not collect all the variables included in the pSOFA subscores and this would have required a modified approach to assign phenotype membership, which excluded neurologic and hepatic subscores.

BOTTOM LINE

The PHES phenotype of pediatric sepsis is reproducible and of high prognostic value in identifying patients at high risk of MODS. Future research is necessary to determine whether real-time risk stratification using EHR data can be used to accurately identify at-risk patients for targeted interventions.

2

Hospital-Onset Bacteremia Among Neonatal Intensive Care Unit Patients

JAMA Pediatrics published online June 24, 2024
DOI: 10.1001/jamapediatrics.2024.1840

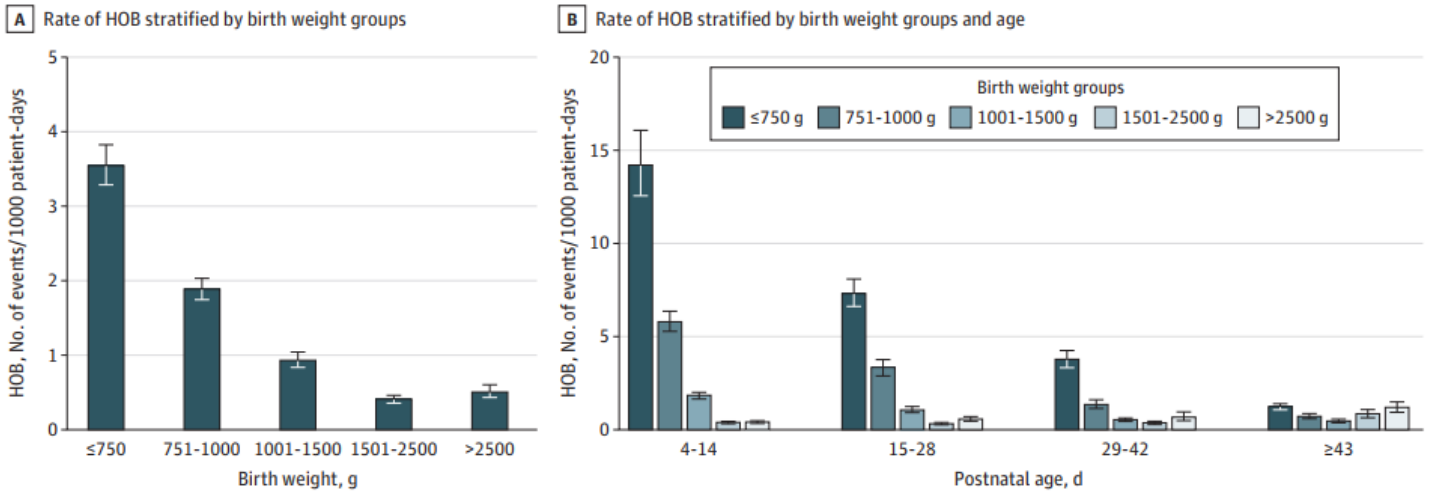
This is a retrospective multicenter cohort study and emulated trial from 2016 to 2021 included a convenience sample of 322 NICUs in the US. Participants were infants admitted to participating NICUs for 4 or more days. The primary goal was to estimate the rate of hospital-onset bacteremia or fungemia (HOB) [defined as a positive blood culture for bacteria or fungi on day 4 or later of hospitalization] among infants admitted to the NICU, measure the association of HOB risk with birth weight group and postnatal age, and estimate HOB-attributable mortality. They did not exclude common commensal organisms.

Of 451,443 included infants, 250,763 (55.6%) were male, 200,680 (44.4%) were female, and 62, 091 (13.8%) were born 1500 g or less. Of 9015 HOB events that occurred among 8356 infants (2%) during 8,163,432 days at risk (unadjusted incidence rate, 1.1 per 1000 patient-days; 95% CI, 1.0-1.2), 4888 HOB events (54.2%) occurred in the absence of a central line. Within the first 2 weeks after birth, the HOB rate was 14.2 per 1000 patient-days (95% CI, 12.6-16.1) among infants born 750 g or less, to 0.4 events per 1000 patient-days among infants born more than 2500 g (95% CI, 0.4-0.5). Among infants born 750 g or less, the relative HOB risk decreased by 90% after day 42 compared with days 4 to 14 (incidence rate ratio [IRR], 0.10; 95% CI, 0.1-0.1). Conversely, among infants born more than 2500 g, the relative HOB risk increased by 50% after day 42 compared with days 4 to 14 (IRR, 1.5, 95% CI, 1.2-1.9). Compared with otherwise similar infants without HOB, infants with HOB had an absolute difference in attributable mortality of 5.5% (95% CI, 4.7-6.3).

Primary Goal

1. Estimate the rate of hospital-onset bacteremia or fungemia (HOB) among infants admitted to the NICU
2. Measure the association of HOB risk with birth weight group and postnatal age
3. Estimate HOB-attributable mortality

HOB: defined as a positive blood culture for bacteria or fungi on day 4 or later of hospitalization



Dr. Septimus's Annotations

The CDC has proposed a new surveillance measure, (HOB), to broaden surveillance for health care–associated bloodstream infections in hospitalized patients. However, the epidemiology of HOB in infants born full term and late preterm is not well characterized. HOB was defined as a positive blood culture on or after day 4 of admission. HOB can

be reported electronically without the need for medical record review, shifting hospital resources from time-intensive surveillance to quality improvement initiatives. Among all HOB events, 54% occurred in the absence of a central line, therefore, more than half of NICU HOB would not be captured in CLABSI reporting. 77% of HOB events occurred among preterm infants with birth weight less than 1500 g, and HOB was associated with 5.5% (95% CI, 4.7-6.3) increased attributable mortality. The study observed that among the lowest-birth weight preterm infants, most HOB events occurred at 4 to 14 days after birth. The adjusted incidence rate of HOB for these infants declined significantly over time, while infants with birth weight more than 2500 g had higher adjusted incidence rates of HOB at 15 to 28 days of age compared to 4 to 14 days of age.

BOTTOM LINE

This study found that HOB events in the NICU are associated with increased mortality. Birth weight is an important risk factor for HOB. Among all HOB events, 54% occurred in the absence of a central line.

Trends in Empiric Broad-Spectrum Antibiotic Use for Suspected Community-Onset Sepsis in US Hospitals.

JAMA Network Open 2024;7(6):e2418923.
DOI: 10.1001/jamanetworkopen.2024.18923

To assess the extent to which community-onset sepsis is driving broad-spectrum antibiotic use, the investigators analyzed data on nearly 6.3 million adults admitted to 241 US hospitals from 2017 through 2021. The main outcomes were annual rates of empiric anti-MRSA and/or antipseudomonal beta-lactam antibiotic use—the two primary types of empiric broad-spectrum antibiotics used for sepsis—and the proportion of use that was likely unnecessary based on the absence of beta-lactam–resistant gram-positive pathogens or ceftriaxone-resistant gram-negative pathogens.

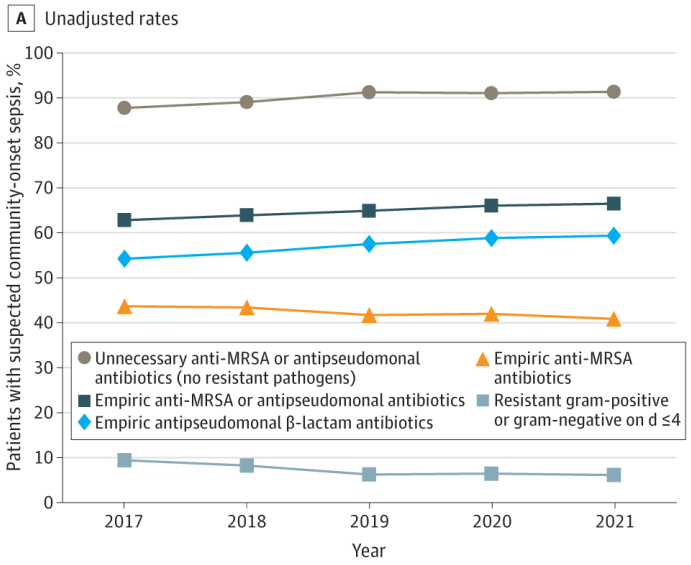
Of the 6,272,538 hospitalizations (median patient age, 66; 49.6% male; 73.1% White) during the study period, 894,724 (14.3%) had suspected community-onset sepsis. Those patients accounted for 50.1% of total inpatient anti-MRSA antibiotic days and 49.3% of total antipseudomonal beta-lactam days. Patients with suspected sepsis who received anti-MRSA or antipseudomonal therapy tended to be more severely ill than those who did not.

The most common empiric antibiotic was vancomycin (41.2%), followed by ceftriaxone (37.8%), piperacillin-tazobactam (31.1%), and cefepime (24.8%).

Most Common Empiric Antibiotics	
41.2%	Vancomycin
37.8%	Ceftriaxone
31.1%	Piperacillin-tazobactam
24.8%	Cefepime

During the study period, the proportion of patients with suspected sepsis who received anti-MRSA or antipseudomonal agents rose from 63.0% to 66.7% (adjusted odds ratio [aOR] per year, 1.03; 95% confidence interval [CI], 1.03 to 1.04). The increase was driven primarily by antipseudomonal beta-lactam use, which increased from 54.4% in 2017 to 59.6% in 2021.

However, resistant organisms were isolated in only 65,434 (7.3%) of all suspected sepsis cases, and the proportion of patients who had any resistant organism decreased from 9.6% in 2017 to 7.3% in 2021 (aOR per year, 0.87; 95% CI, 0.87 to 0.88). Most patients with suspected sepsis who were treated with anti-MRSA and/or antipseudomonal agents—90.5%—had no resistant organisms, with the proportion increasing from 88.0% in 2017 to 91.6% in 2021 (aOR per year, 1.12; 95% CI, 1.11 to 1.13). The fraction of patients who received inappropriately narrow-spectrum antibiotics was stable over time for those with resistant gram-positive organisms (aOR per year, 0.98; 95% CI, 0.96 to 1.00) but declined for those with resistant gram-negative organisms (aOR per year, 0.89; 95% CI, 0.87 to 0.90).



Dr. Septimus's Annotations

Broad-spectrum antibiotic use for patients with suspected community-onset sepsis rose over time but the percentage of cases with resistant organisms decreased. There was a decrease in patients receiving inappropriately narrow therapy but the absolute number who received unnecessarily broad treatment was nearly 50-fold higher than the number who were undertreated. The increase in broad-spectrum antibiotic prescribing was not associated with improvements in mortality for patients with suspected community-onset sepsis during the study period.

> **...[S]everal possible reasons why broad-spectrum antibiotic use for suspected sepsis is increasing, includ[es] the ongoing success of the Surviving Sepsis Campaign, the implementation of SEP-1, state sepsis regulatory measures, and the sepsis quality improvement initiatives..."**

The investigators believe there are several possible reasons why broad-spectrum antibiotic use for suspected sepsis is increasing, including the ongoing success of the Surviving Sepsis Campaign, the implementation of SEP-1, state sepsis regulatory measures, and the sepsis quality improvement initiatives these measures have encouraged.

The authors say the results of this study should not be interpreted as critical of the prescribing of front-line providers, because broad-spectrum antibiotics are required by CMS Severe Sepsis and Septic Shock Bundle within 3 hours of sepsis onset, while the Surviving Sepsis Campaign's 1-Hour Bundle calls for administration of broad-spectrum agents within 1 hour. These initiatives, they say may be among the reasons why broad-spectrum antibiotic use for suspected sepsis is increasing. In addition, ED clinicians often must make treatment decisions with incomplete information. Some antibiotic-resistant infections may have been missed because cultures were not obtained (e.g., sputum for pneumonia or sampling from intra-abdominal infections) and some cultures may also have been falsely negative due to prior antibiotic administration. They focused on community-onset sepsis rather than hospital-onset sepsis (where resistant organisms are more prevalent), thus precluding generalizing their findings to all patients with sepsis, but community-onset sepsis accounts for most sepsis cases. [Crit Care Med. 2019; 47:1169-1176] They did not account for allergies as a potential reason for broad-spectrum antibiotic use (e.g., vancomycin in a patient with a β-lactam allergy), nor the neutropenic population where guidelines recommend antipseudomonal coverage even when cultures are negative. The finding that CO infections due to antibiotic-resistant organisms is less than 10% is consistent with the two Inspire Trials recently published called Stewardship Prompts to Improve Antibiotic Selection for Pneumonia and UTI [JAMA published online April 19, 2024 reviewed in the May ID Watch].

BOTTOM LINE

The investigators found that patients with suspected community-onset sepsis accounted for half of total inpatient antipseudomonal beta-lactam antibiotic and anti–MRSA antibiotic days. But antibiotic-resistant organisms were isolated from less than 10% of sepsis patients, and the proportion with resistant infections declined over time, while the proportion who received broad-spectrum antibiotics increased.

4

Review of the In Vitro Microbiological Activity of Mecillinam Against Common Uropathogens in Uncomplicated Urinary Tract Infection: Focus on Resistant Pathogens

Open Forum Infectious Diseases published online May 24, 2024
DOI: 10.1093/ofid/ofae296

Despite this extensive clinical history of use in some countries, pivmecillinam has only recently (2024) received approval in the US for the treatment of uncomplicated UTIs (uUTIs) by the FDA. [see June ID Watch] The authors set out to review the evidence of the susceptibility of common uUTI-causing uropathogens to mecillinam and describe the available susceptibility surveillance data.

They performed a structured literature search to review the available evidence on susceptibility of common uUTI-causing uropathogens to mecillinam. Among 38 studies included in this literature review, susceptibility rates for E coli to mecillinam— including resistant phenotypes such as extended-spectrum β-lactamase–producing (ESBL) E. coli—exceed 90% in most studies. High rates of susceptibility were also reported among many other uropathogens including Klebsiella spp., Enterobacter spp., and Citrobacter spp. Based on the current susceptibilities and current prescribing climate within the US, pivmecillinam represents a viable first-line treatment option for patients with uUTI.

Dr. Septimus's Annotations

Pivmecillinam, an oral prodrug of mecillinam, has been approved for the treatment of uUTI in Canada and Europe since the 1980s. It is recommended as a first-line agent for, the management of uUTIs in several expert guidelines including those from the Infectious Diseases Society of America (IDSA) and the European Society of Clinical Microbiology and Infectious Diseases [J Glob Antimicrob Resist 2021; 28:18–29; Clin Infect Dis 2011; 52: e103–120; Bonkat G, Bartoletti R, Bruyere F, et al. EAU guidelines on urological infections. 2021. Available at: Urological Infections - INTRODUCTION - UrowebUrological-infections-2021.pdf]. The efficacy and safety of pivmecillinam have been comprehensively documented over the years. Microbiological response rates for pivmecillinam in uUTI have been reported to be between 75% and 94% [16–19], with clinical response rates ranging from 82% to 95% [Scand J Infect Dis 2002; 34:487–92; PLoS Med 2018; 15:e1002569]

BOTTOM LINE

Data from this literature review demonstrates that pivmecillinam has high microbiological activity at its current susceptibility breakpoints against E. coli and other Enterobacterales, including those that produce ESBLs. Importantly, there is no clear evidence to suggest that resistance to mecillinam among common uropathogens has increased during the >40 years of its use in practice.

5

Clinical sub-phenotypes of Staphylococcus aureus bacteraemia

Clinical Infectious Diseases published online June 24, 2024
DOI: 10.1093/cid/ciae338

The investigators studied three cohorts of hospitalized adults with S aureus bacteremia (SAB): a UK retrospective observational study (Edinburgh cohort, n=458), the UK ARREST randomized trial (n=758), and the Spanish SAFO randomized trial (n=214). Latent class analysis was used to identify sub-phenotypes using routinely collected clinical data, without considering outcomes. Mortality and microbiologic outcomes were then compared between sub-phenotypes. Patients had predominantly methicillin-susceptible SAB(MSSA) (1366/1430,95.5%).

They identified five distinct, reproducible clinical sub-phenotypes: (A) SAB associated with older age and comorbidity, (B) nosocomial intravenous catheter-associated SAB in younger people without comorbidity, (C) community-acquired metastatic SAB, (D) SAB associated with chronic kidney disease, and (E) SAB associated with injection drug use. Survival and microbiologic outcomes differed between the sub-phenotypes. 84-day mortality was highest in sub-phenotype A, and lowest in B and E. Microbiologic outcomes were worse in sub-phenotype C. In a secondary analysis of the ARREST trial, adjunctive rifampicin was associated with increased 84-day mortality in sub-phenotype B and improved microbiologic outcomes in sub-phenotype C.

Dr. Septimus's Annotations

In hospitalized patients with predominantly MSSA bacteremia, five sub-phenotypes were identified using routinely available clinical data. These sub-phenotypes differ in survival and microbiologic outcomes. Despite using model parameters such as BIC there is a degree of subjectivity with the class selection based on clinical interpretability. Second, the class defining variables included were restricted to routinely available clinical data. Inclusion of inflammation biomarkers could provide additional biological insights. Third, the included cohorts were from countries with a low prevalence of MRSA. In addition, the definitions of microbiologic outcomes used in the cohorts were different, preventing direct comparison.

In the US decisions regarding type and length of therapy are guided by response to initial therapy which include time to clearance of bacteremia, source control, presence of locally complicated or metastatic infection, echocardiographic findings, or the presence of one of several risk factors (presence of prosthetic material, persistent fever, and skin findings suggestive of systemic infection). [Clin Infect Dis. 2011;52(3): e18-55] This paper does not fully address these factors. The approach suggested in this paper need to be confirmed in a prospective trial to include variables defining complicated versus uncomplicated SAB.

BOTTOM LINE

The findings in this paper suggest that clinically relevant sub-phenotypes do exist within SAB and suggest that patient stratification within SAB clinical trials will be required to identify strategies to improve outcomes for patients.

6

Risk Factors for Persistent Staphylococcus aureus Bacteremia in Children

Pediatric Infectious Disease Journal published online June 21, 2024
DOI: 10.1097/INF.0000000000004439

This is a single-center retrospective secondary analysis of a prospective observational study of pediatric patients hospitalized with S. aureus infection over a 3.5-year period at a large, quaternary, children's hospital.

259 children with confirmed S. aureus infection were enrolled in the study. 65 of these were found to have bacteremia (SAB), with 28 (43%) developing persistent bacteremia. Persistent SAB was defined as positive blood cultures on two or more hospital days, despite appropriate antibiotic therapy. Immunocompromised children were excluded from this study. Patients with persistent SAB were culture-positive for a median of 3.5 days compared with 1 day for those without ($P \leq 0.001$). Children with persistent SAB were more likely to have an identified osteoarticular source of infection (93%, n = 26 vs. 62%, n = 23; P = 0.008) and had a shorter median duration to culture positivity than those without persistent SAB (16 hours vs. 20 hours; $P \leq 0.001$). In addition, children with persistent SAB had higher median values of presenting ESR, peak ESR, presenting CRP and peak CRP. Hospital length of stay was longer in children with persistent SAB compared with those without. There was no documented mortality in our cohort.

Characteristic	Nonpersistent Bacteremia, N=37	Persistent Bacteremia, N=28	*P* value
Presenting CRP (mg/dL)	6 (2-10)	13 (6-22)	0.006
Not Reported	5	3	
Peak CRP (mg/dL)	8 (5-15)	9 (8-26)	0.004
Not Reported	9	1	
Presenting ESR (mm/h)	35 (18-52)	52 (43-70)	0.008
Not Reported	8	3	
Peak ESR (mm/h)	53 (30-72)	68 (48-97)	0.023
Not Reported	14	1	

Dr. Septimus's Annotations

This study aimed to identify potential risk factors for pediatric persistent SAB through the exploration of clinical characteristics, management, and outcomes of children admitted with SAB at a quaternary pediatric hospital. Persistent SAB has been associated with increased morbidity and mortality in both adults and children. [J Pediatr. 2019; 208:214–220.e2.; Arch Intern Med. 2007;167:1861–1867] In this cohort, they report that persistent SAB is associated with shorter time-to-positivity, increased need for procedural source control and an osteoarticular site of infection. In addition, they observed higher presenting and peak values for select inflammatory markers (ESR and CRP), increased duration of fever, increased peak temperature and increased hospital LOS in patients with persistent SAB.

This is a single-center study that may not be broadly applicable due to a lack of racial and ethnic diversity within the cohort and regional variability in S. aureus strains and virulence. Immunocompromised children were excluded from this study, and their results may not be applicable to this population. In addition, the sample size is small, limiting our results to descriptive findings and univariate analysis. Finally, this study was a retrospective secondary analysis of a prospectively enrolled cohort. Enrollment was limited to standard business hours on weekdays only.

BOTTOM LINE

These findings suggest that a shorter time to culture positivity, osteoarticular infection, and higher presenting and peak values for select inflammatory markers are potential risk factors for persistent SAB in children.

Association between butyrate-producing gut bacteria and the risk of infectious disease hospitalisation: results from two observational, population-based microbiome studies

Lancet Microbe Published Online June 24, 2024
DOI: 10.1016/S2666-5247(24)00079-X

This is an observational microbiome study to characterized gut microbiota using 16S rRNA gene sequencing in independent population-based cohorts from the Netherlands (derivation cohort) and Finland (validation cohort). The Netherlands cohort included adults (aged 18–70 years at inclusion). They were randomly sampled from the municipality register of Amsterdam. In Finland cohort conducted in six regions in Finland they did a population survey that included a random sample of adults (aged 25–74 years). In both cohorts, participants completed questionnaires, underwent a physical examination, and provided a fecal sample at inclusion (January 3, 2013, to November 27, 2015, for the Netherlands participants and January 21 to April 19, 2002, for the Finland participants. For inclusion in this study, a fecal sample needed to be provided and successfully sequenced, and national registry data needed to be available. Primary predictor variables were microbiota composition, diversity, and relative abundance of butyrate-producing bacteria. The primary outcome was hospitalization or mortality due to any infectious disease during 5–7-year follow-up after fecal sample collection, based on national registry data. They examined associations between microbiota and infection risk using microbial ecology and Cox proportional hazards.

They profiled gut microbiota from 10,699 participants (4248 [39.7%] from the derivation cohort and 6451 [60.3%] from the validation cohort). 602 (5.6%) participants (152 [3.6%] from the derivation cohort; 450 [7.0%] from the validation cohort) were hospitalized or died due to infections during follow-up. The gut microbiota composition of these participants differed from those without hospitalization for infections (derivation p=0.041; validation p=0.0002). Specifically, higher relative abundance of butyrate-producing bacteria was associated with a reduced risk of hospitalization for infections (derivation cohort cause-specific hazard ratio 0.75 [95% CI 0.60–0.94] per 10% increase in butyrate producers, p=0.013; validation cohort 0.86 [0.77–0.96] per 10% increase, p=0.0077). These associations remained unchanged following adjustment for demographics, lifestyle, antibiotic exposure, and comorbidities.

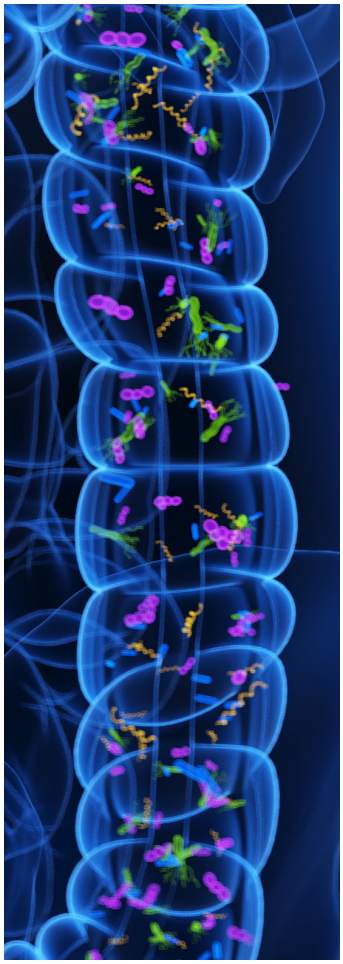
Dr. Septimus's Annotations

They showed that gut microbiota was associated with the risk of infectious disease-related hospitalization and mortality in the general population. Higher abundance of anaerobic butyrate-producing bacteria was associated with protection against severe infections, even when adjusted for demographics, lifestyle, antibiotic exposure, and comorbidities. This is the largest study linking gut microbiota to severe infection susceptibility in humans, and the first to identify an association between butyrate-producing bacteria and favorable long-term outcomes, outside of animal experiments or groups at high risk. Gut microbiota are often disrupted in patients hospitalized for severe infections, which has been associated with clinical outcomes. [Lancet Gastroenterol Hepatol 2017; 2: 135–43] However, these disruptions could be either a consequence of disease, [Clin Infect Dis 2020; 71: 2669–78] or precede the infection and affect susceptibility. Here, the investigators showed that gut microbiota, characterized before infection onset, differed between participants hospitalized for infections during follow-up and those without hospitalization for infections, indicating that gut microbiota was associated with the susceptibility to severe infections. Their findings corroborate the

> **"Higher abundance of anaerobic butyrate-producing bacteria was associated with protection against severe infections..."**

previously described effect of anaerobic microbiota depletion on infection risk and adverse clinical outcomes in selected groups at high risk.[Transl Stroke Res 2021;12: 581–92 , J Med Virol 2023; 95: e29083] The investigators confirmed these adverse effects of antianaerobic antibiotics in 15,908 emergency department patients.[Eur Respir J 2023; 61: 2300413] In June 2024 ID Watch among patients with suspected sepsis and no clear indication for antianaerobic coverage, administration of piperacillin-tazobactam was associated with higher mortality and increased duration of organ dysfunction compared with cefepime.[JAMA Intern Med published online May 13, 2024] These findings suggest that the widespread use of empirical antianaerobic antibiotics in sepsis may be harmful. This study also defines potential opportunities for interventions such as evaluating gut microbiota-directed therapies (such as targeted delivery of butyrate-producing bacteria or limiting gut anaerobe depletion) aiming to decrease the susceptibility to systemic infections.

Microbiota were characterized only at a single timepoint. Gut microbiota might change over time, potentially obscuring the effect on outcomes at distant timepoints. The potentially beneficial effects of butyrate-producing bacteria might extend beyond butyrate as several butyrate producers are capable of the biosynthesis of secondary bile acids and other metabolites with potential immunomodulatory effects. As with all observational studies, their findings do not necessarily prove causality.



BOTTOM LINE

The investigators showed that gut microbiome composition, specifically colonization with anaerobic butyrate producing bacteria, was associated with a reduced risk of hospitalization for infectious diseases. Further studies should investigate whether modulation of the microbiome can reduce the risk of severe infections.

Extended-Infusion β-Lactam Therapy, Mortality, and Subsequent Antibiotic Resistance Among Hospitalized Adults With Gram-Negative Bloodstream Infections

JAMA Network Open. 2024;7(7): e2418234.
DOI: 10.1001/jamanetworkopen.2024.18234

In this study the investigators did a matched cohort consisting of 352 in the extended infusion beta-lactam (EI-BL) 1:3 propensity score matching (PSM) group and 1,056 in the intermittent infusion (II) II-BL 1:3 PSM group. Among 1,408 matched patients, 79 (22%) in the EI-BL group died by day 90, compared with 294 (28%) in the II-BL group (adjusted odds ratio [aOR], 0.91; 95% CI, 0.52 to 0.97). But in a stratified analysis, the mortality benefit associated with EI-BL therapy was seen only in patients with critical illness (aOR; 0.47; 95% CI, 0.28 to 0.81) and those with an elevated beta-lactam MIC (aOR, 0.06; 95% CI, 0.01 to 0.66).

Of the 4,861 GN-BSI patients in the study (median age, 67 years; 52.4% male), 352 (7.2%) received EI-BL therapy, and 4,509 (92.7%) received II-BL therapy. The most common bacterial species among patients were E coli (50.8%), K pneumoniae (17.3%), and P aeruginosa (8.7%). Patients who received EI-BL were more likely to be severely immunocompromised (38% vs 29%), receive care in the ICU (46% vs 31%), and have a Pitt bacteremia score of 4 or higher (26% vs 19%).

There was no difference in the odds of recurrent infection between the groups (aOR, 0.96; 95% CI, 0.64 to 1.45), and among patients who had a recurrent infection with the same bacterial species, emergence of resistance was similar in the EI-BL group (2.9%) and the II-BL group (7.2%). But only 10% of patients having a recurrent infection with the same bacterial species; therefore, the study was underpowered to investigate the effects of EI-BL on subsequent emergence of resistance.

Adverse events were low in the entire PSM cohort (5%), but EI-BL therapy was associated with increased odds of catheter complications (aOR, 3.14; 95% CI, 1.66 to 5.96) and antibiotic discontinuation because of adverse events (aOR, 3.66; 95% CI, 1.68 to 7.95).

Dr. Septimus's Annotations

Recently antimicrobial susceptibility testing standards have incorporated extended infusion (EI) recommendations in the interpretation of antimicrobial susceptibility testing results. As an example, in the 2022 to 2023 CLSI updates, an isolate with MIC of 16 µg/mL is categorized as susceptible dose-dependent (SDD), predicated on the dose of piperacillin-tazobactam being 4.5 grams every 8 hours administered over 4 hours or 4.5 grams every 6 hours over 3 hours. [Clin Infect Dis. 2023; 77:1585-1590] Intermittent infusion would only be recommended for isolates with MIC ≤ 8 µg/mL, which are categorized as susceptible. Several systematic reviews and meta-analyses have been conducted to evaluate the benefits of EI. Among hospitalized patients with confirmed gram-negative infections, compared with II, EI was associated with mortality benefits (risk ratio [RR], 0.67 [95% CI, 0.55-0.81]; P = .001; I2 = 4.52%) but there was no difference in clinical cure rate, intensive care stay, or hospital length of stay. [Expert Rev Anti Infect Ther. Published online March 5, 2024] Among patients with febrile neutropenia, however, a mortality benefit was not observed (pooled RR, 0.83 [95% CI, 0.47-1.48]). [J Infect. 2023;87(3):190-198] Most of these studies were observational or open-label designs. Beyond mortality, many potentially relevant clinical, safety, and microbiological end points are not as well studied.

"...while [Extended Infusion β-lactam] therapy may be associated with positive outcomes, the benefits may not surpass the risks if applied to all patients...."

The current study supports prior knowledge about EI of β-lactam implemented in many centers in recent years. By improving how β-lactams are administered, EI can overcome isolates with a higher MICs. The study also supports that EI may have an advantage over II in patients with more severe infections. The current study also addresses several gaps in knowledge for antimicrobial stewardship clinicians. First, the study population included those with severe immune compromise, such as patients with bone marrow transplants or solid organ transplant and patients with neutropenia, all of whom need effective antimicrobials. Second, the investigators evaluated treatment-related adverse events which are pertinent balancing measures for quality improvement initiatives. EI was associated with a higher odds of vascular catheter complications compared with II (aOR, 3.14 [95% CI, 1.66-5.96]; P < .001).

BOTTOM LINE

The investigators say: "Taken together, these results suggest that while EI-BL therapy may be associated with positive outcomes, the benefits may not surpass the risks if applied to all patients. Rather, a more targeted approach may be necessary for patients who are severely ill or those known to have or be at reasonable risk for infection with an elevated β-lactam MIC."

8 Povidone Iodine vs Chlorhexidine Gluconate in Alcohol for Preoperative Skin Antisepsis A Randomized Clinical Trial

JAMA published online June 17, 2024
DOI: 10.1001/jama.2024.8531

This study was done to determine whether povidone iodine in alcohol is noninferior to chlorhexidine gluconate in alcohol to prevent SSIs after cardiac or abdominal surgery. This was a multicenter, cluster-randomized, crossover, noninferiority trial enrolled over 3000 patients undergoing cardiac (65%) or abdominal (35%) operations across 3 tertiary care hospitals in Switzerland. The primary outcome was the development of an SSI within 30 days after abdominal

surgery and up to 1 year after cardiac surgery. The prep in this trial was povidone iodine containing 50.0 g propan-2-ol, 1 g povidone iodine in 100 mL.

SSIs were identified among 80 patients (5.1%) in the povidone iodine group vs 97 (5.5%) in the chlorhexidine gluconate group, an absolute difference of 0.4% (95% CI, −1.0% to 2.0%), not exceeding the predefined noninferiority margin of −2.5%. The authors conclude that povidone iodine in alcohol as preoperative skin antisepsis was noninferior to chlorhexidine gluconate in alcohol in preventing SSIs after cardiac or abdominal surgery, a finding consistent with the prior SKINFECT trial that demonstrated that preoperative skin disinfection with chlorhexidine-alcohol is similar to iodine-alcohol in reducing SSI risk.[BJS Open. 2019;3(5):617-622]

Dr. Septimus's Annotations

WHO guidelines recommend chlorhexidine-alcohol rather than aqueous povidone iodine or povidone iodine with alcohol for surgical skin preparation based on "low to moderate" quality of evidence. [Lancet Infect Dis. 2016;16(12):e276-e287] The recent Compendium recommended using alcohol-containing preoperative skin preparatory agents if no contraindication exists (quality of evidence: High). Infect Control Hosp Epidemiol,2023; 44: s100-s125] They report "the most effective antiseptic to combine with alcohol remains unclear; however, data from recent trials favor the use of CHG–alcohol over povidone-iodine–alcohol." In a recent study reviewed in March 2024 ID Watch patients who were undergoing surgical fixation of a closed fracture of a lower limb or the pelvis, found that the risk of SSIs was lower with skin antisepsis provided by iodine povacrylex in alcohol than with antisepsis provided by chlorhexidine gluconate in alcohol. [N Engl J Med 2024; 390:409-20] In contrast a trial in women undergoing C-section reported SSI rates were higher in the povidone iodine group (7.3%) compared with chlorhexidine gluconate (4%). [N Engl J Med. 2016;374(7):647-655.] To make matters more confusing the iodophor alcohol in the C-section trial was different from the trial reported in March 2024 ID Watch. The iodophor that was used in that trial differs from povidone iodine. Iodine povacrylex is an iodophor that is available in alcohol and unique due to its copolymer, povacrylex. The structure of the iodine povacrylex copolymer may provide important benefits beyond those of traditional povidone iodine for the prevention of SSIs. Iodine is inactivated by organic matter, but povacrylex is resistant to fluids and blood, thereby potentially offering longer protection than povidone iodine or other agents. The prep in the new JAMA trial was povidone iodine containing 50.0 g propan-2-ol, 1 g povidone iodine in 100 mL, resulting in 10% free available iodine.

BOTTOM LINE

This trial provides robust evidence on the effectiveness, safety, and comparative benefits of iodophor-alcohol vs CHG-alcohol. Importantly, post discharge patient follow-up was exceptionally good and ensured adequate identification of outcomes. The risk of confounding through contaminated operations, where proper skin preparation might be less relevant, was reduced by only including elective operations.

9

Initial micafungin treatment does not improve outcomes compared to fluconazole treatment in immunocompromised and critically ill patients with candidaemia

Journal of Antimicrobial Chemotherapy published online 2024 Jun 4
DOI: 10.1093/jac/dkae175

Due to escalating azole-resistant *Candida* strains, guidelines of the Infectious Disease Society of America (IDSA) recommend first-line echinocandins for candidiasis in critically ill patients [Clin Infect Dis. 2016 Feb 15;62(4): e1-50]; however, despite in vitro activity, echinocandin use has not yet been shown to improve certain outcomes. (e.g., reduced mortality)

In this paper investigators performed a retrospective cohort study of 197 patients at two US hospitals who were immunocompromised or who were admitted to the ICU for candidemia. Participants had received at least 3 days of initial therapy with fluconazole or micafungin. Complete response (the primary outcome, a composite of clinical improvement and blood-culture sterilization) as well as survival were assessed on day 14.

A total of 197 patients were included; 76 received fluconazole and 121 received micafungin. There was no difference in complete response between the fluconazole and micafungin groups (ICU: 38% versus 40%, P = 0.87; immunocompromised: 57% versus 59%, P = 0.80). Secondary outcomes including survival were also similar. In multivariable analysis, among ICU patients, Pitt bacteremia score < 4 (P = 0.002) and time to antifungal (P = 0.037) were associated with meeting the primary outcome; white blood cell count > 11 cells × 103 /μL on day 0 (P < 0.001) and *Candida* isolated from a non-blood site (P = 0.025) were associated with not meeting the primary outcome. Among immunocompromised patients, white blood cells > 11 × 103 /μL (P = 0.003) and *Candida* isolated from a non-blood site (P = 0.026) were associated with not meeting the primary outcome. In other words, in the multivariable model, severity of illness rather than initial antifungal choice drove clinical outcomes, such as the Pitt bacteremia score, baseline white blood cell count, and isolation of *Candida* from a non-blood site.

Table 4. Multivariable analysis of factors associated with complete response at day 14 among ICU patients

Variable	Odds ratio^{unadjusted} (95% CI)	*P* value	Odds ratio^{adj} (95% CI)	*P* value
Micafungin therapy	1.06 (0.51, 2.20)	0.867	0.94 (0.36, 2.45)	0.897
Median time to antifungal	1.01 (1.00, 1.02)	**0.036**	1.02 (1.00, 1.03)	**0.037**
Age in years	1.01 (0.99, 1.03)	0.397	1.02 (0.99, 1.04)	0.195
Dialysis at time of candidaemia	0.49 (0.29, 0.81)	**0.005**	0.76 (0.41, 1.43)	0.392
White blood count ≥11 on day 0	0.22 (0.10, 0.47)	**<0.001**	0.13 (0.05, 0.35)	**<0.001**
Total parenteral nutrition	0.82 (0.29, 2.38)	0.721	1.66 (0.40, 6.83)	0.485
Length of stay before candidaemia	0.97 (0.94, 0.99)	**0.013**	0.98 (0.95, 1.01)	0.155
Candida isolated from non-blood site	0.35 (0.12, 0.99)	**0.048**	0.21 (0.06, 0.82)	**0.025**
Pitt bacteraemia score <4	3.42 (1.62, 7.25)	**0.001**	4.69 (1.76, 12.5)	**0.002**

Complete response at day 14: microbiological success (sterilization of blood cultures), clinical success (temperature <38°C, white blood cell count <11 cells×10^3/μL and not requiring vasopressors) and survival. *P* values <0.05 considered significant (bolded).

Dr. Septimus's Annotations

Candida species did not differ between fluconazole and micafungin recipients. Outcomes were similar in the immunocompromised and ICU groups, regardless of antifungal therapy. In multivariate analysis, early initiation of antifungal therapy in the ICU group was associated with complete response. In both the ICU and immunocompromised groups, Candida isolation from a nonblood site and leukocytosis were associated with failure to achieve complete response. The sample size was small, but among nonneutropenic patients with candidemia automatically jumping to an echinocandin may not be necessary.

BOTTOM LINE

This study suggests that among ICU or immunocompromised patients, severity of illness rather than initial antifungal choice drove clinical outcomes.

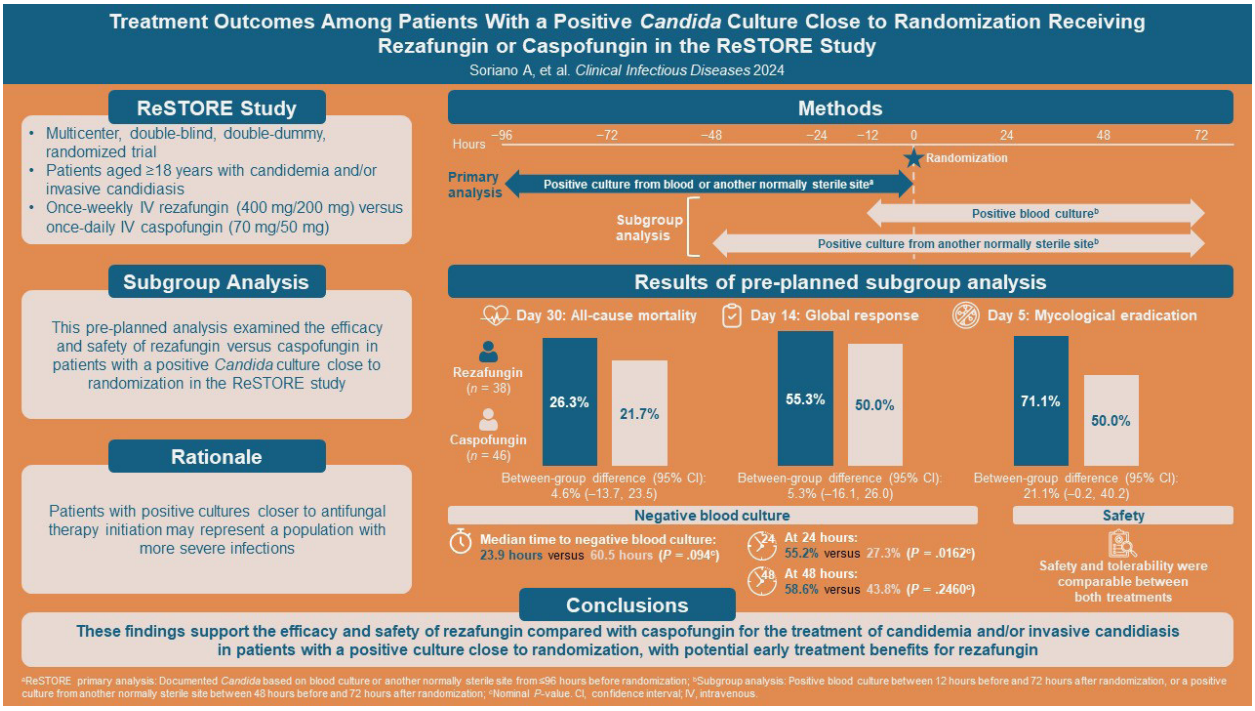
10

Treatment Outcomes Among Patients With a Positive Candida Culture Close to Randomization Receiving Rezafungin or Caspofungin in the restore Study

Clinical Infectious Diseases published online July 11, 2024
DOI: 10.1093/cid/ciae363

ReSTORE was a multicenter, double-blind, double-dummy, randomized trial in patients aged ≥18 years with candidemia and/or invasive candidiasis (IC) treated with once-weekly intravenous rezafungin (400 mg/200 mg) or once-daily intravenous caspofungin (70 mg/50 mg). This analysis comprised patients with a positive blood culture drawn between 12 hours before and 72 hours after randomization, or a positive culture from another normally sterile site sampled between 48 hours before and 72 hours after randomization. Efficacy endpoints included Day 30 all causes mortality (ACM), Day 14 global cure rate, and Day 5 and 14 mycological response. Adverse events were evaluated.

The analysis included 38 patients randomized to rezafungin and 46 to caspofungin. In the rezafungin and caspofungin groups, respectively: Day 30 ACM was 26.3% and 21.7% (between-group difference [95% confidence interval] 4.6% [−13.7, 23.5]); Day 14 global response was 55.3% and 50.0% (between-group difference 5.3% [−16.1, 26.0]); and Day 5 mycological eradication was 71.1% and 50.0% (between-group difference 21.1% [−0.2, 40.2]). Safety was comparable between treatments.



Dr. Septimus's Annotations

Echinocandins are recommended as first-line antifungal treatment for candidemia and IC in Europe and the US [Clin Infect Dis 2016; 62: e1–50; Clin Microbiol Infect 2012; 18:19–37]. Rezafungin is a novel FDA and European Commission approved echinocandin that is structurally similar to current echinocandins but has differentiated stability and pharmacokinetics. [J Fungi (Basel) 2020; 6:262]. Its low clearance and prolonged half-life versus other echinocandins enable once-weekly intravenous administration resulting in front loaded exposure that maximizes the drug effect early in therapy. Prior trials

suggest early benefits of rezafungin versus caspofungin, including more rapid clearance of candidemia, and reported similar safety profiles for rezafungin and caspofungin [Lancet 2023; 401:49–59]. The small sample size of the subgroup population means that these findings should be interpreted with caution and that further investigation is needed.

BOTTOM LINE

This analysis supports previously described findings from ReSTORE and demonstrates the efficacy and safety of weekly rezafungin for the treatment of candidemia and/or IC in patients. Mycology eradication favored Rezafungin.

11

Identifying and remediating super-splasher sinks to reduce dispersal of pathogens from sink drains

Open Forum Infectious Diseases published online May 30, 2024
DOI: 10.1093/ofid/ofae293

The investigators tested the hypothesis that simulations using fluorescent gel could be useful to identify a sub-set of sinks that pose a risk for dispersal of bacteria. They also evaluated the impact of a plumbing intervention to address modifiable factors (i.e., high water inflow rate, slow outflow) associated with dispersal. A convenience sample of sinks in unoccupied medical-surgical and burn unit patient rooms was assessed for dispersal of water droplets, fluorescent gel, and gram-negative bacilli. Before the evaluations, the sink bowl and the adjacent countertop or other surfaces were disinfected with a commercial hydrogen peroxide disinfectant, but the drain was not decontaminated. To assess efficacy of disinfection, Replicate Organism Detection and Counting (RODAC) plates with MacConkey agar (Hardy Diagnostics) were used to sample surfaces inside and within 30.4 cm outside the bowl. The characteristics of the sinks were recorded, including bowl depth (i.e., vertical distance from strainer to sink edge), faucet location (i.e., directly over strainer versus offset), flow rates and automated versus manual. 30 sinks that dispersed fluorescent gel outside the bowl were included in an intervention to reduce dispersal. In the initial intervention, plumbing staff reduced the flow rate for sinks with flow rate >80 mL/min by adjusting the valves regulating water inflow. If backup of water and/or slow outflow was still observed, the plumbers snaked the drain to remove any obstruction. Immediately and 6 months after the intervention, the sinks were reassessed for dispersal of fluorescent gel and gram-negative bacilli.

There was a positive association between flow rate and dispersal of water droplets (P<0.001), and a nonsignificant trend toward an association between flow rate and dispersal of fluorescence (P=0.08) and gram-negative bacilli (P=0.06). The sensitivity, specificity, PPV, and NPV of fluorescence dispersal for detection of gram-negative bacilli dispersal was 100% (95% CI, 63%-100%), 65% (54%-74%), 20% (9%-35%), and 100% (94%-100%), respectively. Of the 41 sinks that dispersed fluorescence outside the bowl, 16 (39.0%) had evidence of water backup and/or slow outflow. Of the 29 intervention sinks, 12 (41.4%) only required a reduction in flow, 10 (34.5%) required a reduction in flow followed by snaking due to persistent backup of water and/or slow outflow, and 7 (24.1%) required only snaking to remove a partial obstruction. None of the sinks dispersed fluorescent gel or gram-negative bacilli after the intervention.

Dr. Septimus's Annotations

Outbreaks due to gram-negative bacilli have been linked to sinks and other wastewater drainage sites [Infect Control Hosp Epidemiol 2024; 45:284-291] In response to outbreaks, interventions such as disinfection of drains with an EPA-registered disinfectant with biofilm claims, replacement of drainage pipes and traps, and installation of heater-vibrator devices for trap disinfection can be considered. [Infect Control Hosp Epidemiol 2023;44:355-376] In this study they

showed that environmental contamination from sink drains likely varies among sinks — with some acting as "super-spreaders" — and that potentially modifiable factors (i.e., rates of faucet flow and bowl drainage) may contribute to bacterial dispersal. They used fluorescent gel in a study of 102 sinks to indicate whether bacterial dispersal from the drain could be easily identified beyond the bowl. Fluorescence dispersal outside the bowl had 100% sensitivity and 65% specificity for estimating concurrent bacterial spread, which was remediated in 29 of 29 evaluated sinks through reduction of faucet flow, improvement in drain outflow, or both. There were a few limitations to the study. There was imperfect sensitivity of screening cultures (the specificity of fluorescence dispersal for detection of dispersal of gram-negative bacilli was only 65%) and they sampled only 59% of sinks in the ICU. Despite some of the limitations, the analysis raises concerns about the contribution of contaminated plumbing and spread of gram-negative bacteria. The intervention was very successful although the clinical impact remains to be determined.

BOTTOM LINE

Interventions to remediate modifiable factors such as high flow rate and slow outflow can be effective in reducing the risk for dispersal from these sinks.

12

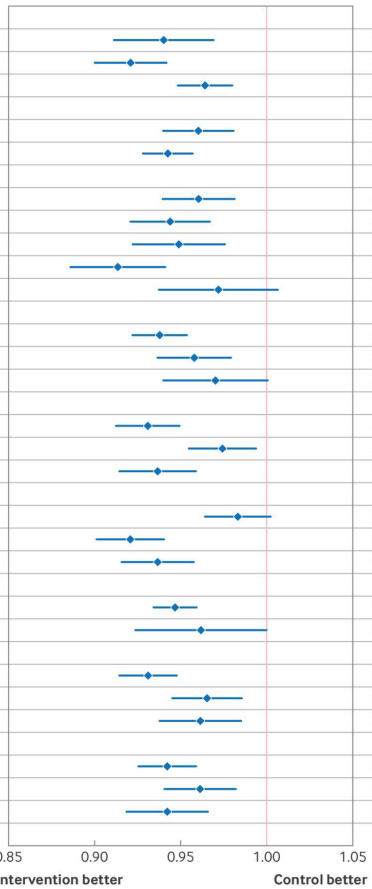
Mailed feedback to primary care physicians on antibiotic prescribing for patients aged 65 years and older: pragmatic, factorial randomised controlled trial

The BMJ 2024;385: e079329
DOI: 10.1136/ bmj-2024-07932

Overprescription of antibiotics by primary care clinicians is a major modifiable driver of antibiotic resistance. Evidence suggests that peer-comparison feedback can reduce antibiotic overprescription, but the optimal content and delivery of such feedback is unclear.

Investigators randomized 5000 family physicians in Ontario, Canada, to receive either mailed feedback (with data on individual prescribing rates compared with peers' prescribing rates, plus educational information on optimal prescribing) or no mailed feedback (control group). Clinicians in the intervention group were randomized further to (a) receiving personalized prescribing data that were adjusted, versus not adjusted, for case mix, and (b) receiving information on potential harms of antibiotics, versus not receiving such information.

Outcome	Baseline, mean (SD)		Six months, mean (SD)		Adjusted rate ratio (95% CI)
	Control	Intervention	Control	Intervention	
Years in practice					
<11	68.1 (36.3)	61.5 (31.7)	73.5 (47.9)	63.8 (38.7)	0.94 (0.91 to 0.97)
11-24	57.4 (34.4)	57.6 (34.2)	63.2 (40.7)	59.0 (41.7)	0.92 (0.90 to 0.94)
≥25	51.8 (34.7)	50.8 (32.3)	55.1 (40.6)	52.7 (37.5)	0.96 (0.95 to 0.98)
Sex					
Female	52.5 (30.2)	54.4 (32.9)	56.8 (36.8)	56.0 (39.6)	0.96 (0.94 to 0.98)
Male	56.5 (37.4)	54.0 (33.1)	60.7 (44.3)	55.9 (38.9)	0.94 (0.93 to 0.96)
Neighbourhood income quintile of physician practice					
1 (low)	53.2 (37.5)	53.4 (34.2)	57.0 (43.5)	55.1 (41.2)	0.96 (0.94 to 0.98)
2	56.0 (35.3)	54.0 (30.9)	60.4 (40.1)	55.6 (36.8)	0.94 (0.92 to 0.97)
3	55.2 (32.0)	52.6 (34.6)	59.9 (38.5)	53.9 (38.2)	0.95 (0.92 to 0.98)
4	51.2 (30.5)	54.8 (31.4)	57.9 (41.2)	57.5 (37.0)	0.91 (0.89 to 0.94)
5 (high)	66.3 (38.0)	57.6 (33.9)	66.8 (47.9)	59.5 (41.9)	0.97 (0.94 to 1.01)
Visit volume					
2 (high)	47.6 (31.4)	45.5 (27.9)	51.7 (36.4)	47.7 (30.6)	0.94 (0.92 to 0.95)
1 (medium)	61.8 (35.2)	64.7 (34.3)	69.3 (40.5)	66.3 (38.5)	0.96 (0.94 to 0.98)
0 (low)	78.0 (39.7)	74.0 (38.2)	82.7 (59.6)	78.5 (63.2)	0.97 (0.94 to 1.00)
Continuity score					
2 (high)	48.7 (30.1)	49.7 (29.3)	54.4 (38.5)	51.2 (32.5)	0.93 (0.91 to 0.95)
1 (medium)	55.4 (35.9)	52.4 (30.0)	57.3 (38.9)	54.1 (33.2)	0.97 (0.96 to 0.99)
0 (low)	64.6 (39.1)	63.2 (39.9)	72.3 (50.0)	66.8 (53.3)	0.94 (0.92 to 0.96)
Percent of patient population over age 85					
2 (high)	54.0 (35.9)	54.0 (32.4)	56.0 (41.2)	56.1 (38.4)	0.98 (0.96 to 1.00)
1 (medium)	55.2 (35.0)	53.4 (31.9)	61.2 (42.3)	55.3 (39.3)	0.92 (0.90 to 0.94)
0 (low)	56.9 (34.5)	52.7 (35.2)	62.1 (42.5)	56.6 (39.8)	0.94 (0.92 to 0.96)
Rural practice					
Yes	78.6 (41.4)	75.0 (34.0)	84.7 (51.0)	78.1 (43.2)	0.95 (0.94 to 0.96)
No	53.5 (34.2)	52.7 (32.5)	57.8 (40.8)	54.4 (38.3)	0.96 (0.93 to 1.00)
Baseline abx prescribing rate					
2 (high)	105.5 (32.0)	100.8 (26.0)	112.7 (46.1)	100.4 (44.9)	0.93 (0.92 to 0.95)
1 (medium)	56.4 (8.4)	56.4 (8.5)	61.0 (22.4)	58.9 (21.2)	0.97 (0.95 to 0.98)
0 (low)	27.0 (9.5)	26.8 (9.9)	30.9 (15.0)	29.6 (15.8)	0.96 (0.94 to 0.98)
Baseline abx prescribing rate from virtual visits					
2 (high)	80.2 (35.0)	77.8 (29.5)	85.4 (43.9)	78.5 (37.7)	0.94 (0.93 to 0.96)
1 (medium)	46.5 (21.4)	47.4 (23.2)	51.0 (26.5)	49.8 (29.8)	0.96 (0.94 to 0.98)
0 (low)	38.4 (33.5)	39.2 (33.2)	42.0 (41.4)	41.1 (39.8)	0.94 (0.92 to 0.97)



Compared with controls, the intervention group had significantly lower mean rates of overall antibiotic prescribing (59 vs. 56 prescriptions per 1000 patient visits; relative rate, 0.95), apparently unnecessary antibiotic prescriptions (e.g., for viral illnesses; RR, 0.89), long-duration antibiotic prescriptions (RR, 0.85), and broad-spectrum antibiotic prescriptions (RR, 0.94) in the first 6 months after the mailings. No differences were observed among recipients who received various versions of the feedback reports. However, only 18% of samples of intervention physicians confirmed receipt of feedback letters.

Dr. Septimus's *Annotations*

In this large, pragmatic randomized controlled trial with over 5000 primary care physicians, a mailed letter to physicians led to a significant 5% relative reduction in overall antibiotic prescribing rate compared with physicians in the control group. They observed improvements in antibiotic prescribing on all outcomes evaluated including an 11% relative reduction in unnecessary antibiotic prescriptions, 15% relative reduction in antibiotic durations more than seven days, and a 6% relative reduction on broad-spectrum antibiotic prescribing. The study was limited because many physicians failed to open or read the mailing. Despite this some improvement was observed.

Best practice recommendations have been published on optimizing audit and feedback of antibiotics in primary care. [Antimicrob Resist Infect Control 2023; 12:72] Antibiotic audit and feedback should be simple and include a single central figure. Prescribers should be able to understand the data within seconds and connect the data directly to a desired action. Data that are too subtle, complex, provide multiple metrics or multiple comparators are less likely to be used by physicians and will not drive behavior change.[JAMA Intern Med 2023;183:220-2; Implement Sci 2021;16:19] Regarding harms information, data show that physicians frequently perceive an imbalance in risks by underestimating the harms of unnecessary antibiotic prescribing and overestimating the risks of not prescribing antibiotics. Further research is needed into implementing cointerventions such as public education, communication interventions, point-of-care testing, and other quality improvement initiatives implemented and evaluated alongside audit and feedback to further reduce unnecessary antibiotic prescribing in primary care

BOTTOM LINE

A mailed antibiotic feedback letter with peer comparison can be effective at reducing antibiotic prescribing by primary care physicians. The intervention should be simple and direct, leading to a desired action.

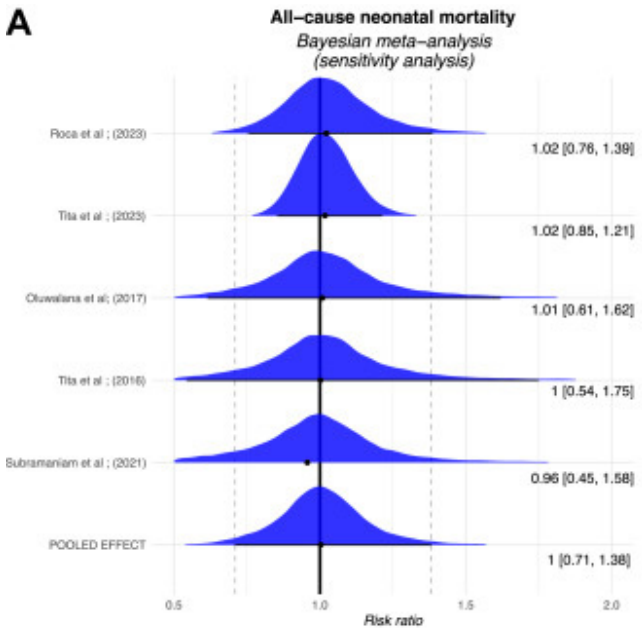
13

PeRinatal, neOnatal, and Maternal OuTcomEs with azithromycin prophylaxis in pregnancy and labour (PROMOTE-PROPHYLAXIS): systematic review and meta-analysis

eClinicalMedicine 2024;73: 102691
DOI: 10. 1016/j.eclinm.2024. 102691

The authors explored whether azithromycin prophylaxis in pregnant women improves maternal and neonatal outcomes. They systematically synthesized the evidence by searching seven databases (PubMed, Scopus, Embase, Cochrane Central Register of Controlled Trials, EBSCOHost, ProQuest, and Web of Science) till September 11, 2023, for RCTs on efficacy and safety of azithromycin prophylaxis to pregnant women. The primary outcome was neonatal mortality. Intrapartum and antenatal administration were assessed separately. They used search terms, including controlled vocabulary, for keywords about each component of this research question. We used the Risk of Bias 2 tool to assess the risk of bias. The certainty of evidence was evaluated using the GRADE framework.

They screened 2161 records and retrieved 20 RCTs (56,381 participants). They found that prophylactic azithromycin therapy among pregnant women has an uncertain effect on maternal or neonatal mortality (low to very low certainty evidence). However, intrapartum azithromycin was probably associated with lesser maternal infections, endometritis, surgical site infections (SSI), and reduced antibiotic usage (low to moderate certainty evidence). In neonates, it was associated with reduced superficial skin infection, omphalitis and antibiotic use.



Dr. Septimus's Annotations

Initial RCTs showed that prophylactic azithromycin in pregnant women improved maternal and neonatal outcomes; however, the recent evidence did not show any benefit to neonatal survival. There is conflicting evidence over the role of azithromycin prophylaxis in antenatal and intrapartum periods. The authors explored whether azithromycin prophylaxis in pregnant women improves maternal and neonatal outcomes. Azithromycin prophylaxis possibly does not reduce maternal and neonatal mortality; however, there is probably a reduction in maternal and neonatal infections and antibiotic usage with single-dose intrapartum azithromycin prophylaxis in pregnant women. There is limited data on antimicrobial resistance and other long-term adverse outcomes. In July 2024 ID Watch there was a review on the "Impact of Intrapartum Azithromycin on the Carriage and Antibiotic Resistance of Escherichia coli and Klebsiella pneumoniae in Mothers and their Newborns." [Clin Infect Dis published online May 16, 2024] They found that intrapartum azithromycin decreases carriage of E. coli and increases carriage of K. pneumoniae in the gut of neonates. The intervention also increases carriage of azithromycin-resistant E. coli and K. pneumoniae isolates.

BOTTOM LINE

This review supports intrapartum azithromycin prophylaxis in reducing SSIs, but caution is warranted, considering the lack of data on antimicrobial resistance and other long-term adverse outcomes.

14

Long-Term Outcomes Associated With β-Lactam Allergies

JAMA Network Open. 2024;7(5): e2412313.
DOI: 10.1001/jamanetworkopen.2024.12313

This was a longitudinal retrospective cohort study conducted at a single regional health care system in Pennsylvania. Electronic health records were analyzed for patients who had an index encounter with a diagnosis of sepsis, pneumonia, or urinary tract infection. β-lactam (BL) allergy status was defined as the presence of any penicillin, cephalosporin, carbapenem, or aztreonam as an allergy in the patient's allergy list. Allergy lists were derived from pharmacy discharge summaries and were recorded as free text. Independent variables included age, sex, race, baseline serum creatinine (SCr) level, Van Walraven comorbidity score and Elixhauser Comorbidity Index score, the number of health care encounters per patient, an indicator for ICU admission, dialysis utilization during each encounter, and an indicator for the individual hospital at which the health care encounter occurred. The primary outcome was all-cause mortality, defined using data from the Social Security Death Index. Secondary outcomes included the occurrence of AKI, grouped as stage 2 and 3 or stage 3 AKI. Additional secondary outcomes included occurrence of infection with MRSA, C difficile, or VRE.

A total of 20,092 patients (mean [SD] age, 62.9 [19.7] years; 12,231 females [60.9%]), of whom 4211 (21.0%) had BL documented allergy and 15,881 (79.0%) did not, met the inclusion criteria. A total of 3513 patients (17.5%) were Black, 15,358 (76.4%) were White, and 1221 (6.0%) were another race. Using generalized estimating equations, documented BL allergies were not significantly associated with the odds of mortality (odds ratio [OR], 1.02; 95% CI, 0.96-1.09). BL allergies were associated with increased odds of MRSA infection (OR, 1.44; 95% CI, 1.36-1.53), VRE infection (OR, 1.18; 95% CI, 1.05-1.32), and the pooled rate of the 3 evaluated antibiotic-resistant infections (OR, 1.33; 95% CI, 1.30-1.36) but were not associated with C difficile infection (OR, 1.04; 95% CI, 0.94-1.16), stage 2 and 3 AKI (OR, 1.02; 95% CI, 0.96-1.10), or stage 3 AKI (OR, 1.06; 95% CI, 0.98-1.14).

Dr. Septimus's Annotations

Allergies to BL class antibiotics are the most reported drug allergy in the US, with 5% to 13% of the population reporting an allergy to at least 1 BL-class antibiotic. [Allergy. 2016;71:1305-1313] Patients with documented BL allergies incur increased rates of readmission, increased risk of a surgical site infection, antibiotic-resistant infections, adverse events, and longer lengths of stay (LOSs) compared with patients without documented BL allergies.[Clin Infect Dis. 2016;63:904-910] As a result of the harm associated with inpatient encounters for patients with documented BL allergies, there has been a push to delabeling of erroneous BL allergies, since more than 90% of the patients with documented BL allergies can in fact safely be given a BL.[Allergy. 2017; 72:1288-1296] However, the long-term clinical impact of BL allergies remains unclear.

"...findings suggest that documented BL allergies are associated with long-term clinical harm..."

There has been only 1 previous set of long-term (>5 years follow-up) studies on the clinical outcomes of BL allergies, and they found a 14% increase in all-cause mortality and significant increases risk of both MRSA and C difficile. [BMJ. 2018;361: k2400. J Gen Intern Med. 2019;34(9):1685-1687] The results of this study are similar to the previous studies in terms of finding significant associations between documented BL allergies and an increase in MRSA infection, but the results in this paper also found a significant association of VRE infection with documented BL allergies, as well as the risk of the pooled rate of infection with MRSA, C difficile, and VRE. In addition, the primary results did not find a significant difference in all-cause mortality associated with documented BL allergies. However, they did find a significant association of all-cause mortality with documented BL allergy status when using a time-varying allergy status, so the long-term association of documented BL allergy status with all-cause mortality remains unclear. Compared with the previous studies by Blumenthal et al, [J Gen Intern Med. 2019;34(9):1685-1687] this study provides a unique perspective using data from a different region and the consideration of documented BL allergy status to act as a dynamic variable. Their analysis was not able to evaluate whether the cause of death was related to infectious causes, which would be valuable to understanding whether documented BL allergies have a differential effect on the cause of death. Lastly, they were unable to account for the severity of BL allergies, which would be of interest to examining whether more severe reactions are underlying the observed higher rates of mortality and resistant infections due to necessitating a major change in clinical practice than less severe allergies.

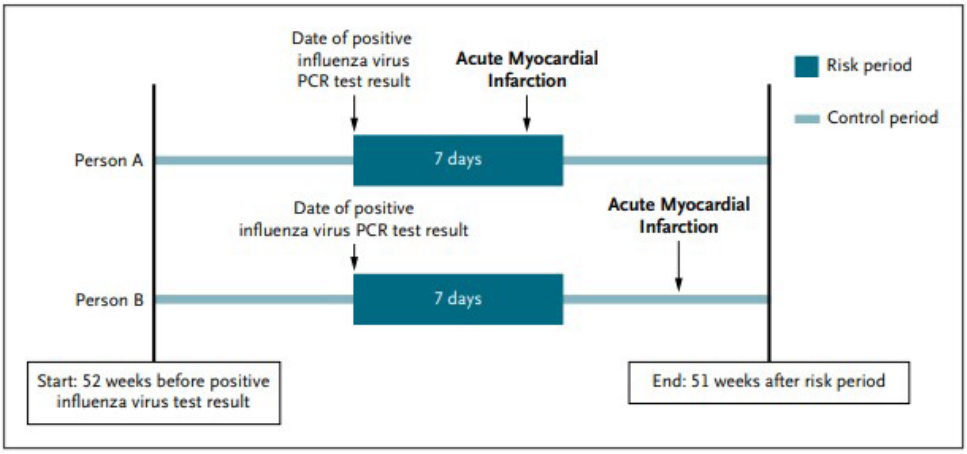
BOTTOM LINE

These findings suggest that documented BL allergies are associated with long-term clinical harm, and health systems should prioritize initiatives to maximize the use of first-line antimicrobials and reduce unnecessary BL avoidance.

Influenza Infection and Acute Myocardial Infarction

NEJM Evidence 2024; 3 (7)
DOI: 10.1056/EVIDoa2300361

This is an observational, registry-based, self-controlled case series study to evaluate the association between laboratory-confirmed influenza infection and occurrence of acute myocardial infarction. Laboratory records on respiratory virus PCR testing from 16 laboratories across the Netherlands were linked to national mortality, hospitalization, medication, and administrative registries. Influenza infection was defined as a positive PCR test result. Acute myocardial infarction was defined as a registered diagnostic code for either acute myocardial infarction hospitalization or death. Using a self-controlled case series method, they then compared the incidence of acute myocardial infarction during the risk period (days 1 to 7 after influenza infection) versus the control period (1 year before and 51 weeks after the risk period).



Between 2008 and 2019, they identified 158,777 PCR tests for influenza in the study population; 26,221 were positive for influenza, constituting 23,405 unique influenza illness episodes. A total of 406 episodes were identified with acute myocardial infarction occurring within 1 year before and 1 year after confirmed influenza infection and were included in analysis. The adjusted relative incidence of acute myocardial infarction during the risk period compared with the control period was 6.16 (95% confidence interval [CI], 4.11 to 9.24). The relative incidence of acute myocardial infarction in individuals without prior hospitalization for coronary artery disease was 16.60 (95% CI, 10.45 to 26.37) compared with 1.43 (95% CI, 0.53 to 3.84) for those with prior admission for coronary artery disease.

Dr. Septimus's Annotations

In this study, there was a sixfold higher incidence of acute myocardial infarction in the first week after diagnosis of influenza infection compared with a control period of 1 year before until 1 year after infection and a greater than 10-fold higher relative incidence of acute myocardial infarction in individuals without prior hospitalization for coronary artery disease. The has been observed in other studies. [N Engl J Med 2018; 378:345-353; PLoS One 2020;15: e0243248] The results in this study indicate that the increased risk of acute myocardial infarction may not be limited to influenza

infections and may extend to all acute respiratory infections severe enough to qualify for microbiologic testing. They and others have identified point estimates of 3.38 to 3.51 for RSV and 2.77 to 4.06 for other respiratory virus infections. [Eur Respir J 2018; 51:1701794] Proposed mechanisms are the effects on the inflammatory and coagulation pathways along with an increased metabolic demand, leading to destabilization of vulnerable atherosclerotic plaques and subsequent occlusion. Influenza infection date of onset was specified as the day the specimen was collected. The actual date of infection likely occurred earlier. However, the results were robust in sensitivity analyses, including induction intervals of 2, 4, and 7 days. No national registry for influenza vaccination exists in the Netherlands, precluding subgroup analyses for influenza vaccination. An important central question is whether the associations represent a true causal link between influenza and acute myocardial infarction.

BOTTOM LINE

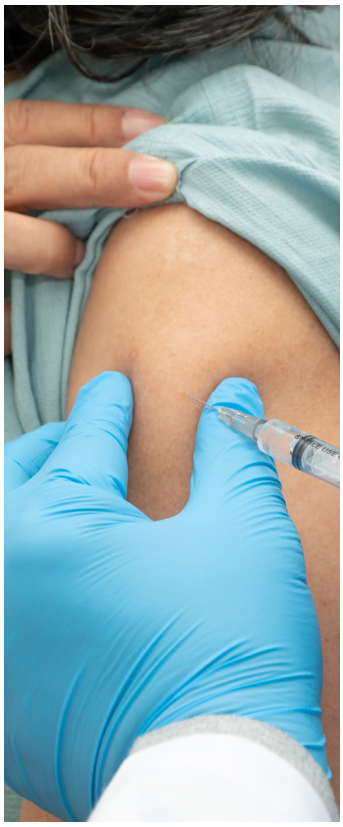
In this study influenza infection was associated with increased risk of acute myocardial infarction. This is one more reason to get an influenza vaccine yearly.

16

CDC panel revises RSV vaccine recommendations for adults

June 26, 2024

The CDC Advisory Committee on Immunization Practices (ACIP)updated its recommendations for use of the RSV vaccine in adults, which now recommends that all people ages 75 and older receive a single lifetime dose, and that people ages 60 to 74 who have certain underlying conditions also receive a dose of the vaccine. Conditions include lung disease, cardiovascular disease, moderate or severe immune compromise, diabetes with end-organ damage, severe obesity, neurologic or neuromuscular conditions, advanced chronic kidney disease, liver disorders, and hematologic disorders. The vote was unanimous. The ACIP postponed a recommendation for use of Arexvy in people ages 50 to 59, due to a lack of data that would support a population-based recommendation and lingering concerns about the risk of Guillain-Barre syndrome (GBS) following RSV vaccination.



Dr. Septimus's Annotations

Since the CDC first recommended the vaccine for use in ages 60 and older in June 2023, the FDA at the end of May approved for use in older adults, an mRNA product made by Moderna. The FDA recently approved expanded use of Arexvy, made by GSK, for at-risk adults ages 50 to 59.

17

Nirsevimab and Hospitalization for RSV Bronchiolitis

New England Journal of Medicine 2024;391:144-54.
DOI: 10.1056/NEJMoa2314885

The investigators conducted a prospective, multicenter, matched case–control study to analyze the effectiveness of nirsevimab therapy against hospitalization for RSV-associated bronchiolitis in infants younger than 12 months of

age. Case patients were infants younger than 12 months of age who were hospitalized for RSV-associated bronchiolitis between October 15 and December 10, 2023. Control patients were infants with clinical visits to the same hospitals for conditions unrelated to RSV infection. Case patients were matched to control patients in a 2:1 ratio on the basis of age, date of hospital visit, and study center. They calculated the effectiveness of nirsevimab therapy against hospitalization for RSV-associated bronchiolitis (primary outcome) by means of a multivariate conditional logistic-regression model with adjustment for confounders. At all the participating centers, all the infants who had been admitted for bronchiolitis underwent nasopharyngeal sampling for RSV testing by means of PCR assay at admission.

Overall, 60 case patients (8.7%) and 97 control patients (28.1%) had received nirsevimab previously. The estimated adjusted effectiveness of nirsevimab therapy against hospitalization for RSV-associated bronchiolitis was 83.0% (95% confidence interval [CI], 73.4 to 89.2). The effectiveness of nirsevimab therapy against RSV-associated bronchiolitis resulting in critical care was 69.6% (95% CI, 42.9 to 83.8) (27 of 193 case patients [14.0%] vs. 47 of 146 matched control patients [32.2%]) and against RSV-associated bronchiolitis resulting in ventilatory support was 67.2% (95% CI, 38.6 to 82.5) (27 of 189 case patients [14.3%] vs. 46 of 151 matched control patients [30.5%]).

Analysis	Case Patients	Control Patients	Effectiveness (95% CI)
	no. who received nirsevimab/total no. (%)		*percent*
Primary analysis	60/690 (8.7)	97/345 (28.1)	83.0 (73.4 to 89.2)
Sensitivity analyses			
Previous nirsevimab receipt regardless of time	75/690 (10.9)	120/345 (34.8)	86.6 (78.8 to 91.5)
Bronchiolitis defined as the first wheezing attack	56/618 (9.1)	96/327 (29.4)	84.9 (75.4 to 90.7)
Propensity-score analysis	60/690 (8.7)	97/345 (28.1)	78.2 (65.7 to 86.2)
Multivariate model with complete case analysis	56/624 (9.0)	90/284 (31.7)	84.8 (74.9 to 90.7)
Multivariate model adjusted for previous RSV infection	60/690 (8.7)	97/345 (28.1)	83.1 (73.5 to 89.2)
Multivariate model adjusted for socioeconomic level	60/690 (8.7)	97/345 (28.1)	83.4 (73.8 to 89.4)
Multivariate conditional regression model including matching covariates	60/690 (8.7)	97/345 (28.1)	84.1 (74.9 to 90.0)
Standard logistic-regression model including unmatched patients	61/724 (8.4)	102/360 (28.3)	77.1 (67.4 to 84.0)
Multivariate model with gestational age at birth and birth weight as categorical variables	60/690 (8.7)	97/345 (28.1)	84.1 (74.9 to 90.0)
Subgroup analyses			
Age			
<3 mo	53/332 (16.0)	76/150 (50.7)	82.4 (69.3 to 89.9)
≥3 mo	7/358 (2.0)	21/195 (10.8)	82.7 (52.8 to 93.7)
≥1 Risk factor for severe bronchiolitis			
Yes	9/37 (24)	10/20 (50)	64.8 (−17.2 to 89.4)
No	50/623 (8.0)	83/295 (28.1)	78.2 (67.9 to 85.2)
RSV bronchiolitis with ventilatory support	27/189 (14.3)	46/151 (30.5)	67.2 (38.6 to 82.5)
RSV bronchiolitis with PICU admission	27/193 (14.0)	47/146 (32.2)	69.6 (42.9 to 83.8)

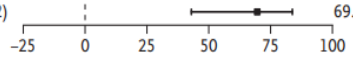


Figure 2. Effectiveness of Nirsevimab against Hospitalization for RSV-Associated Bronchiolitis.

Dr. Septimus's Annotations

RSV is the leading causative agent of bronchiolitis and is estimated to be responsible for 33.1 million cases of lower respiratory tract infection in children younger than 5 years of age annually, with 3.2 million hospitalizations and more than 100,000 deaths worldwide each year.[Lancet 2017;390:946-58] Nirsevimab is a monoclonal antibody against RSV that has enhanced neutralizing activity and an extended half-life in vivo, which enable its implementation in the general population.[Sci Transl Med 2017;9: eaaj1928] Double-blind, randomized, placebo-controlled trials have shown the efficacy of nirsevimab therapy in reducing the risk of RSV-associated lower respiratory tract infection leading to medical care among healthy preterm and full-term infants over a 5-month period. [N Engl J Med 2022; 386:837-46]

In this study, the investigators estimated the post licensure effectiveness of nirsevimab therapy against hospitalization for RSV-associated bronchiolitis among infants younger than 12 months of age and found an overall effectiveness of 83.0%. This level of effectiveness was consistent across age groups. In addition, nirsevimab therapy was effective against the most severe forms of RSV-associated bronchiolitis which may lead to PICU admission and ventilatory support.

This was an observational case–control study design which does not allow for the drawing of any causative conclusions. Testing for RSV was not performed in control patients, which may have influenced the study results. The study was powered to analyze the effectiveness of nirsevimab therapy against overall RSV-associated bronchiolitis leading to hospitalization. Subgroup analyses — in particular, the analysis involving infants with at least one risk factor for severe bronchiolitis — was underpowered.

BOTTOM LINE

Nirsevimab therapy was effective in reducing the risk of hospitalized RSV-associated bronchiolitis.

18

Nonadjuvanted Bivalent Respiratory Syncytial Virus Vaccination and Perinatal Outcomes

JAMA Network Open 2024;7(7):e2419268.
DOI: 10.1001/jamanetworkopen.2024.19268

The investigators set out to determine if there is an association between nonadjuvanted bivalent respiratory syncytial virus prefusion F (RSVpreF) protein subunit vaccination during pregnancy and preterm birth. Prenatal RSV vaccination with the RSVpreF vaccine was captured from the health system's electronic health records. They then performed a retrospective observational cohort study at 2 New York City hospitals within 1 health care system among patients who gave birth to singleton gestations at 32 weeks' gestation or later from September 22, 2023, to January 31, 2024. The primary outcome is preterm birth (PTB), defined as less than 37 weeks' gestation. Secondary outcomes included hypertensive disorders of pregnancy (HDP), stillbirth, small-for–gestational age birth weight, neonatal intensive care unit (NICU) admission, neonatal respiratory distress with NICU admission, neonatal jaundice or hyperbilirubinemia, neonatal hypoglycemia, and neonatal sepsis. Logistic regression models were used to estimate odds ratios (ORs), and multivariable logistic regression models and time-dependent covariate Cox regression models were performed.

Of 2973 pregnant individuals (median [IQR] age, 34.9 [32.4-37.7] years), 1026 (34.5%) received prenatal RSVpreF vaccination. During the study period, 60 patients who had evidence of prenatal vaccination (5.9%) experienced PTB vs 131 of those who did not (6.7%). Prenatal vaccination was not associated with an increased risk for PTB after adjusting for potential confounders (adjusted OR, 0.87; 95% CI, 0.62-1.20). There were no significant differences in pregnancy and neonatal outcomes based on vaccination status in the logistic regression models, but an increased risk of HDP in the time-dependent model was seen (HR, 1.43; 95% CI, 1.16-1.77).

Dr. Septimus's Annotations

The FDA approved the bivalent RSV prefusion F (RSVpreF) protein-based vaccine (Pfizer) for administration from 32 to 36 weeks of pregnancy. Although prelicensure clinical trial data supported the safety and efficacy of the RSVpreF vaccine,[N Engl J Med. 2023;388:1451-1464] concerns have been raised regarding a 1% higher rate of preterm birth observed in the RSVpreF intervention arm compared with the control arm in phase 3 clinical trials. These concerns were additionally fueled by the 1.9% higher rate of preterm birth observed in the intervention arm of the phase 3 clinical trial for the RSV prefusion F3 vaccine that ultimately led to the premature stop to the trial. [N Engl J Med. 2024; 390:1009-1021] Results from

this retrospective study provide some of the first post marketing safety data to document pregnancy outcomes following RSVpreF vaccination between 32 and 36 weeks of pregnancy. While the results provide initial reassurance that the vaccine was not associated with preterm birth some findings warrant further investigation. First vaccination showed an increased rate of hypertensive disorders of pregnancy (hazard ratio [HR], 1.43; 95% CI, 1.16-1.77). This increase was most apparent for gestational hypertension. Hypertensive disorders can occur with an early-onset at 20 to 33 weeks of gestation or with a late-onset on or after 34 weeks of gestation. Results were not stratified by onset of labor, making it difficult to determine whether preterm birth with a spontaneous onset may differ by vaccination status; 63% of preterm births among RSVpreF vaccinated pregnancies and 53% of preterm births among unvaccinated pregnancy had a spontaneous onset.

Clinical trial data show the RSVpreF vaccine is 57% effective against RSV-associated lower respiratory tract illness and 82% effective against medically attended severe lower respiratory tract illness in infants up to 3 months of age. [N Engl J Med. 2023; 388:1451-1464] Therefore despite the need for further research and surveillance, results from this study should offer initial reassurance to health care professionals, and pregnant patients.

BOTTOM LINE

In combination with the data from prelicensure clinical trials, this post marketing study does not support an increased risk of preterm birth attributed to RSVpreF vaccination when the vaccine is administered between 32 and 37 weeks of gestation, suggesting the benefits of vaccination greatly outweigh the risks.

19

CDC Health Alert: Increased Risk of Dengue Virus Infections in the United States

June 25, 2024

Global incidence of dengue in 2024 has been the highest on record for this calendar year; many countries are reporting higher-than-usual. In 2024, CDC has reported a record-breaking number of dengue cases, exceeding the highest number ever recorded in a single year. From January 1 – June 24, 2024, countries in the Americas reported more than 9.7 million dengue cases, twice as many as in all of 2023 (4.6 million cases). In the US, Puerto Rico has declared a public health emergency (1,498 cases) and a higher-than-expected number of dengue cases have been identified among US travelers (745 cases) from January 1 – June 24, 2024. In the setting of increased global and domestic incidence of dengue, The CDC recommends healthcare providers should take steps including:

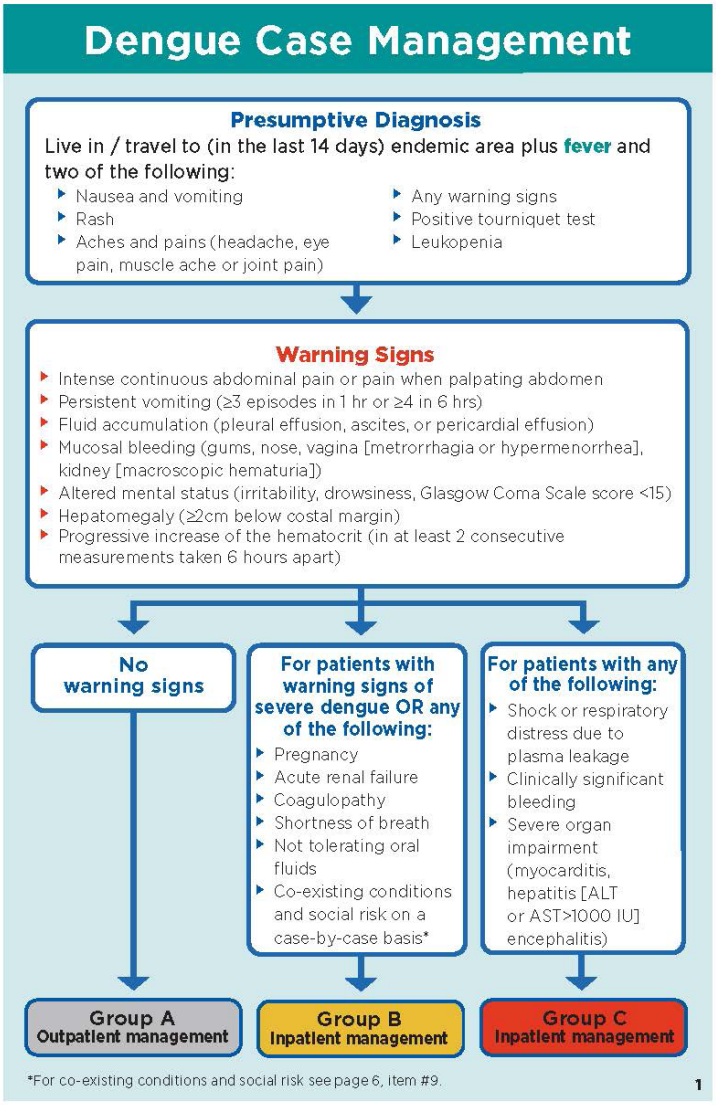
1. Have increased suspicion of dengue among people with fever who have been in areas with frequent or continuous dengue transmission within 14 days before illness onset,
2. Order appropriate diagnostic tests for acute DENV infection: RT-PCR and IgM antibody tests, or non-structural protein 1 [NS1] antigen tests and IgM antibody tests [the test sensitivity of RT-PCR and NS1 antigen tests decrease after the first 7 days],
3. Ensure timely reporting of dengue cases to public health authorities, and
4. Promote mosquito bite prevention measures among people living in or visiting areas with frequent or continuous dengue transmission. [insect repellent, wear loose-fitting, long-sleeved pants and shirts, use air conditioning and window screens, dump and drain container that hold water]

Dr. Septimus's Annotations

Dengue is the most common arboviral disease globally. It is caused by four distinct but closely related dengue viruses (DENV-1, -2, -3, and -4). DENVs are transmitted through bites of infected Aedes species mosquito vectors. Infection with one DENV generally induces life-long protection against infection from that specific DENV but only protects against other DENVs for several months to years. Six US territories and freely associated states are

classified as: Puerto Rico, American Samoa, the U.S. Virgin Islands, the Federated States of Micronesia, the Republic of Marshall Islands, and the Republic of Palau. In the rest of the US, local transmission of DENV has been limited, with sporadic cases or small outbreaks in Florida, Hawaii, and Texas. However, confirmed local DENV transmission has also been reported by Arizona and California over the past two years.

Approximately one in four DENV infections are symptomatic and can be mild or severe. Symptoms begin after an incubation period of 5–7 days (range 3–10 days) and present as fever accompanied by symptoms such as nausea, vomiting, rash, muscle aches, joint pain, bone pain, pain behind the eyes, headache, or low white blood cell counts are specific clinical findings that predict progression to severe disease. Warning signs include abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation (e.g., ascites, pleural effusion), mucosal bleeding, lethargy or restlessness, progressive increase of hematocrit, or liver enlargement >2cm. Severe disease, with associated severe bleeding, shock or respiratory distress caused by plasma leakage, or end-organ impairment, develops in 1 in 20 people with symptomatic dengue. Infants aged ≤1-year, pregnant people, adults aged ≥65 years, and people with altered immunity are at increased risk of severe dengue. Although a second DENV infection (i.e., with a different DENV from the first infection) carries a higher risk of severe disease than a first, third, or fourth infection, any infection can lead to severe disease. There are no antiviral medications approved to treat dengue. Treatment is supportive and requires careful volume management.



BOTTOM LINE

Maintain a high suspicion for dengue among patients with fever and recent travel (within 14 days before illness onset) to high-risk areas.

20

Rates of resistance to ceftazidime-avibactam and ceftolozane-tazobactam among patients treated for multidrug-resistant Pseudomonas aeruginosa bacteremia or pneumonia

Clinical Infectious Disease published online June 21,2024
DOI: 10.1093/cid/ciae332

Ceftazidime-avibactam (CZA) and ceftolozane-tazobactam (C/T) are considered first-line agents for treatment of MDR P. aeruginosa; however, comparative effectiveness data are limited. The objective of this study was to define the rate of treatment emergent resistance among consecutive patients with MDR P. aeruginosa pneumonia and bacteremia followed for 90 days. Development of resistance within 90 days of treatment initiation was defined as ≥4-fold increased MIC from baseline. Secondary endpoints included survival, microbiologic failure, and recurrent infections. Antibiotic MICs were categorized using CLSI interpretive criteria.

Adult patients with MDR P. aeruginosa infections treated for >48 hours with CZA or C/T were included. The study time period included a C/T shortage where CZA was recommended as first-line therapy for MDR P. aeruginosa infections. Pneumonia was defined as a new/worsening infiltrate on radiograph imaging plus purulent secretions, increased oxygen requirements, worsening cough/dyspnea, fever, leukocytosis, and/or tachypnea. Only the first eligible treatment course with either CZA or C/T was evaluated. Patients with cystic fibrosis, respiratory colonization, or tracheitis were excluded. MICs were determined by broth microdilution (BMD) in triplicate. Patients infected by isolates demonstrating baseline resistance (MIC >8 mg/L) to study drug were excluded. Isolates underwent whole-genome sequencing (WGS).

113 patients who received CZA (n=20) or C/T (n=93) were included; 63% were male, the median (IQR) Charlson Comorbidity Index was 5 (3-7), and 26% of patients were solid-organ or stem-cell transplant recipients. At treatment initiation, 35% of patients had septic shock, 84% had pneumonia, and 73% received mechanical ventilation. Patient demographics, severity of illness, and treatment characteristics were similar for patients treated with either agent. Compared to CZA-treated patients, those who received C/T were less likely to receive prolonged infusions (20% vs. 45%; P=0.04) and more likely to receive combination therapy (67% vs. 30%; P=0.005). Endovascular infections or empyema were numerically more common among patients who received C/T. Following treatment initiation, rates of 30-day survival, microbiologic failure, and recurrent infections did not vary between groups. Isolates were available for all patients treated with CZA and 94% (87/93) of patients treated with C/T. Baseline median (range) MICs were 4 (2–8) and 2 (0.25–8) mg/L for CZA and C/T, respectively. Isolates demonstrating ≥4-fold MIC increase from baseline by BMD were identified in 40% (8/20) and 10% (9/87) of patients treated with CZA or C/T, respectively (P=0.003). Corresponding median MICs of CZA- or C/T-resistant isolates were 16 (8–128) and 64 (8–512) mg/L, respectively. Prior exposure to cefepime was more common among patients who developed resistance (n=17) compared to those who did not (n=96); however, this was not statistically significant (P=0.10). Associations with prior meropenem or piperacillin/tazobactam were not significant. No other clinical factors, including receipt of prolonged infusion, combination therapy, or optimized doses were associated with resistance. WGS showed that CZA resistance was associated with new mutations in ampC and efflux regulatory pathways.

Dr. Septimus's Annotations

In this study, treatment-emergent resistance occurred more commonly among patients treated with CZA compared to C/T for MDR P. aeruginosa pneumonia and bacteremia. The investigators confirmed their findings through a propensity score matched analysis. Lower rates of resistance development following treatment with C/T may be due to structure modifications for ceftolozane that, in comparison to ceftazidime, were designed to provide increased stability against PDC hydrolysis, enhanced affinity for penicillin-binding proteins, decreased efflux, and improved outer membrane permeability.[Int J Infect Dis. 2017; 62:39-43] By comparison, the addition of avibactam to ceftazidime improves stability against PDC hydrolysis, but does not overcome other mechanisms of resistance encountered in MDR P. aeruginosa. [Clin Infect Dis. 2021; 73(11): e4521-e4530] During the study period, metallo-β-lactamases or other β-lactamases associated with study drug resistance were not identified at their center, a finding that is consistent with the US epidemiology of carbapenem-resistant P. aeruginosa. [Antimicrob Agents Chemother. 2017; 61: e01589-17] By WGS analyses they found that MDR P. aeruginosa isolates were highly diverse. The conclusions in this study are limited by the retrospective, single-center design that included a small number of patients treated with CZA.

BOTTOM LINE

Treatment-emergent resistance occurred more commonly among patients treated with CZA compared to C/T for MDR P. aeruginosa pneumonia and bacteremia.

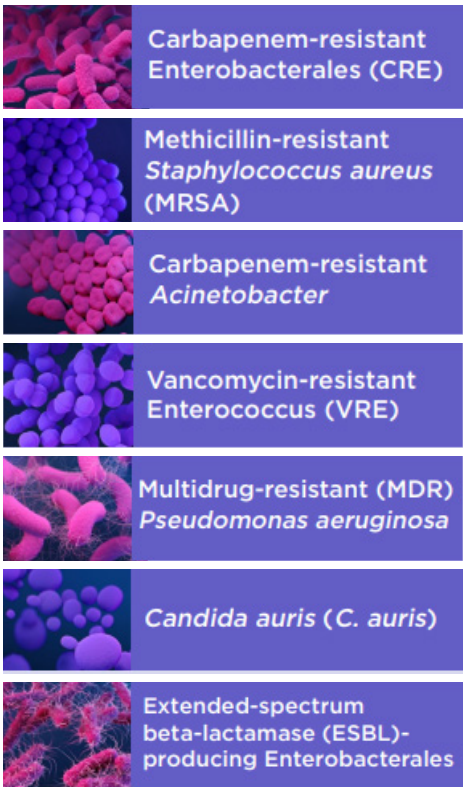
21

ANTIMICROBIAL RESISTANCE THREATS in the United States, 2021-2022

Key findings

- Bacterial antimicrobial-resistant hospital-onset infections caused by the pathogens listed above increased by a combined 20% during the COVID-19 pandemic compared to the pre-pandemic period, peaking in 2021. In 2022, rates for all but one of these pathogens (MRSA) remained above pre-pandemic levels.
- The number of reported clinical cases of C. auris increased nearly five-fold from 2019 to 2022. Clinical cases are identified when specimens collected from patients during routine clinical care test positive for C. auris.

CDC used new data to analyze the U.S. burden of the following antimicrobial-resistant pathogens typically found in health care settings:



AR Threats

	Threat	Change in Rates or Number of Infections***			
		2020 vs. 2019	2021 vs. 2020	2022 vs. 2021	2022 vs. 2019
URGENT*	Hospital-onset CRE	▲ Increase	▲ Increase	▬ Stable	▲ Increase
URGENT*	Hospital-onset Carbapenem-resistant *Acinetobacter*	▬ Stable	▬ Stable	▬ Stable	▲ Increase**
URGENT*	Clinical Cases of *C. auris*	▲ Increase	▲ Increase	▲ Increase	▲ Increase
SERIOUS*	Hospital-onset MRSA	▲ Increase	▬ Stable	▼ Decrease	▬ Stable
SERIOUS*	Hospital-onset VRE	▲ Increase	▲ Increase	▬ Stable	▲ Increase
SERIOUS*	Hospital-onset ESBL-producing Enterobacterales	▲ Increase	▬ Stable	▬ Stable	▲ Increase
SERIOUS*	Hospital-onset MDR *Pseudomonas aeruginosa*	▲ Increase	▲ Increase	▬ Stable	▲ Increase

Dr. Septimus's Annotations

The increases in antimicrobial resistance (AR) burden seen in 2020 and 2021 are due in part to the impact of Covid-19. This resulted in longer hospital stays for hospitalized patients, challenged the execution of infection prevention practices, and increased inappropriate antimicrobial use. Starting in 2025, CDC will release estimates for at least 19 AR threats and an update on the US burden of antimicrobial resistance, by pathogen.

With American Rescue Plan Act funding, the CDC supported healthcare and public health professionals' efforts to prevent AMR through programs targeting healthcare-associated infections and AMR, antibiotic stewardship programs, and the CDC's Antimicrobial Resistance Laboratory Network. Unfortunately, the House Appropriations bill passed last week decreases funding for the CDC by 20%, eliminates the Agency for Healthcare Research and Quality, while significantly restructuring the NIH. Enacting these cuts will hinder efforts to combat the threat of antimicrobial resistance.

BOTTOM LINE

The 20% rise in these pathogens from before to during the pandemic peaked in 2021, but in 2022, all pathogens except MRSA remained above prepandemic levels. Sufficient funding is essential to promote effective infection practices and adequate laboratory capacity to rapidly identify and treat resistant infections.

22

Infectious Diseases Society of America 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections

Infectious Disease Society of America

Table 2: 2024 Clinical and Laboratory Standards Institute Breakpoints for Select Gram-Negative Organisms and Antibiotic Combinations as Suggested in the IDSA AMR Guidance Document[1]

Antibiotic	Enterobacterales (µg/mL)	*Pseudomonas aeruginosa* (µg/mL)	Carbapenem-Resistant *Acinetobacter baumannii* (µg/mL)	*Stenotrophomonas maltophilia* (µg/mL)
Amikacin	≤4	≤16[2]	--	--
Ampicillin-sulbactam	--	--	≤8/4	--
Aztreonam	≤4	≤8	--	--
Cefepime	≤2[3]	≤8	--	--
Cefiderocol	≤4	≤4	≤4	≤1
Ceftazidime	≤4	≤8	--	--
Ceftazidime-avibactam	≤8/4	≤8/4	--	--
Ceftolozane-tazobactam	≤2/4	≤4/4	--	--
Ciprofloxacin	≤0.25	≤0.5	--	--
Colistin or Polymyxin B	--[4]	--[4]	--[4]	--
Doxycycline	≤4	--	--	--
Ertapenem	≤0.5	--	--	--
Fosfomycin	≤64[5]	--	--	--
Gentamicin	≤2	--	--	--
Imipenem	≤1	≤2	--	--
Imipenem-relebactam	≤1/4	≤2/4	--	--
Levofloxacin	≤0.5	≤1	--	≤2
Meropenem	≤1	≤2	--	--
Meropenem-vaborbactam	≤4/8	--	--	--
Minocycline	≤4	--	≤4	≤1
Nitrofurantoin	≤32	--	--	--
Piperacillin-tazobactam	≤8/4[6]	≤16/4	--	--
Plazomicin	≤2	--	--	--
Sulbactam-durlobactam	--	--	≤4/4	--
Tigecycline	--[7]	--	--[8]	--[8]
Trimethoprim-sulfamethoxazole	≤2/38	--	--	≤2/38
Tobramycin	≤2	≤1	--	--

[1]For full details of antibiotic susceptibility testing interpretations refer to: Clinical and Laboratory Standards Institute. 2024. M100: Performance Standards for Antimicrobial Susceptibility Testing. 34th ed. Wayne, PA. CLSI M100 document is updated annually; susceptibility criteria subject to changes in 2025. [2]Breakpoints only available for infections originating from the urinary tract. [3]Cefepime MICs of 4-8 µg/mL are susceptible dose-dependent. [4]No susceptible category for colistin or polymyxin B; MICs ≤2 µg/mL considered intermediate. [5]Applies to *Escherichia coli* urinary tract isolates only. [6]Piperacillin-tazobactam MICs of 16 µg/mL are considered susceptible dose-dependent. [7]No CLSI breakpoint. FDA defines susceptibility as MICs ≤2 µg/mL. [8]Neither CLSI nor FDA breakpoints are available.

ESBL-E

- Fosfomycin continues to not be suggested for pyelonephritis and complicated urinary tract infections (cUTI). IV fosfomycin is not available in the US.
- For patients who are critically ill and have hypoalbuminemia, meropenem is the preferred carbapenems. Ertapenem, in contrast to meropenem and imipenem, is highly protein bound leading to a relatively prolonged serum half-life. In patients with hypoalbuminemia, the free fraction of ertapenem increases, leading to increased ertapenem clearance and a significant decrease in the serum half-life of this agent, which may not be optimal with daily dosing of this agent. An observational study of 279 patients with Enterobacterales infections found that hypoalbuminemia (defined as serum albumin <2.5 g/dL) was associated with an approximately five- times higher odds of 30-day mortality for patients receiving ertapenem compared to those receiving meropenem or imipenem. Clinical literature regarding the use of ertapenem, relative to other carbapenems, in critically ill patients is limited and conflicting. However, given known pharmacokinetic (PK) alterations in patients with critical illness and limitations in the pharmacokinetic and pharmacodynamic (PK/PD) profile of ertapenem, the panel suggests the use of meropenem rather than ertapenem, as initial therapy in critically ill patients with ESBL-E infections.
- Piperacillin-tazobactam continues to not be preferred for the treatment of pyelonephritis and cUTI; however, it was acknowledged that if piperacillin-tazobactam was initiated for pyelonephritis or cUTI caused and clinical improvement occurs, the decision to continue piperacillin-tazobactam should be made with the understanding that theoretically there may be an increased risk for microbiological failure with this approach. The authors do admit that the Merino Trial data was subsequently reanalyzed only including patients with clinical isolates against which piperacillin-tazobactam MICs were ≤16 µg/mL by broth microdilution. Reanalyzing the data from 320 (82%) patients with clinical isolates available for retesting, 30-day mortality occurred in 9% versus 4% of those in the piperacillin-tazobactam and meropenem arms, respectively. Although the absolute risk difference was attenuated and no longer significant in the reanalysis, the panel still suggests carbapenem therapy as the preferred treatment of ESBL-producing bloodstream infections due to the notable direction of the risk difference.
- A re-review of available data and newer data indicate that ceftolozane-tazobactam is likely to be effective against ESBL-E; however, it suggested that this agent be preserved for the treatment of DTR aeruginosa or polymicrobial infections (e.g., both DTR P. aeruginosa and ESBL-E).

AmpC-E

- The term “moderate to high risk” clinically significant AmpC production was replaced with “moderate risk” throughout.
- Enterobacter cloacae complex, Klebsiella aerogenes, and Citrobacter freundii are the most common Enterobacterales at moderate risk for clinically significant inducible AmpC production.
- It was clarified that even without upregulation of AmpC production, basal production of AmpC β-lactamases by organisms with inducible ampC expression leads to intrinsic resistance to ampicillin, amoxicillin-clavulanate, ampicillin-sulbactam, and first- and second-generation cephalosporins.
- The suggestion that cefepime is not advised for Enterobacter cloacae, Citrobacter freundii, and Klebsiella aerogenes with cefepime MICs of 4-8 µg/mL because of concerns for an increased risk of ESBL production in this cefepime MIC range was removed in light of newer data and a rereview of existing data. Available US data does not suggest there is a clear association between cefepime susceptible dose-dependent MICs (i.e., MICs 4-8 µg/mL) and ESBL production.
- They state in light of both the advantages of cefepime as a compound and no clear clinical failure signals in the literature when administered for the treatment of AmpC-E infections, the panel suggests cefepime as a preferred treatment option for E. cloacae, K. aerogenes, and C. freundii

infections.

CRE

- An increase in the prevalence of CRE isolates producing metallo-beta-lactamases (MBL) in the US (e.g., NDM, VIM, IMP) is acknowledged.
- A description of a CLSI endorsed method (i.e., broth disk elution method) to test for activity of the combination of ceftazidime-avibactam and aztreonam for MBL-producing Enterobacterales is discussed. -see table above
- Ceftazidime-avibactam in combination with aztreonam, or cefiderocol as monotherapy, are preferred treatment options for NDM and other MBL-producing Enterobacterales infections.
- Dosing suggestions for ceftazidime-avibactam in combination with aztreonam are updated. Both agents are suggested to be administered every 8 hours to facilitate simultaneous administration in clinical practice.
- TMP-SMX, ciprofloxacin, or levofloxacin are preferred treatment options for pyelonephritis or cUTI caused by CRE, if susceptibility is demonstrated.

DTR P. aeruginosa

- For infections caused by P. aeruginosa isolates not susceptible to any carbapenem agent but susceptible to traditional β-lactams (e.g., cefepime), administration of a traditional agent as high-dose extended-infusion therapy continues to be suggested, although the panel no longer emphasizes the importance of repeating AST on the initial isolate before administration of the traditional agent given the frequency with which this susceptibility profile occurs.
- A new question has been added "Are there differences in percent activity against DTR aeruginosa across available β-lactam agents?" Differences in DTR P. aeruginosa susceptibility percentages to the newer β-lactams are described along with regional differences in enzymatic mechanisms of resistance that contribute to some of these differences.
- Once-daily tobramycin or amikacin were added as alternative treatment options for pyelonephritis or cUTI caused by DTR aeruginosa given the prolonged duration of activity of these agents in the renal cortex and the convenience of once daily dosing.
- For patients infected with DTR P. aeruginosa isolates that are MBL-producing, the preferred treatment is cefiderocol.
- The panel does not suggest the use of nebulized antibiotics for the treatment of respiratory infections caused by DTR P. aeruginosa.

CRAB

- Sulbactam-durlobactam, in combination with meropenem or imipenem, was added as the preferred agent for the treatment of CRAB infections.
- High-dose ampicillin-sulbactam in combination with at least one other agent has been changed from a preferred to an alternative regimen if sulbactam-durlobactam is not available.
- The suggested dosing of high-dose ampicillin-sulbactam has been adjusted to be 27 grams of ampicillin-sulbactam (18 grams ampicillin, 9 grams sulbactam) daily.

S. maltophilia

- Although generally believed to be less pathogenic than many other nosocomial organisms, S. maltophilia produces biofilm and virulence factors that enable colonization or infection in vulnerable hosts, such as those with underlying lung disease, persons who inject drugs, and people with hematological malignancies.
- An L1 MBL and L2 serine β-lactamase render most conventional β-lactams ineffective against S. maltophilia. L1 hydrolyzes penicillins, cephalosporins, and carbapenems, but not aztreonam. However, L2 hydrolyzes extended spectrum cephalosporins and aztreonam.
- Questions have been adjusted to list agents in order of preference (i.e., cefiderocol minocycline, TMP-SMX, or levofloxacin), ceftazidime-avibactam and aztreonam, minocycline [with a second agent], TMP-SMX [with a second agent], or levofloxacin [with a second agent].
- A description of a CLSI endorsed method (i.e., broth disk elution method) to test for activity of the combination of ceftazidime-avibactam and aztreonam for maltophilia activity is discussed
- Tigecycline has been removed as a component of combination therapy.

Dr. Septimus's Annotations

- Updated guidance from the CLSI advising against the testing of ceftazidime for maltophilia infections has been added.

23

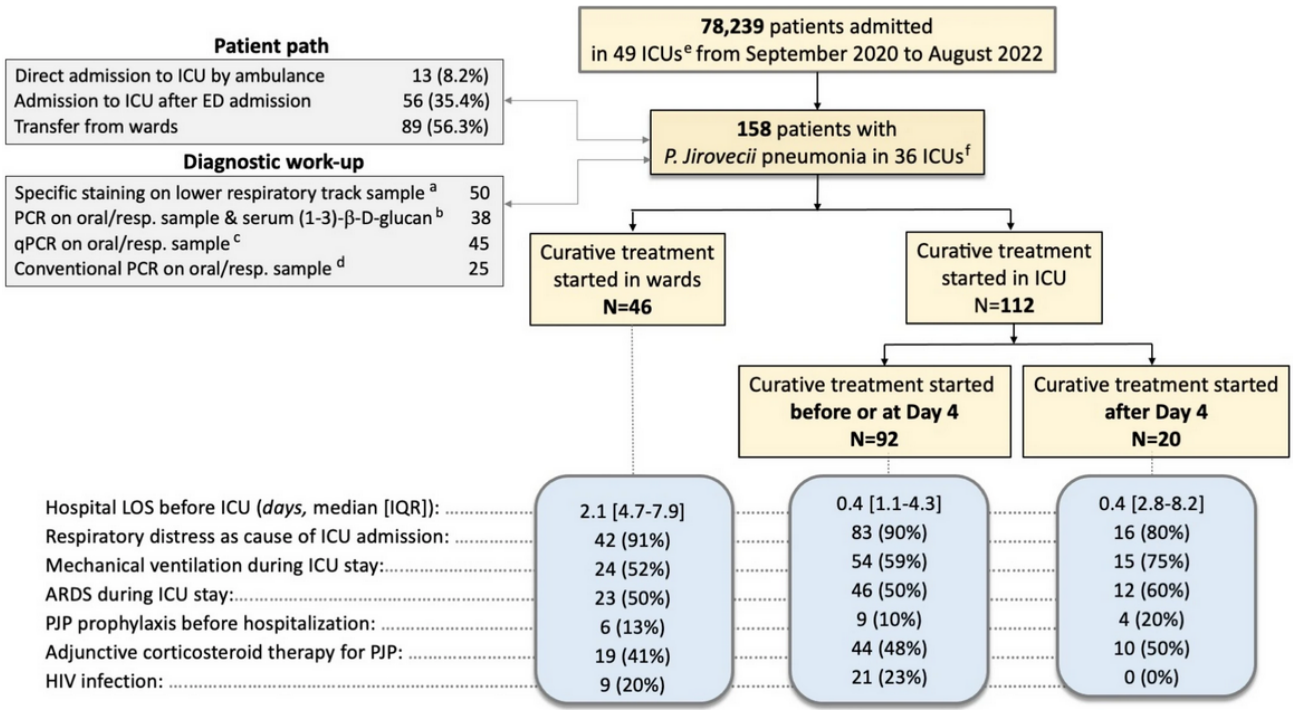
Pneumocystis pneumonia in intensive care: clinical spectrum, prophylaxis patterns, antibiotic treatment delay impact, and role of corticosteroids. A French multicentre prospective cohort study

Intensive Care Medicine published online June 3, 2024
DOI: 10.1007/s00134-024-07489-2

I commend IDSA for updating this guidance yearly. As the recent CDC report above, AR continues to rise. Funding is inadequate, but we must do our part to execute evidence based diagnostic and antimicrobial stewardship along with robust infection prevention to address this public health crisis.

This is a multicenter, prospective observational study involving 49 adult ICUs. The study was designed to evaluate the severity, the clinical spectrum, and outcomes of patients with severe PJP, and to assess the association between delayed antibiotic treatment and adjunctive corticosteroid therapy with mortality.

The study included 158 patients with PJP from September 2020 to August 2022. Their main reason for admission was acute respiratory failure (n=150, 94.9%). 12% of them received antibiotic prophylaxis for PJP before ICU admission. Upon ICU admission, 105 patients (66.5%) were on ongoing or recent immunosuppressive drug therapy, including corticosteroids. Of these, 66 patients (41.8%) were using more than one type of immunosuppressive drug, and 29 patients (18.4%) were on more than two. Immunosuppression was associated with various conditions: solid-organ cancer or hematologic

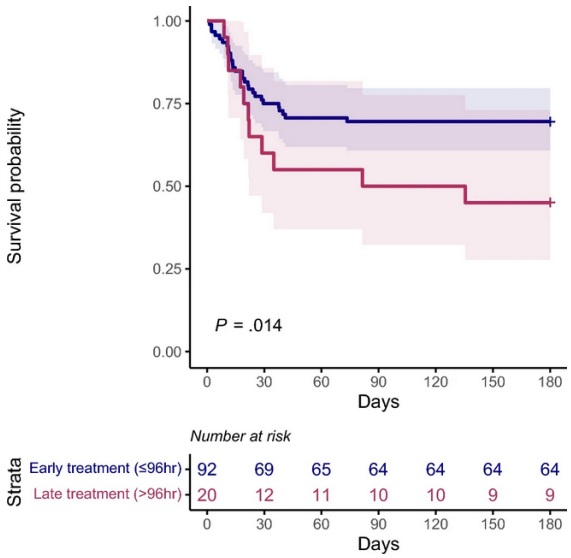


malignancies in 66 (41.8%) patients, HIV infection in 29 (18.4%) patients, and solid-organ transplant in 14 (8.9%) patients. Among the remaining 49 (31%) patients, 36 (73.5%) presented diverse inflammatory/autoimmune diseases 7 (14.3%) were solely on corticosteroid therapy causing immunosuppression, and 6 (12.2%) had no identified cause of immunosuppression.

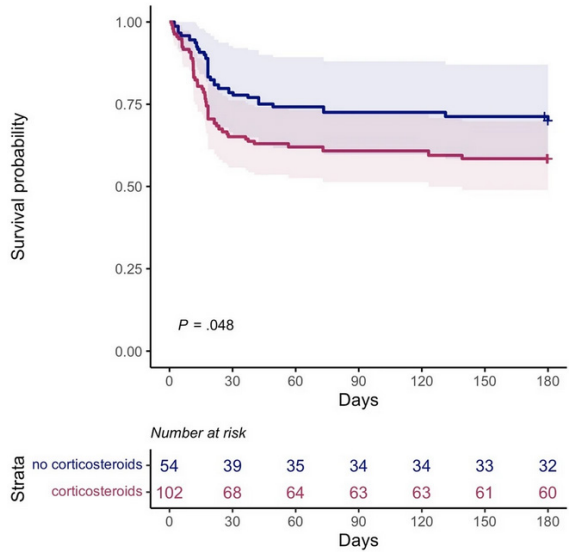
ICU, hospital, and 6-month mortality were 31.6%, 35.4%, and 40.5%, respectively. Using time-to-event analysis with a propensity score-based inverse probability of treatment weighting, the initiation of appropriate antibiotic treatment after 96 hours of ICU admission was associated with faster occurrence of death [time ratio: 6.75; (95% CI): 1.48–30.82; P=0.014]. The use of corticosteroids for PJP was associated with faster occurrence of death (time ratio: 2.48; 95% CI 1.01–6.08; P=0.048). Notably, upon data review, it was observed that 70 cases (44.3%) could not be definitively classified as proven or probable PJP. However, these cases had been classified as such by bedside clinicians, and thus, for the sake of analysis, they were retained in the dataset.

This study demonstrates that for optimal outcomes in critically ill immunocompromised patients with pneumonia, PJP should be considered and should be treated in a timely manner. As in recent studies [Am J Transplant 2024; 4:653; Chest 2018 154:536] the benefit of adjunctive steroids in HIV negative patients could not be demonstrated. Although this was a prospective study, the study was not designed to evaluate the effects of steroids. This study also showed that primary PJP prophylaxis is often overlooked.

Survival probability according to early or late (after the 96th hour of ICU) curative antibiotic treatment of PJP



Survival probability according to the use of adjunctive corticosteroid therapy for PJP in the whole study population (N = 158)



24

Risks of SARS-CoV-2 JN.1 infection and COVID-19 associated emergency-department (ED) visits/hospitalizations following updated boosters and prior infection: a population-based cohort study

Clinical Infectious Disease published online June 26, 2024
DOI: 10.1093/cid/ciae339

BOTTOM LINE

This study showed that few patients with PJP admitted to the ICU received prophylactic antibiotic therapy, that delay in appropriate antibiotic treatment was common and that both delay in appropriate antibiotic treatment and adjunctive corticosteroids for PJP were associated with accelerated mortality.

The investigators conducted a retrospective population-based cohort study amongst all boosted Singaporeans aged ≥18 years during a Covid-19 wave predominantly driven by JN.1, from November 26, 2023, to January 13, 2024. Multivariable Cox regression was utilized to assess risk of SARS-CoV-2 infection and Covid-19 associated ED visits/hospitalizations, stratified by vaccination status/prior infection; with individuals last boosted ≥1 year utilized as the reference category. Vaccination and infection status were classified using national registries.

Over 3 million boosted adult Singaporeans were included in the study population, accounting for 146,863,476 person-days of observation. During the JN.1 outbreak, 28,160 SARS-CoV-2 infections were recorded, with 2,926 hospitalizations and 3,747 ED-visits. Compared with individuals last boosted ≥1 year prior with ancestral monovalent vaccines, receipt of an updated XBB.1.5 booster 8-120 days prior was associated with lower risk of JN.1 infection (adjusted hazard-ratio, aHR=0.59[0.52-0.66]), Covid-19 associated ED-visits (aHR=0.50[0.34-0.73]) and hospitalizations(aHR=0.58[0.37-0.91]), while receipt of a bivalent booster 121-365 days prior was associated with lower risk of JN.1 infection (aHR=0.92[0.88-0.95]) and ED-visits (aHR=0.80[0.70-0.90]). Lower risk of Covid-19 hospitalization during the JN.1 outbreak (aHR=0.57[0.33-0.97]) was still observed following receipt of an updated XBB.1.5 booster 8-120 days prior, even when analysis was restricted to previously infected individuals.

Dr. Septimus's Annotations

"...[R]ecent receipt within the past year of an additional updated [bivalent or monovalent XBB1.5] booster... was overall associated with lower risk of JN.1 infection and Covid-19 related healthcare utilization..."

Concern remains that JN.1[now KP] may potentially evade current Covid-19 vaccines, including those that have been updated to target newer SARS-CoV-2 variants. However, in-vitro studies have yielded conflicting results. Neutralizing antibody response six months after the BNT162b2(Pfizer) bivalent booster was lowest against JN.1, compared with other SARS-CoV-2 variants.[Int J Infect Dis. 2024 Apr 5:107028] Similarly, neutralization escape against BA.2.86 and JN.1 has been reported for monovalent XBB1.5 boosters, with JN.1 demonstrating more resistance to XBB.1.5 vaccine sera compared with BA.2.86.[Euro Surveill. 2024 Jan;29(2):2300740] In contrast, other in-vitro studies have demonstrated continued ability of XBB.1.5-containing mRNA vaccines to elicit robust antibody responses, with cross neutralization of JN.1.[J Infect Dis. 2024 Feb 13:jiae067] Real-world, population-based estimates of the protection conferred by updated Covid-19 vaccines against JN.1-associated infection and healthcare utilization are needed.

In this population-based cohort study of boosted adult Singaporeans aged ≥18 years during an outbreak driven by the SARS-CoV-2 JN.1 variant, recent receipt within the past year of an additional updated booster (bivalent/ monovalent XBB1.5) was overall associated with lower risk of JN.1 infection and Covid-19 related healthcare utilization, compared with individuals boosted ≥1 year prior before the rollout of bivalent/ XBB1.5 monovalent vaccines. Sequencing was not routinely performed, however JN.1 accounted for ≥90% of sequenced cases on national genomic surveillance. There may also have been residual confounding from other unmeasured factors, such as receipt of Covid-19 therapeutics, that might be associated with subsequent hospitalization and were not

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COVID-19 by the Numbers

July 14, 2024

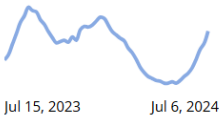
Early Indicators

Test Positivity

% Test Positivity

11.0%

Week ending July 6, 2024
Previous week 9.1%

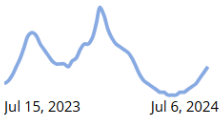


Emergency Department Visits

% Diagnosed as COVID-19

1.3%

Week ending July 6, 2024
Previous week 1.1%



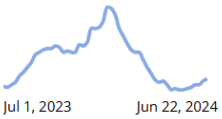
Severity Indicators

Hospitalizations

Hospitalization Rate per 100,000 population

2.0

Week ending June 22, 2024
Previous week 1.8

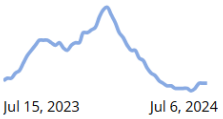


Deaths

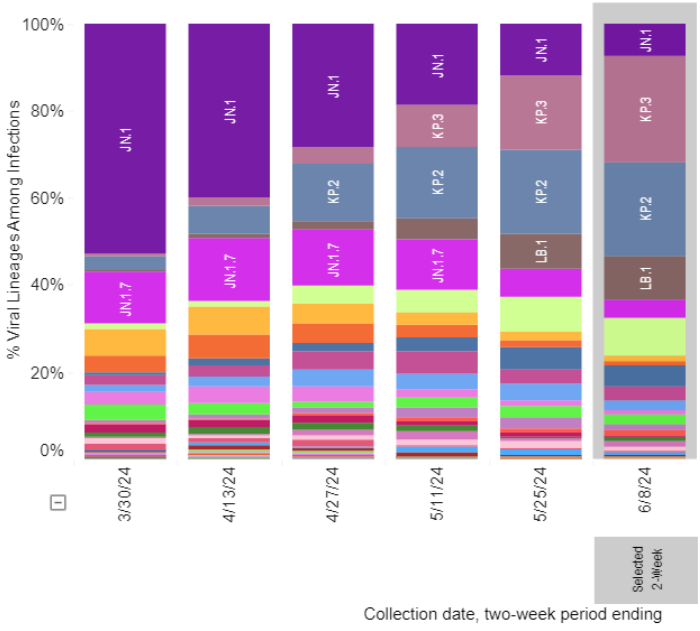
% of All Deaths in U.S. Due to COVID-19

0.8%

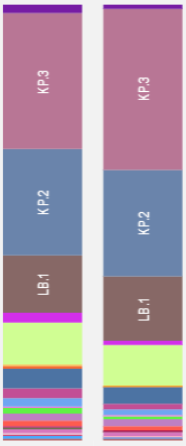
Week ending July 6, 2024
Previous week 0.8%



Weighted Estimates: Variant proportions based on reported genomic sequencing results

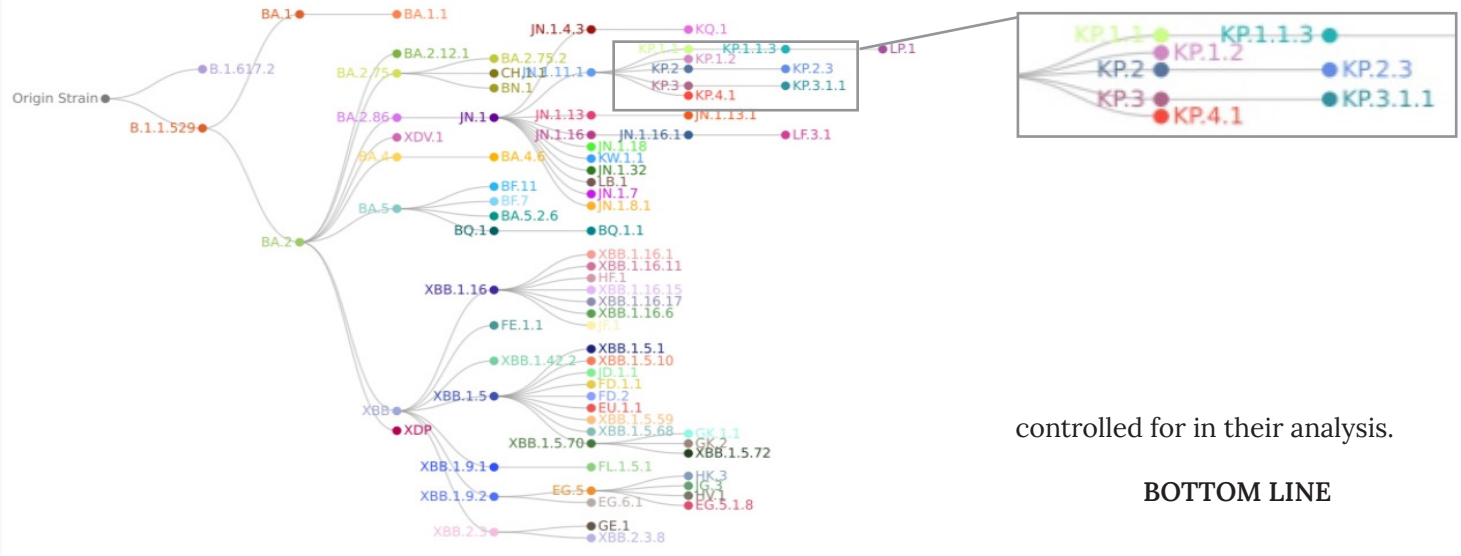


Nowcast:** Model-based projected estimates of variant proportions



USA

WHO label	Lineage #		%Total	95%CI
Omicron	KP.3		24.5%	18.4-31.6%
	KP.2		21.5%	17.5-25.9%
	LB.1		10.0%	5.2-17.0%
	KP.1.1		8.9%	4.6-15.2%
	JN.1		7.4%	4.8-10.9%
	JN.1.16.1		4.8%	2.5-8.2%
	JN.1.7	†	4.0%	1.7-7.9%
	JN.1.16		3.1%	1.6-5.4%
	JN.1.18		2.2%	1.2-3.7%
	JN.1.11.1		2.1%	1.1-3.7%
	XDV.1	†	1.4%	0.2-5.0%
	KP.4.1	†	1.3%	0.4-3.4%
	JN.1.13.1	†	1.2%	0.3-3.0%
	KS.1	†	1.1%	0.4-2.6%
	KQ.1	†	1.1%	0.1-3.7%
	JN.1.8.1	†	1.0%	0.3-2.4%
	JN.1.32	†	0.8%	0.0-4.4%
	KW.1.1	†	0.8%	0.2-2.2%
	XDP	†	0.6%	0.1-1.8%
	KV.2	†	0.3%	0.0-1.2%
	JN.1.4.3	†	0.3%	0.0-1.5%
	BA.2	†	0.0%	0.0-0.4%



controlled for in their analysis.

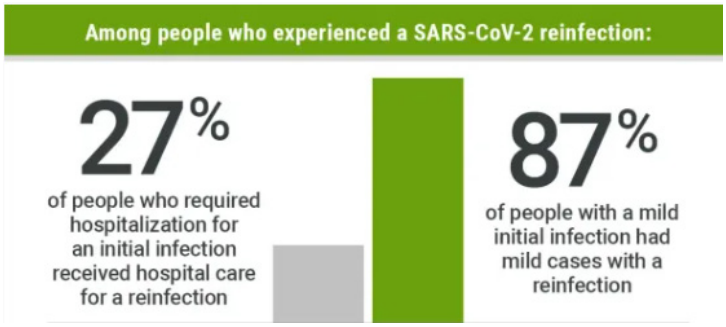
BOTTOM LINE

26

Insights from an N3C RECOVER EHR-based cohort study characterizing SARS-CoV-2 reinfections and Long COVID

Communications Medicine published online July 11, 2024
DOI: 10.1038/s43856-024-00539-2

Recent receipt of updated boosters (bivalent/XBB1.5) within the past year conferred protection against SARS-CoV-2 infection and ED-visits/hospitalization during a JN.1 variant wave, in both previously infected and uninfected individuals. CDC recommends all Americans ages 6 months and older should receive one of the new Covid-19 vaccines when they become available this fall. The vaccine by Novavax will target JN.1, the variant that prevailed for months in the winter and spring. The vaccines to be made by Pfizer and Moderna are aimed at KP.2, which a dominant variant in last few months.



KP variants now make up over 50% of strains in US. JN.1 is down <10% and LB.1 is unchanged. Test positivity and ED visits are up. Actual admission for Covid-19 and deaths are up slightly.

The investigators used an electronic health record (EHR) study cohort of over 3 million patients from the National COVID Cohort Collaborative as part of the NIH Researching COVID to Enhance Recovery Initiative. They calculated summary statistics, effect sizes, and Kaplan–Meier curves to better understand Covid-19 reinfections.

Dr. Septimus's Annotations

The investigators validated previous findings of reinfection incidence (7%), the occurrence of most reinfections during the Omicron period, and evidence of multiple reinfections. They present findings that the proportion of Long COVID diagnoses is higher following initial infection than reinfection for infections in the same time period. They report lower albumin levels leading up to reinfection and a statistically significant association of severity between initial infection and reinfection (chi-squared value: 25,697, p-value: <0.0001). Individuals who experienced severe initial and first reinfection were older in age and at a higher mortality risk than those who had mild initial infection and reinfection.

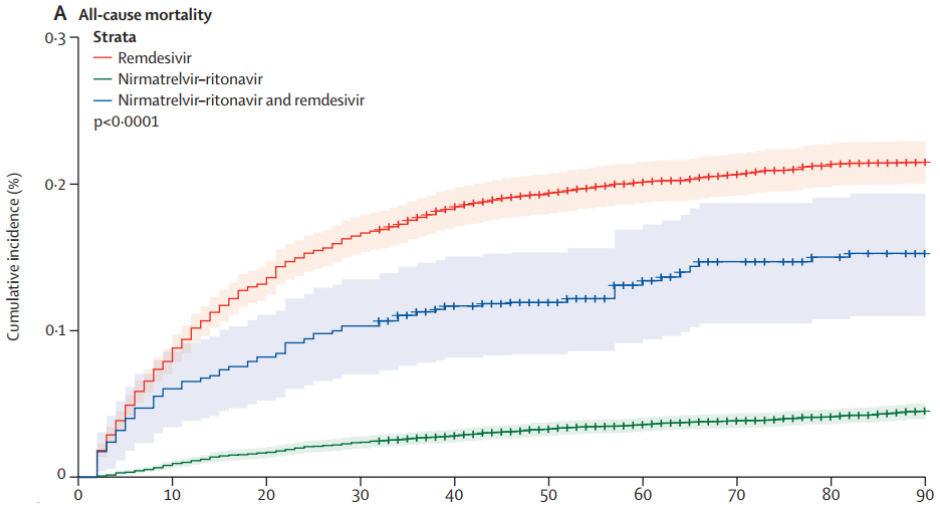
More than three years after the start of the Covid-19 pandemic, patients are reporting multiple episodes of Covid-19 infections. The current study investigated Covid-19 reinfections in a large EHR cohort of over 3 million patients. They used data summary techniques and statistical tests to characterize reinfections and their relationships with disease severity, biomarkers, and Long COVID. They found that individuals with severe initial infection are more likely to experience severe reinfection, that albumin levels were lower, leading to reinfection, and that a lower proportion of individuals are diagnosed with

Comparative effectiveness of combination therapy with nirmatrelvir–ritonavir and remdesivir versus monotherapy with remdesivir or nirmatrelvir–ritonavir in patients hospitalised with COVID-19: a target trial emulation study

The Lancet Infectious Disease published online July 15, 2024
DOI: 10.1016/S1473-3099(24)00353-0

Long COVID following reinfection than initial infection.

A major limitation of this analysis is that they were limited to EHR collected at specific hospitals; they could merge patient records between hospitals. It was also not feasible to include the results of home Covid-19 tests. They were limited to the analyses of biomarkers, severity, and Long COVID diagnosis to only the first Covid-19 reinfection.



BOTTOM LINE

In this large patient cohort, they found that the severity of reinfection appears to be associated with the severity of initial infection and that Long COVID diagnoses appear to occur more often following initial infection than reinfection. Future research is necessary to better understand Covid-19 reinfections.

Investigators analyzed the electronic health records of a weighted sample of adults hospitalized for Covid-19 who received either nirmatrelvir-ritonavir plus remdesivir (18,410 patients) or drug alone (18,178 for remdesivir, 18,287 for nirmatrelvir-ritonavir) within 5 days of hospitalization from March 16 to Dec 31, 2022. The study period spanned SARS-CoV-2 Omicron variant predominance. Median follow-up was 84 days, and the average age of participants was 75 years.

In total, 7,050 participants died of any cause (cumulative incidence, 12.9%; remdesivir alone, 20.5%; nirmatrelvir-ritonavir alone, 4.2%; and combination therapy, 14.0%). There were also 3,688 ICU admissions or ventilations (cumulative incidence, 6.7%; remdesivir alone, 11.2%; nirmatrelvir-ritonavir alone, 1.1%; and combination treatment, 7.9%). The risk of death was lower in recipients of nirmatrelvir-ritonavir only (hazard ratio [HR], 0.18; absolute risk reduction [ARR], −16.3%) or a combination of remdesivir and nirmatrelvir-ritonavir (HR, 0.66; ARR, −6.5%) than in those given remdesivir alone.

Findings were comparable for ICU admission or ventilation (nirmatrelvir-ritonavir alone HR, 0.09; ARR, −10.0% and

Dr. Septimus's Annotations

combination therapy HR, 0.68; ARR, −3.2%). Relative to combination therapy, nirmatrelvir-ritonavir monotherapy was tied to a much lower risk of death (HR, 0.27; ARR, −9.8%) and ICU admission or ventilation (HR, 0.13; ARR, −6.8%).

Recipients of nirmatrelvir-ritonavir alone had a significantly reduced risk of heart attack, acute kidney injury, anemia, hyperglycemia, and abnormal blood clotting than those receiving remdesivir alone. Patients given combination treatment

had a significantly lower risk of abnormal clotting than those receiving remdesivir alone. These benefits were consistent across differing Covid-19 vaccination statuses, admission criteria, respiratory support modalities, and underlying comorbidities. The cumulative incidence of common adverse events such as ischemic stroke, rash, gastrointestinal symptoms, and hypoglycemia was similar regardless of treatment type.

Previous data suggest that for those with Covid-19, nirmatrelvir–ritonavir monotherapy is more suitable for early outpatient treatment to prevent severe infection, whereas remdesivir monotherapy is more appropriate for hospitalized patients with moderate disease. In 2023 a multicenter randomized controlled trial done in China revealed that nirmatrelvir–ritonavir did not lower 28-day mortality rates in patients with Covid-19 who also had significant comorbidities.[Lancet Reg Health West Pac 2023; 33: 1–11] In addition, no significant variations were observed in the duration of SARS-CoV-2 RNA clearance or incidence of adverse events between the nirmatrelvir–ritonavir group and the group receiving standard treatment. However, the study had a small sample size, with only 264 patients, and wide confidence intervals in subgroup analysis. Up until now there has been very limited data on combination therapy. The findings in this study highlight the significant effect of nirmatrelvir–ritonavir monotherapy, which was associated with lower mortality and reduced intensive care unit admission or ventilatory support compared with remdesivir monotherapy and nirmatrelvir–ritonavir and remdesivir combination therapy. Recipients of nirmatrelvir-ritonavir alone also had a significantly reduced risk of heart attack, acute kidney injury, anemia, hyperglycemia, and abnormal blood clotting than those receiving remdesivir

28 Oral Nirmatrelvir–Ritonavir as Postexposure Prophylaxis for Covid-19

New England Journal of Medicine 2024;391:224-34.
DOI: 10.1056/NEJMoa2309002

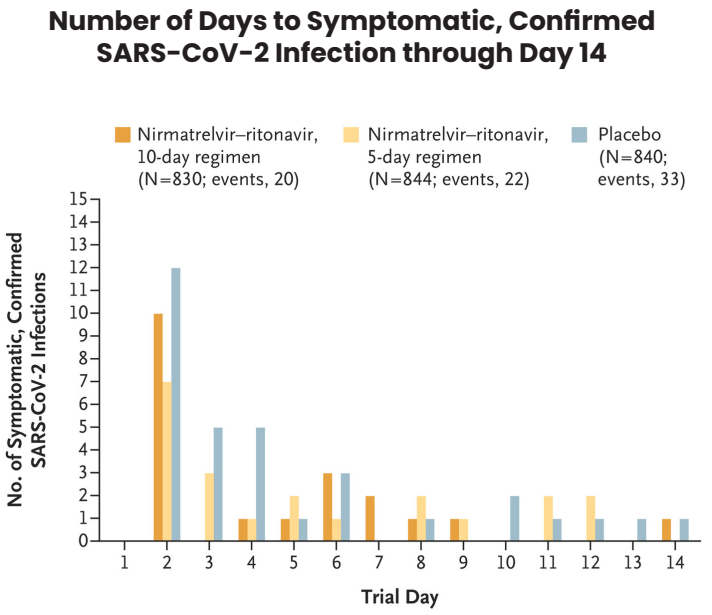
alone. The study was well designed target emulation trial, exploring predicted outcomes and adjusting for potential bias of confounders, but it was not a randomized clinical trial directly comparing outcomes.

BOTTOM LINE

Nirmatrelvir–ritonavir monotherapy was associated with lower mortality and reduced ICU admission or ventilatory support compared with remdesivir monotherapy and nirmatrelvir–ritonavir and remdesivir combination therapy. The absence of nirmatrelvir–ritonavir from current guidelines for treating high-risk hospitalized adults with Covid-19 highlights an opportunity for improvement.

The investigators conducted a double-blind trial to assess the efficacy and safety of nirmatrelvir–ritonavir in asymptomatic, rapid antigen test–negative adults who had been exposed to household contact with Covid-19 within 96 hours before randomization. The participants were randomly assigned in a 1:1:1 ratio to receive nirmatrelvir–ritonavir every 12 hours for 5 days or for 10 days or matching placebo for 5 or 10 days. The primary end point was the development of symptomatic SARS-CoV-2 infection, confirmed on PCR or rapid antigen testing, through 14 days in participants who had a negative RT-PCR test at baseline.

A total of 2736 participants were randomly assigned



to a trial group — 921 to the 5-day nirmatrelvir–ritonavir group, 917 to the 10-day nirmatrelvir–ritonavir group, and 898 to the placebo group. The study found that across more than 2,700 exposed adults in the trial, symptomatic confirmed infections at 14 days occurred in 2.6% of those taking a 5-day course of the antiviral medication, 2.4% of those receiving a 10-day course, and 3.9% of the placebo

Dr. Septimus's Annotations

recipients The differences versus the placebo group were not statistically significant. The incidence of adverse events was similar across the trial groups, with dysgeusia being the most frequently reported adverse event (in 5.9% and 6.8% of the participants in the 5-day and 10-day nirmatrelvir–ritonavir groups, respectively, and in 0.7% of those in the placebo group.

Demographic and Covid-19–related characteristics were similar in the two groups. 46.8% of the participants were men, the median age was 42 years (range, 18 to 91), and 72.0 to 73.3% of the participants across the trial groups had coexisting medical conditions associated with the risk of severe Covid-19. Vaccinations rates were the same in all groups.

In this placebo-controlled trial, postexposure prophylaxis with nirmatrelvir–ritonavir did not result in a significant reduction in the risk of development of symptomatic SARS-CoV-2 infection among participants who were household contacts of persons with Covid-19 and initially had a negative PCR or rapid antigen test. An important aspect of the current trial is that a substantial percentage of participants were seropositive for SARS-CoV-2 (approximately 91%) at baseline. Seroprevalence is likely to remain more than 90% because of previous infection and/or vaccination. It is possible that high baseline seropositivity rates observed in this trial led to the lower-than-expected rates of household transmission. Given the distinctive taste of nirmatrelvir–ritonavir, participants may have suspected that they were receiving active medication, which may have limited the effectiveness of the blinding. Another limitation is the lack of detailed data on the index patients (e.g., diagnostic details and details on treatments), since they are not direct participants in the trial and have not given consent to provide information.

Earlier this year[ID watch May 2024], the same investigators published a study examining the efficacy of nirmatrelvir–ritonavir treatment in patients who are at standard risk for severe Covid-19 or who are fully vaccinated and have at least one risk factor for severe Covid-19.[N Engl J Med 2024;390:1186-95] They reported 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, however, the study participants were younger without significant comorbidities.

BOTTOM LINE

In this placebo-controlled trial, postexposure prophylaxis with nirmatrelvir–ritonavir for 5 or 10 days did not significantly reduce the risk of symptomatic SARS-CoV-2 infection.