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Infectious Diseases Watch

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General Infectious Diseases

Procalcitonin monitoring and antibiotic duration in presumed lower respiratory tract infections: a propensity score-matched cohort across the Veterans Health Administration

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The goal of this study was to compare antibiotic duration for LRTIs with and without procalcitonin testing in real-life practice. The investigators performed a retrospective cohort study that included all acute-care hospital admissions for presumed LRTIs between January 2018 to December 2021 at 81 Veterans Affairs facilities with on-site procalcitonin testing. The exposure was procalcitonin testing; the primary outcome was antibiotic duration. We used 1:1 nearest-neighbor propensity score matching to estimate the difference in outcome between procalcitonin-tested and non-tested patients. Hospital encounters for presumed LRTIs were identified by either (1) ICD-10 codes for pneumonia or acute exacerbations of COPD during the hospital stay or at hospital discharge; or (2) receipt of an antibacterial regimen specific for community-acquired pneumonia (e.g., a macrolide plus an anti-pneumococcal beta-lactam) during the first 48 hours of the treatment course. Cases of pneumonia were classified as community-acquired versus hospital-acquired based on the timing of antibacterial initiation (≤ 48 hours from admission versus >48 hours after admission, respectively).

The primary outcome was length of antibiotic therapy, defined as the number of unique inpatient calendar days a patient received a antibacterial agent, regardless of the number of different drugs administered. Length of therapy included the sum of both inpatient and post-discharge antibiotic therapy. Post-discharge therapy was defined as previously described.15 Secondary outcomes were chosen to describe additional markers of antibiotic duration as well as potential antibiotic associated complications. Days of therapy was defined as the aggregate sum of days for which any amount of a specific antibiotic agent was administered. Patients were considered to have antibiotic associated diarrhea if they had a stool sample collected for *Clostridioides difficile* testing on or after hospital day 4 and within 30 days of hospital discharge; patients were considered to have *C. difficile* infection (CDI) if they received an antibiotic for CDI (oral vancomycin, metronidazole, or fidaxomicin) within 72 hours of a positive *C. difficile* test result. Hospital-readmission and/or death was measured as a composite outcome within 30 days of the patient's discharge.

35,610 patients with LRTIs were included (6,015 [16.9%] with procalcitonin testing; 29,595 [83.1%] without testing). In tested patients, the median number of procalcitonin levels checked

was 2 (interquartile range, 1-3). Mean antibiotic duration was 10.0 days in the procalcitonin group compared to 8.3 days in non-tested patients (unadjusted difference 1.7 days; $p < 0.0001$). After propensity-score matching with 3,903 pairs, antibiotic duration remained greater in the procalcitonin group (9.6 days vs. 9.2 days; $p < 0.0001$). In a sub-group analysis of 2,241 tested patients with a procalcitonin value at the standard threshold for antibiotic discontinuation, antibiotic duration was shorter in tested vs. non-tested patients with a mean difference of 0.1 days ($p<0.01$). The procalcitonin-tested group also had more days of antibiotic therapy (unadjusted mean difference 1.1 days; $p<0.01$) and an increased odds of antibiotic-associated diarrhea (OR 1.48, 95% CI, 1.26-1.74) but similar rates of *C. difficile* infection (OR 1.23, 95% CI: 0.76-2.00)

Among procalcitonin values checked after the first 48 hours of antibiotics, there were 3,435 (57.1%) patients who had a procalcitonin value that met the standard threshold for antibiotic discontinuation (i.e. procalcitonin ≤ 0.25 ng/mL or >80% decrease from their maximum procalcitonin value): 1,057 (30.8%) of these patients had antibiotics stopped within 24 hours of meeting this threshold while 1,737 (50.6%) remained on antibiotics for more than 24 hours after the threshold was reached. For the latter category, the mean duration of excess antibiotics after meeting the discontinuation threshold was 3.2 days (standard deviation 2.7). The remaining 641 (18.7%) patients had antibiotics stopped more than 24 hours before the procalcitonin threshold for antibiotic discontinuation was met.

Comment*:* In this retrospective propensity-matched cohort of patients with presumed LRTIs across a geographically diverse group of hospitals, patients who underwent procalcitonin testing did not have a meaningful reduction in antibiotic duration compared to those who were not tested. Their findings contrast with the majority of the published clinical trials on procalcitonin use in acute respiratory infections. A meta-analysis of 24 largely European randomized controlled trials found that the measurement of procalcitonin in acute respiratory infections reduced antibiotic exposure by 2.4 days (8.1 vs. 5.7 days).[Lancet Infect Dis. 2018;18:95- 107. However, in a more recent multicenter randomized controlled trial of patients presenting to EDs at US hospitals for a presumed LRTI, there was no significant difference in the antibiotic length of therapy or antibiotic-related adverse events with a procalcitonin-guided protocol.[N Engl J Med. 2018;379:236-249]

There may also have been inter-provider variability in both procalcitonin testing and antibiotic use, which we were unable to account for in our analysis. Residual confounding could explain why patients who had procalcitonin monitoring also had more adverse outcomes than patients who were not tested. Second, we were unable to differentiate antibiotic use intended to treat LRTIs from antibiotic use for non-respiratory infections. They relied on diagnostic codes and, in some cases, antibiotic selection to characterize clinical suspicion for LRTIs without a more in-depth validation of this diagnosis. While patients without confirmed LRTIs may have been inadvertently included in our analysis,

In the end I believe poor implementation of procalcitonin testing may have undermined its effectiveness. This lack of effectiveness may be the result of testing practices that differed from how procalcitonin has been studied. In these hospitals, the test was not ordered routinely on eligible patients, procalcitonin levels were not serially monitored, and standard procalcitonin thresholds for stopping antibiotics were frequently not followed. The inadequate implementation of procalcitonin in this study was similar to a study in community hospitals especially in regard

to serial monitoring and discontinuing of antibiotics when thresholds were reached to stop antibiotics. [A J Health-Sys Pharm 2020, 77: 632–635].

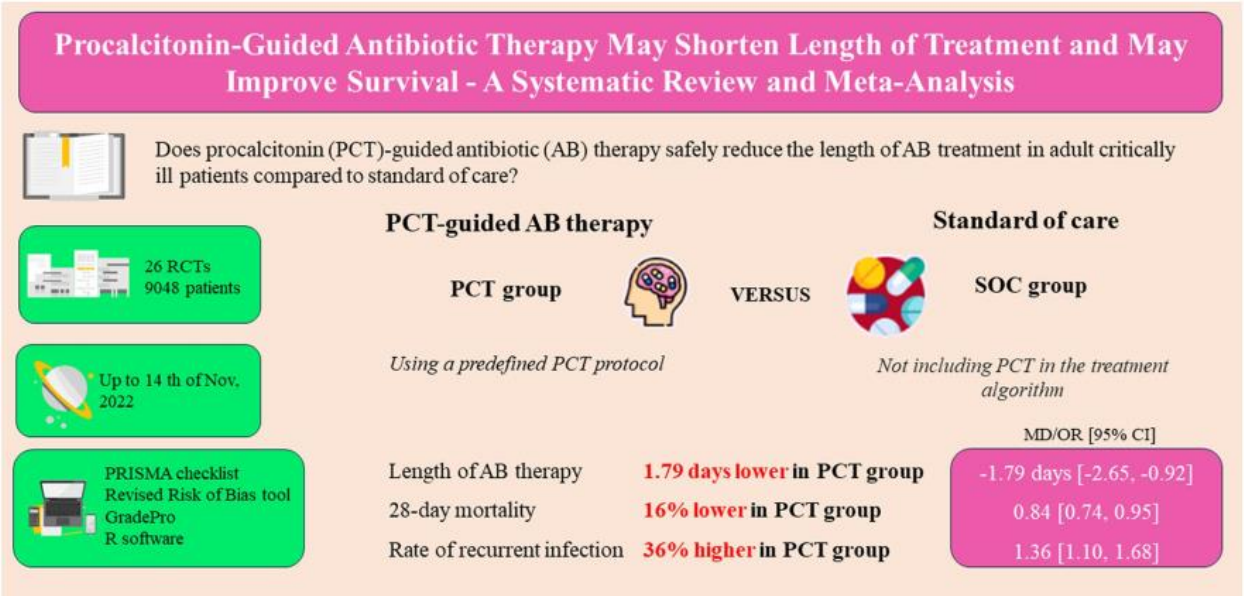
Bottom line: These results suggest that facilities should develop and enforce criteria for PCT use in not only patients with LRTI, but other infections as well See next article.

Procalcitonin-guided antibiotic therapy may shorten length of treatment and may improve survival—a systematic review and meta-analysis Critical Care (2023) 27:394

doi.org/10.1186/s13054-023-04677-2

The authors aim was to compare the effects of PCT-guided AB therapy with standard of care (SOC) in critically ill patients. They searched databases CENTRAL, Embase and Medline. They included randomized controlled trials (RCTs) comparing PCT-guided AB therapy (PCT group) with SOC reporting on length of AB therapy, mortality, recurrent and secondary infection, ICU length of stay (LOS), hospital LOS or healthcare costs. They also did subgroup analyses in studies applying the Sepsis-3 definition. In the statistical analysis, a random-effects model was used to pool effect sizes.

They included 26 RCTs (*n*= 9048 patients) in the quantitative analysis. In comparison with SOC, length of AB therapy was significantly shorter in the PCT group (MD - 1.79 days, 95% CI: -2.65, - 0.92) and was associated with a significantly lower 28-day mortality (OR 0.84, 95% CI: 0.74, 0.95). In Sepsis-3 patients, mortality benefit was more pronounced (OR 0.46 95% CI: 0.27, 0.79). Odds of recurrent infection, however, were significantly higher in the PCT group (OR 1.36, 95% CI: 1.10, 1.68), but there was no significant difference in the odds of secondary infection (OR 0.81, 95% CI: 0.54, 1.21), ICU and hospital length of stay (MD - 0.67 days 95% CI: - 1.76, 0.41 and MD - 1.23 days, 95% CI: - 3.13, 0.67, respectively).



Comment: PCT-guided AB therapy may be associated with reduced AB use, lower 28-day mortality but higher infection recurrence, with similar ICU and hospital length of stay. In the control arm, SOC was not “standardized” as different AB guidelines were applied in different

institutions that could potentially result in longer duration of AB therapy in some regions, thus overestimating the effect of PCT guidance. Second, PCT guidance was not standardized as studies applied different PCT protocols: 16 out of 26 included studies used PCT protocol to stop ABs, 3 used PCT protocol to start ABs, while 7 used PCT guidance for both starting and stopping AB therapy. Furthermore, not all studies reported on all outcomes. They did not know whether patients received appropriate or inappropriate ABs in the same or similar proportion in the PCT-guided and control groups as this outcome was only reported in 5 studies. Lastly all studies excluded immunocompromised patients.

Bottom line: Their results suggest the need for better designed studies investigating the role of PCT-guided AB stewardship in critically ill patients. The higher risk of recurrence needs further study.

Switch to oral antibiotics in gram-negative bacteraemia; A randomised, open-label, clinical trial. Clin Microbiol Infect published online October 17, 2023

https://doi.org/10.1016/j.cmi.2023.10.014

The investigators set out to study if it is safe to switch from IV to oral antibiotics for patients with gram-negative BSIs which has traditionally been managed with a full course of IV antibiotics. To address this issue, they performed a multicenter open-label, randomized trial of adults with monomicrobial Enterobacterales bacteremia caused by a strain susceptible to ≥1 oral beta-lactam, quinolone, or trimethoprim/sulfamethoxazole. Inclusion criteria included completion of 3–5 days of microbiologically active IV therapy, being afebrile and hemodynamically stable for ≥48 hours, and absence of an uncontrolled source of infection. Pregnancy, endocarditis, and neurological infections were exclusion criteria. Randomization, stratified by urinary source of bacteremia, was to continue IV (IV Group) or to switch to oral therapy (Oral Group). Agents and duration of therapy were determined by the treating physicians. The primary endpoint was treatment failure, defined as death, need for additional antimicrobial therapy, microbiological relapse, or infection-related re-admission within 90 days. The non-inferiority threshold was set at 10% in the 95% CI for the difference in the proportion with treatment failure between the Oral and IV Groups in the modified intention-to-treat population. Using an estimated primary outcome rate of 16%, it was estimated that the inclusion of 438 evaluable subjects in the primary endpoint analysis would result in 80% power to demonstrate non-inferiority of oral switch within a 10% margin of a 95% CI, with a two-sided Type I error rate of 5%. However, the Covid-19 pandemic resulted in severe disruption of clinical research at all the study sites. Given the severe and persistent impact on recruitment, and in consultation with the study's Data Safety and Monitoring Board, the Study Steering Committee decided to close the trial for further enrollment early.

In the end a total of 176 adults (mean age, 57) with gram-negative BSIs were enrolled. The source of bacteremia was most often the urinary tract (60%). E coli (67%) and Klebsiella spp. (24%) were the most prevalent pathogens. Of the tested isolates, 16% were ESBL producers and 3% were resistant to carbapenems. Eligible participants were randomized after 3–5 days of IV therapy to continued IV treatment or a switch to oral therapy provided they had received adequate source control, they were afebrile and hemodynamically stable for ≥48 hours, and the isolate was susceptible to an oral antibiotic.

The median duration of antibiotic treatment was 11 days (IV group) and 14 days (oral group). Treatment failure (relapse, death, need for additional antimicrobial therapy, or 90-day infection-related readmission) occurred with similar frequency in the IV (26%) and oral (22%) groups. Hospital stay was significantly longer in the IV group than the oral group (9 vs. 6 days).

Comment: Switching from intravenous to oral antibiotic therapy has been shown to be as efficacious as continued IV treatment, even for infective endocarditis [N Engl J Med 2019; 380:415] or bone and joint infections [N Engl J Med 2019; 380:425]. More than 70% of the patients who were screened for enrolment in this study were not eligible, suggesting that switch to oral therapy may not be feasible in many patients with Enterobacterales bacteremia. Approximately 23% of those who were screened were excluded because of a lack of an active oral antimicrobial agent. Oral options for the treatment of multidrug resistant Enterobacterales may expand further with the potential future availability of oral carbapenems (e.g., tebipenem) and newer oral beta lactam/b-lactamase inhibitors (e.g., ceftibuten/avibactam). The study was small due to Covid-19 and the duration of therapy especially for oral therapy was longer than recommended.

Bottom line: Despite some limitations this study adds to the growing evidence that patients who respond to initial IV therapy and have source control can be safely switched to oral therapy providing the organism is susceptible and the oral agent has good oral bioavailability.

Risk factors for recurrence of community-onset urinary tract infections caused by extended spectrum cephalosporin resistant Enterobacterales OFID published online November 8, 2023

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Extended spectrum cephalosporin-resistant Enterobacterales (ESCrE) are increasingly reported as a cause of community-onset urinary tract infections (UTIs), including recurrent infections. The investigators in this paper evaluated risk factors for recurrence among patients with community onset ESCrE UTI. To address this question, the investigators performed a retrospective cohort study including adults with community-onset ESCrE UTI in Duke University Health System from April 2018 through December 2021. ESCrE UTI recurrence by the same species was assessed 14 to 180 days (i.e. 6 months) after completion of antibiotic treatment. They evaluated the relationships between candidate risk factors and time to recurrence using Cox proportional hazards regression models.

Among 1,347 patients with community-onset ESCrE UTI, 202 (15.0%) experienced recurrent infection during the 6-month follow-up period. In univariate analysis, risk factors for UTI recurrence included K. pneumoniae infection (hazard ratio [HR] = 1.6, 95% confidence interval [CI] = 1.1 to 2.1, p = 0.007), diabetes mellitus (HR = 1.5, 95% CI = 1.1 to 2.0, p=0.004), chronic renal insufficiency (HR = 1.6, 95% CI = 1.2 to 2.2, p<0.001), neurogenic bladder (HR = 2.1, 95% CI = 1.4 to 3.0, p<0.001), history of UTI within one year preceding the index ESCrE UTI (HR = 2.8, 95% CI = 2.0 to 3.8, p<0.001), fluoroquinolone non-susceptibility (HR = 1.6, 95% CI = 1.1 to 2.2, p = 0.006), and trimethoprim-sulfamethoxazole non-susceptibility (HR = 1.4, 95% CI = 1.0 to 1.8, p= 0.04). In multivariate analysis, risk factors for rUTI included neurogenic bladder (adjusted HR [aHR] = 1.8, 95% CI = 1.2 to 2.6, p = 0.005), history of UTI within one year (aHR = 2.4, 95% CI = 1.7 to 3.3, p<0.001), and fluoroquinolone non-susceptibility (aHR = 1.5, 95% CI =

1.1 to 2.1, p = 0.02). The association between K. pneumoniae infection and recurrence was not statistically significant in multivariate analysis (aHR = 1.4, 95% CI = 1.0 to 1.9, p = 0.06). Neither inappropriate initial therapy (unadjusted HR = 0.87, 95% CI = 0.66 to 1.15, p = 0.34; aHR = 1.02, 95% CI = 0.75 to 1.39, p = 0.91) nor inappropriate definitive therapy (unadjusted HR = 0.8, 95% CI = 0.6 to 1.2, p = 0.35; aHR = 0.9, 95% CI = 0.6 to 1.4, p = 0.59) predicted recurrence in univariate or multivariate analysis. Duration of antibiotic therapy was also not associated with recurrence (unadjusted HR per one day increase in duration = 1.0, 95% CI = 1.0 – 1.0, p = 0.60; aHR = 1.0, 95% CI = 1.0 – 1.0, p = 0.25). In a sensitivity analysis restricted to patients with specific signs or symptoms of UTI documented in the medical record (N=823), K. pneumoniae infection (aHR = 1.6, 95% CI = 1.0 to 2.3, p= 0.03), neurogenic bladder (aHR = 1.9, 95% CI = 1.2 to 3.1, p = 0.009), and history of UTI within one year (aHR = 2.7, 95% CI = 1.7 to 2.1, p<0.001) were identified as independent risk factors for recurrence. The association between fluoroquinolone nonsusceptibility and recurrence was not statistically significant in this analysis (aHR = 1.5, 95% CI 1.0 to 2.3, p = 0.06).

Comment: This study is the first to examine risk factors for recurrence of community onset ESCrE UTIs. This study and others confirm that the threat of ESCrE is not just limited to healthcare settings but increasingly is being seen in the community. A meta-analysis of ESBL E coli intestinal colonization among healthy individuals reported a global pooled prevalence of 16.5% in 2003-2018, with an increase in pooled prevalence from 2.6% in 2003-2005 to 21.1% in 2015-2018. [J Antimicrob Chemother. 2021; 76:22-29] Additionally, a study of ESBL-producing bacterial infections in community hospitals in the southeastern US demonstrated a significant rise in community-associated ESBL-producing E. coli infections from 2009 to 2014, with community-associated infections comprising nearly one quarter of all ESBL producing E. coli infections in the study cohort. [Infect Control Hosp Epidemiol. 2016;37(1):49-54] Among community-onset ESCrE infections, the majority as expected were UTIs.

Not surprisingly, neurogenic bladder was found to be a strong risk factor for ESCrE UTI recurrence. UTI is a leading cause of morbidity associated with neurogenic bladder, occurring among greater than one-third of patients during the first year after diagnosis and accounting for over 20% of hospitalizations among patients with neurogenic bladder. [Neurourol Urodyn. 2011;30(3):395-401] There was a high prevalence of non-susceptibility to most oral antibiotic agents, including 69% non-susceptibility to fluoroquinolones and 62% non-susceptibility to trimethoprim sulfamethoxazole, highlighting the limited therapeutic options for these infections. Approximately one-half of patients in this cohort initially received an empiric antibiotic agent to which the pathogen was susceptible, with greater than one-quarter receiving ceftriaxone as the initial antibiotic. Given the retrospective nature of this study, the cohort may have included patients with asymptomatic bacteriuria who were inappropriately treated with antibiotics. ESBL phenotypic testing was not routinely performed in their clinical microbiology laboratories, so this study is unable to distinguish between UTIs caused by ESBL-producing versus non-ESBL-producing ESCrE.

Bottom line: This study reflects an unmet need to develop and implement strategies that improve the prediction of ESCrE or ESBL UTI at the point of care.

Editor's Choice

IWGDF/IDSA Guidelines on the Diagnosis and Treatment of Diabetes-related Foot Infections (IWGDF/IDSA 2023) Clin Infect Dis published online October 2, 2023

doi.org/10.1093/cid/ciad527

Recommendations were recently updated by the International Working Group on the Diabetic Foot/Infectious Diseases Society of America (IWGDF/IDSA) to guide the management and diagnosis of DFI.

Key Recommendations and Updates

- Severity and diagnosis of DFI both depend on local and systemic symptoms.
- Assess inflammatory serum biomarkers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), or procalcitonin (PCT) in a person with diabetes and a possible infected foot ulcer for whom the clinical examination is diagnostically equivocal or uninterpretable.
- Consider culturing tissue aseptically sampled by wound curettage or biopsy.
- If plain x-rays and probe-to-bone testing are inconclusive for suspected osteomyelitis, MRI should be performed.
- Bone sampling (intraoperative or percutaneous) should be obtained for culture in osteomyelitis cases.
- Antibiotics should be avoided in the absence of signs or symptoms of infection in diabetic foot ulcers.
- For DFI involving skin and soft tissue, treatment duration is typically 1–2 weeks (up to 4 weeks if improvement is slow).
- Target aerobic gram-positive pathogens only (beta-hemolytic streptococci [Group B strep] and Staphylococcus aureus including methicillin-resistant strains if indicated) for people with a mild DFI, who have not recently received antibiotic therapy, and who reside in North America or Western Europe.
- Do not empirically target antibiotic therapy against P. aeruginosa in cases of DFI in temperate climates but use empirical treatment of P. aeruginosa if it has been isolated from cultures of the affected site within the previous few weeks, or in a person with moderate or severe infection who resides in Asia.
- In patients with DFI-associated osteomyelitis and amputation with positive bone margins, antibiotics are suggested for 3 weeks; for those patients without amputation, 6 weeks are recommended.
- Urgent surgical consultation should be obtained in cases of severe infection or moderate DFI complicated by extensive gangrene, necrotizing infection, signs suggesting deep (below the fascia) abscess, compartment syndrome, or severe lower limb ischemia.
- In people with diabetes, PAD and a foot ulcer or gangrene with infection involving any portion of the foot obtain an urgent consultation by a surgical specialist as well as a vascular specialist in order to determine the indications and timings of a drainage and/or revascularization procedure.

- Adjunctive therapies (e.g., G-CSF, topical antiseptics, silver, honey, bacteriophages, topical antibiotics, hyperbaric oxygen) are not recommended.

Comment: This is a comprehensive update, but most of recommendations are either low quality or best practice statements. Nonetheless, these guidelines provide a roadmap based on the best available evidence. Facilities should create multidisciplinary teams to manage this patient population. See next article.

Executive Summary: Evaluation and Management of Diabetes-related Foot Infections

Clin Infect Dis 2023; 77:335–337.

doi.org/10.1093/cid/ciad429

Key Recommendations

- *Surgical debridement:* if present, drain deep purulence and excise necrotic tissue. Assess risk of amputation using clinically validated criteria (WIfI[validated predictor of both a patient's risk of amputation and potential benefit from revascularization]) and if elevated request surgical evaluation and risk-benefit/shared decision-making
- *Peripheral artery disease:* Obtain relevant vascular studies (e.g. toe pressure measurements); request vascular surgery evaluation if patient is likely to benefit from revascularization (i.e., by WIfI classification).
- *Antibiotic therapy:* Once patient is stabilized and has responded to initial antimicrobial therapy, select an appropriate oral (or IV) definitive antimicrobial regimen, with considerations including:
    - The results of the patient's deep tissue cultures, or the local epidemiology and antibiogram if cultures are not available.
    - Duration appropriate to the degree of infection and surgical management provided.
    - Social factors, including the ability to adhere to the regimen (e.g., affordability, pill burden, ability to store and administer IV antibiotics or travel to infusion centers) and whether giving IV antibiotic therapy inpatient or via SNF facilitates access to other needed care (e.g., wound care)
- *Offloading:* Provide the patient with either a non-removable device (e.g., total contact cast) or removable device (i.e., surgical boot) to provide mechanical off-loading of the diabetic foot wound; consider surgical off-loading referral for select patients who do not heal with mechanical devices.
- *Wound care:* Secure longitudinal outpatient follow up with a wound care specialist who can provide serial assessment, debridement, and appropriate dressings or negative pressure wound therapy. Ensure the patient has access to adequate wound care supplies upon discharge and at each follow up visit.
- *Glycemic control:* Initiate or intensify diabetes treatment to achieve goal HbA1c to optimize wound healing
    - Goal HbA1c for most adults is <7% (comparable continuous glucose monitoring targets are time in range >70% with time below range <4%). Higher or lower glycemic targets may be appropriate based on individual's comorbidities and risk of hypoglycemia.

- *Concurrent foot pathology:* Identify and address other conditions that provide a bacterial portal of entry into the foot or otherwise predispose to infection:
    - Treat onychomycosis and tinea pedis if present
    - Offer compression garments and recommend leg elevation if venous stasis is present and degree of PAD allows.
    - Recommend daily moisturizer to areas of dry, cracked skin.
    - Arrange longitudinal follow-up every three months, preferably by a podiatrist, for secondary prevention and early detection of ulcers/infection.

Comment: This article and the previous review are worth sharing with colleagues involved in the shared decision-making about antimicrobial and surgical therapies for DFI and diabetes-related foot osteomyelitis. The key is multidisciplinary collaborations. I suggest infectious disease clinicians familiarize themselves with the Society for Vascular Surgery's WIfI (Wound, Ischemia, Foot infection) classification system, which iterates on the 2012 IDSA DFI criteria with wound and ischemia staging. WIfI, a validated predictor of both a patient's risk of amputation and potential to benefit from revascularization, incorporates key factors informing our surgical and podiatric colleagues' practice.

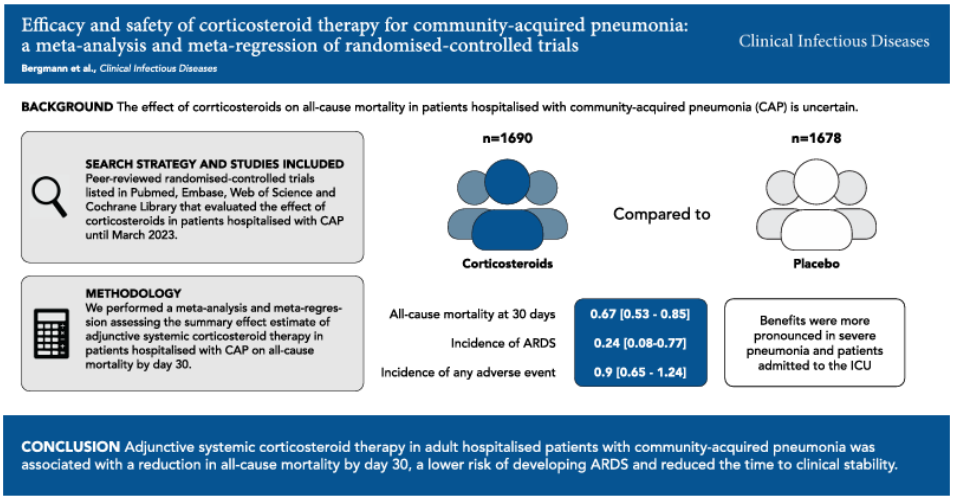
Efficacy and Safety of Corticosteroid Therapy for Community-Acquired Pneumonia: A Meta-Analysis and Meta-Regression of Randomized, Controlled Trials

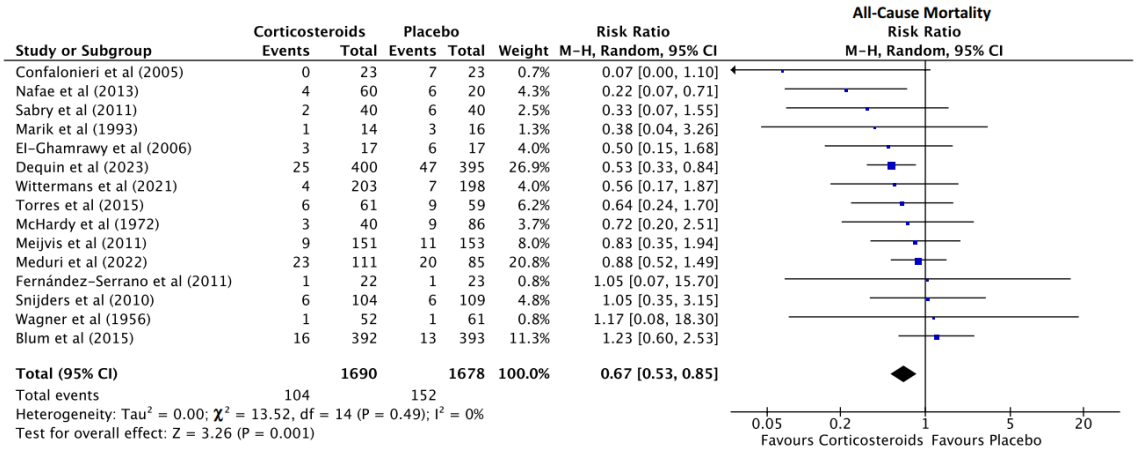
Clin Infect Dis published online October 25, 2023

doi.org/10.1093/cid/ciad496

For this meta-analysis and meta-regression, the authors conducted a systematic search of trials that evaluated the effect of corticosteroid therapy in patients hospitalized with CAP through March 2023. They included randomized, controlled trials, comparing adjunctive corticosteroid therapy with the standard of care alone for treatment of patients hospitalized with CAP and reporting all-cause mortality. They excluded retrospective analyses, observational data, and trial protocols. The primary outcome was all-cause mortality within 30 days after hospital admission. The safety analysis included the frequency of adverse events and steroid-associated adverse events.

The literature search identified 35,713 citations, of which 15 studies and 3367 patients were eligible for the final analysis. The all-cause mortality at 30 days was significantly lower in the corticosteroid group (104 of 1690, 6.15%) than in the control group (152 of 1677, 9.06%; risk ratio [RR], 0.67; 95% confidence interval [CI], .53 to .85; *P* = .001; I2 = 0%). In 9 studies (2549 patients) that reported the occurrence of adverse events, corticosteroid therapy was not associated with an increased risk of developing any adverse event compared with standard care (RR, 0.90; 95% CI, .65 to 1.24; *P* = .5; I2 = 88%).





Comment: Subgroup analysis demonstrated benefits were more pronounced in patients with severe pneumonia and patients admitted to the ICU. This is consistent with recent studies and subgroup analyses suggesting that the benefit of adjunctive corticosteroid therapy may vary depending on the severity of CAP, similar to the results of recent studies reviewed in ID Watch [N Engl J Med 2023; 388:1931-1941; Chest 2023; 163:484-497]. The use of corticosteroids was generally well tolerated and did not result in a higher overall frequency of adverse events. However, they found an increased incidence of hyperglycemia in the corticosteroid group. Despite potential corticosteroid-associated immunosuppression, they did not find any association between adjunctive corticosteroid use and secondary infections. There were differences in various types of corticosteroids, dosing strategies, and routes of administration used in the included studies, which may have introduced heterogenicity into their analysis.

Bottom line: This study and others support use of adjunctive steroids for patients with severe CAP.

Impact of doxycycline on Clostridioides difficile infection in patients hospitalized with community-acquired pneumonia Am J Infect Control published online November 1, 2023

doi.org/10.1016/j.ajic.2023.09.007

This was a retrospective analysis conducted in hospitalized patients in Veterans Affairs Hospitals (VAH) across the US to determine if doxycycline was associated with a decreased risk of CDI. The primary outcome was the development of CDI within 30 days of initiation of doxycycline or azithromycin, as part of a standard pneumonia regimen.

Approximately 156,107 hospitalized patients who received care at a VAH and were diagnosed with CAP during the study timeframe were included. A 17% decreased risk of CDI was identified with doxycycline compared to azithromycin when used with ceftriaxone for the treatment of pneumonia (P = .03). In patients who had a prior history of CDI, doxycycline decreased the incidence of CDI by 45% (odds ratio 0.55; P = .02).

Comment: This study confirms prior studies that demonstrated doxycycline has a lower risk of CDI compared to azithromycin in combination with ceftriaxone in patients treated for CAP. [Clin Infect Dis. 2012; 55:615–620; Clin Infect Dis. 2022; 75:118–24]

The overall incidence of CDI in patients without a prior history of CDI was low at 0.7%. However, the incidence rose significantly in those with a history of CDI (12.2%). In the subset of patients who had CDI within the prior year, doxycycline had the biggest impact on CDI occurrence Although the overall incidence of C difficile was low in this study, patients had a 17% decreased risk of CDI when they received doxycycline with ceftriaxone as opposed to azithromycin in the whole model. In the subset of patients who had no history of CDI in the year prior, doxycycline did not result in a statistical reduction in CDI. In patients who had a prior history of CDI, doxycycline decreased the incidence of CDI by 45%.

This study includes results that may not be generalizable since the study population were predominantly older, male veterans. They were unable to confirm the diagnosis of CAP and instead relied on admission data combined with antibiotic choice and ICD coding. This was an observational study and residual confounding may impact the results. CDI was confirmed with PCR and confirmatory toxin testing and treatment were not used to confirm clinical disease.

Bottom line: Doxycycline was associated with a lower risk of CDI compared to azithromycin when prescribed for CAP especially if they had a history of C diff in the last year. Thus, patients who are at such risk may benefit from doxycycline as a first-line agent for atypical coverage, rather than the use of a macrolide antibiotic, if Legionella is not of concern.

The effectiveness of fascial closure with antimicrobial coated sutures in preventing incisional surgical site infections in gastrointestinal surgery: a systematic review and meta-analysis

J Hosp Infect 2023 Sep 19: S0195-6701(23)00293-1

doi.org/10.1016/j.jhin.2023.09.006

National advisory groups have expressed different views on the use of antimicrobial-coated sutures. The aim of this paper was to conduct a systematic review and meta-analysis of the efficacy of fascial closure using antimicrobial-sutures specifically for the prevention of surgical site infections (SSIs) in GI surgery, as part of the revision of the SSI prevention guidelines of the Japanese Society of Surgical Infectious Diseases (JSSI). They searched CENTRAL, PubMed and ICHUSHI-Web in May 2023, and included randomized controlled trials (RCTs) comparing antimicrobial-coated and non-coated sutures for fascial closure in gastrointestinal surgery (PROSPERO No. CRD42023430377). Three authors independently screened the RCTs. They assessed the risk of bias and the GRADE criteria for the extracted data. The primary outcome was incisional SSI and the secondary outcomes were abdominal wall dehiscence and the length of postoperative hospital stay. This study was supported partially by the JSSI. A total of 10 RCTs and 5396 patients were included.

The use of antimicrobial-coated sutures significantly lowered the risk of incisional SSIs compared with non-coated suture (risk ratio: 0.79, 95% confidence intervals: 0.64e0.98). In subgroup analyses, antimicrobial-coated sutures reduced the risk of SSIs for open surgeries only, and when monofilament sutures were used. However, for colorectal surgeries only, antimicrobial-coated sutures did not reduce the risk of incisional SSI. Antimicrobial-coated

sutures did not reduce the incidence of abdominal wall dehiscence and the length of hospital stay compared with non-coated sutures. The certainty of the evidence was rated as moderate according to the GRADE criteria, because of the risk of bias.

Comment: In conclusion, the use of antimicrobial-coated sutures for fascial closure in GI surgery was associated with a significantly lower risk of SSI than non-coated sutures. A major weakness is that few RCTs described results as a function of wound classification. This is important as wound classification itself is a significant risk factor for SSI and should, therefore, be presented as a stratification factor. In addition, many studies did not report differences in abdominal closure techniques. Of interest, for colorectal surgeries only, antimicrobial-coated sutures did not reduce the risk of incisional SSI. Pre-operative and intra-operative antimicrobial administration are potential confounding factors for the incidence of SSI. A more reliable meta-analysis would be possible if RCTs were performed to address these limitations with uniform study designs for wound classification, fascial closing methods, antibacterial drugs, and stratified data presentation.

Bottom line: Future studies are needed to clarify the positive impact of antimicrobial-coated sutures as a function wound classification, abdominal closure technique used, adverse effects and cost.

Editor's Choice

Contemporary Management of *Staphylococcus aureus* Bacteremia—Controversies in Clinical Practice

Clin Infect Dis published online November 10, 2023

doi.org/10.1093/cid/ciad500

Since the publication of the 2011 IDSA guidelines on management of MRSA infections, the science of S aureus bacteremia (SAB) has evolved with the emergence of newer diagnostic strategies and therapeutic options. In this review, the authors seek to update the evaluation and management of SAB, with special focus on areas where the highest level of evidence is weak.

Traditionally, SAB has been described as "complicated" or "uncomplicated.". This classification uses host factors and clinical course to guide treatment decisions but may not fully account for the heterogeneity of SAB presentations. More recently, experts have argued for a shift towards classifying patients by "risk" for complications, using this distinction to guide further diagnostic evaluation and, ultimately, treatment decisions. [J Infect 2023; 86:9-13] see below.

Conventional Classification	Risk-Informed Evaluation and Treatment
"Uncomplicated SAB" • Exclusion of endocarditis • No implanted prostheses • Negative follow-up cultures at 2–4 d • Defervescence within 72 h of antibiotics • No evidence of metastatic sites of infection "Complicated SAB" • Not meeting criteria for uncomplicated SAB	Predisposing host factors • Implanted prostheses • IDU • History of endocarditis Features of bacteremia • Duration • Community acquisition • Time to positivity • Treatment delay Clinical Course • Persistent fever • Unknown source of infection • Signs of metastatic infection

Abbreviations: IDU, injection drug use; MRSA, methicillin-resistant *Staphylococcus aureus*; SAB, *Staphylococcus aureus* bacteremia.

The minimum evaluation of the patient with SAB should include the following:

- A thorough history and physical examination, evaluating for the source (e.g., onset of symptoms, injection drug use, presence of indwelling lines, evidence of a skin/soft tissue infection), and potential sites of metastatic involvement (e.g., cardiac, skin, osteoarticular)
- Infectious diseases consultation
- Follow-up blood cultures
- Echocardiography

Highlights

- Greater sensitivity of TEE over TTE
- The choice to pursue TEE in the face of a negative TTE should be related to the pretest probability of IE, quality of TTE, and host risk factors. TTE alone may be sufficient in a subset of patients with SAB at relatively lower risk of IE, specifically those with nosocomial acquisition of bacteremia, sterile follow-up blood cultures, no permanent intracardiac device, no hemodialysis dependence, and no clinical signs of IE or a secondary focus of infection. Positive follow-up blood cultures should serve as a warning sign. The overall risk for complications and IE increases with any subsequent positive blood culture. Attributable mortality increases with each day of culture positivity [Clin Infect Dis 2020; 70:568-73]
- The POSITIVE, PREDICT, and VIRSTA prediction rules were used to evaluate in a prospective cohort of patients with SAB, and the VIRSTA score performed best with a negative-predictive value of 99.3% for IE. [Clin Infect Dis 2022; 75:1668-74] see below

POSITIVE Cutoff: >4		PREDICT Cutoff: ≥2 (for Day 5 Score)		VIRSTA Cutoff: ≥3	
Item	Points Assigned	Item	Points Assigned	Item	Points Assigned
TTP <9 h	5	ICD	2	Cerebral or peripheral emboli	5
TTP 9–11 h	3	Permanent pacemaker	3	Meningitis	5
TTP 11–13 h	2	Community acquisition	2	Permanent intracardiac device or previous IE	4
IV drug use	3	Healthcare acquisition	1	Preexisting native valve disease[a]	3
Vascular phenomena[b]	6	Positive culture after 72 h	2	IV drug use	4
Predisposing heart disease[c]	5			Positive culture after 48 h	3
				Community or healthcare-associated bacteremia	2
				Severe sepsis or septic shock	1
				C-reactive protein >190 mg/L	1

- PET/CT is an emerging imaging modality being incorporated into the diagnostic evaluation for SAB and IE. In a recent study of patients with SAB, PET/CT revealed a metastatic focus of infection in 70.8% of cases and was associated with lower mortality. [Clin Infect Dis 2021; 73:e3859-66]
- Evidence-based and guideline-supported practices in the treatment of SAB include the following:
    - Use of cefazolin or an anti-staphylococcal penicillin (ASP) for MSSA
    - Use and appropriate dosing of vancomycin or daptomycin for MRSA
    - Early source control
    - Treatment duration of 4–6 weeks for bacteremia with high-risk features and 2 weeks for uncomplicated SAB
- Whether ASPs versus cefazolin should be selected for the treatment of MSSA bacteremia is controversial. The AHA endocarditis guidelines suggest ASPs as first-line treatment for MSSA endocarditis, with cefazolin listed as an alternative. [Circulation 2015; 132:1435-86]
    - There has been concern about decreased efficacy of cefazolin in isolates noted to have the cefazolin inoculum effect (CzIE), an observed increase in minimum inhibitory concentrations (MICs) to 16 micrograms per mililiter or greater when drug susceptibility testing is performed with a 100-fold higher than standard inoculum of MSSA in vitro. [J Clin Microbiol 2022;60:e02495-21] In an observation study performed in Argentine hospitals where ASPs were not available, higher 30-day mortality (39.5% vs 15.2%) was seen in isolates positive for the CzIE, and multivariate logistic regression identified the CzIE as an independent predictor of mortality in their cohort. [OFID 2018;5:ofy123]
    - The authors conclude that given the uncertainty about the clinical implications of the CzIE, the preferable safety profile of cefazolin compared with ASPs, and the availability of large-scale observational data supporting the efficacy of cefazolin, they feel comfortable using cefazolin in most patients with MSSA bacteremia. My opinion is to initially use ASP for suspected high-inoculum infections.
- Vancomycin continues to be standard of care for most patients with MRSA bacteremia. Revised guidelines on the therapeutic monitoring of vancomycin for serious MRSA infections sought to help better navigate vancomycin's narrow therapeutic index by recommending that dosing be optimized through the use of individualized area under the curve (AUC) monitoring, thereby abandoning the use of trough-only pharmacokinetic monitoring as a surrogate for daily AUC values. [Am J Health Syst Pharm 2020;77:835-864]. Observational data suggest that day-2 AUCs over MIC values of 515 or less are associated with lower rates of AKI without increasing the incidence of treatment failure.
- Aside from vancomycin, daptomycin, is the only other antibiotic with a FDA indication for the treatment of MRSA bacteremia. Many experts argue that, while the FDA approved a dose of 6 mg/kg, higher doses (e.g., 8–12 mg/kg) of daptomycin are warranted in the

treatment of SAB, due to its concentration-dependent bactericidal activity and pharmacokinetic studies suggesting inadequate drug exposure in certain populations at a dose of 6 mg/kg. An analysis from the European Cubicin Outcomes Registry and Experience Study (in which 43% of infections were caused by S. aureus) found that use of doses 8 mg/kg/day or higher demonstrated numerically higher cure rates for patients with IE, were an independent predictor of clinical success, and did not have higher rates of adverse effects when compared with doses of 6 mg/kg/day or less. [Adv Ther 2015; 32:1192-1205] The authors conclude that given clinical experience with doses of up to 12 mg/kg/day (in enterococcal infections) and the relatively low rates of treatment-limiting toxicity, targeting a dose of 8–12 mg/kg/day is reasonable for SAB.

- Therapy for lack of response for MRSA bacteremia:
    - In vitro studies suggest synergistic activity between high-dose daptomycin and ceftaroline. [Antimicrob Agents Chemother 2013;57:66-73] The combination of daptomycin and ceftaroline has been evaluated in a retrospective cohort of 58 patients with MRSA bacteremia, where it was associated with numerically lower 30-day mortality compared with a matched cohort receiving standard-of-care antimicrobials. [OFID 2020;7:ofz538] The authors recommend while robust clinical trial data to support the combination of daptomycin and ceftaroline are limited, they favor this approach for salvage therapy for MRSA bacteremia due to in vitro synergy and the growing body of observational studies (utilizing an every-8-h dosing interval for ceftaroline). In my opinion, combination therapy may be more beneficial if initiated earlier, particularly in patients at higher mortality risk. Blinded, randomized, prospective studies are needed.
- There was an interesting discussion about what to do with prosthetic material that is definitively not the source of bacteremia and if needs to be removed in a case of SAB. In some situations, it may not be feasible, especially for devices/material where removal may be associated with higher morbidity (e.g., pacemakers, prosthetic valves, prosthetic joints). While hematogenous involvement of some devices may be clinically apparent (e.g., cardiovascular implantable electronic device [CIED] pocket infection, knee arthroplasty), others may be less obvious. In a retrospective study of patients with SAB and indwelling CIEDs without initial clinical evidence of a pocket infection, 34% of participants developed a CIED infection during their SAB episode. [Circ Arrhythm Electrophysiol 2013; 8:137-144] The 2010 AHA update on CIED infections suggests complete device removal in the setting of occult SAB due to high rates of bacterial seeding. [Circulation 2010; 121:458-477] In another study investigators found that 34% of patients with a prosthetic joint subsequently developed a periprosthetic joint infection (PJI).[Clin Infect Dis 2001;32:647-649] The use of PET/CT to assess involvement of indwelling protheses may reveal a metastatic focus of infection in patients without clinical evidence of infection.

Comment: The authors provide more recent evidence to update recommendations throughout this review regarding the evaluation and management of SAB, highlighting areas of ongoing uncertainty. Clinical trials are currently underway that hopefully provide answers.

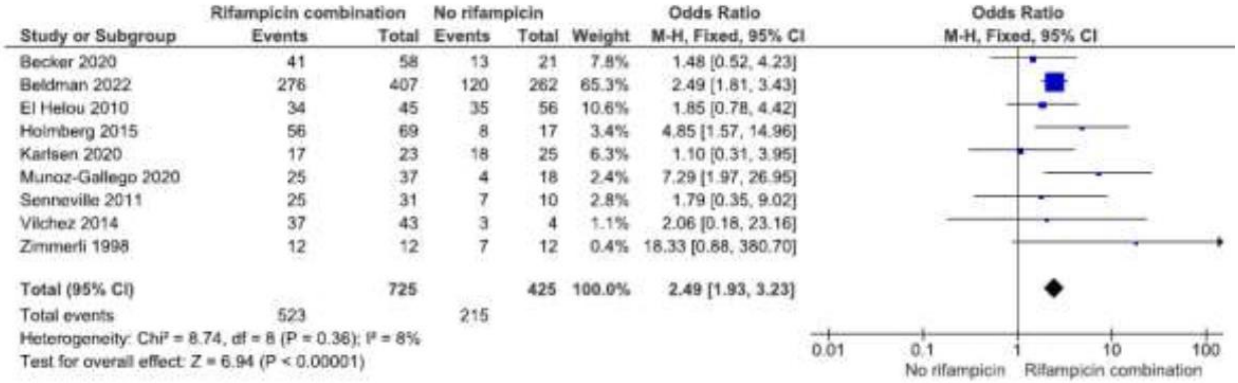
Clinical Outcomes of Rifampicin Combination Therapy in Implant-Associated Infections due to Staphylococci and Streptococci: A Systematic Review and Meta-analyses Int J Antimicrob Agents published online October 22, 2023

DOI: https://doi.org/10.1016/j.ijantimicag.2023.107015

The investigators did a systemic review and meta-analysis to evaluate the clinical outcomes of rifampin combination therapy in comparison to monotherapy in treating prosthetic joint infection (PJI) or prosthetic valve endocarditis (PVE) due to staphylococci and streptococci. They did a systematic search from inception to June 13, 2022, in Embase, Medline, Cochrane, and Web of Science to investigate the clinical outcomes of rifampicin combination therapy in comparison to monotherapy in treating staphylococcal and streptococcal prosthetic joint infection (PJI) or prosthetic valve endocarditis (PVE). Included were randomized clinical trials (RCTs) and observational studies.

Fourteen studies were included. Moderate quality of evidence was found in favor of rifampin in patients with staphylococcal PJI who underwent debridement, antibiotic and implant retention (DAIR) procedure (Odds Ratio 2.49 (95%CI 1.93 to 3.23). Including the two RCT's only, adding rifampin to the antibiotic regimen after DAIR was also in favor of rifampicin but not statistically significant (Risk Ratio 1.27 (0.79 to 2.04), n=126). Pooling data of patients with staphylococcal PJI that underwent a 2-stage procedure showed that adding rifampicin was not associated with added therapeutic success. Limited evidence was found for use of rifampin for PVE caused by staphylococci.

Adjunct rifampin versus no rifampin with joint retention



Comment: Adding rifampin in patients with prosthetic joint infection (PJI) due to staphylococci who underwent debridement surgery with implant retention was associated with a better clinical outcome. This observation was not noticed in patients with PJI due to staphylococci who underwent prosthetic removal presumably since the biofilm was removed with the implant and perhaps due to already excellent outcome in patients who undergo a two-stage approach. Due to the limited number of published studies, conclusion cannot be made on whether adding rifampin in patients with prosthetic valve endocarditis due to staphylococci or streptococci lead to a better clinical outcome. Systemic reviews on combination therapy with rifampin in PJI, have been published primarily focusing on DAIR only. [J Arthroplasty. 2022 37:1650–7]

Bottom line: Rifampin should be used in combination therapy for patients who undergo debridement, antibiotic and implant retention (DAIR) procedure due to staphylococci.

Microbial hitchhikers harbouring antimicrobial-resistance genes in the riverine plastisphere

Microbiome published online November 1, 2023 11:225

doi.org/10.1186/s40168-023-01662-3

To investigate the potential for river plastics to serve as vectors for pathogenic bacteria and reservoirs for ARGs, the researchers submerged strips of low-density polyethylene (LDPE)—the type of plastic used for plastic bags, shrink wrap, and thin container lids—for 7 days in the River Sowe, 1 kilometer (0.6 miles) downstream from a wastewater treatment plant. Some of the strips had been heated in an oven for 6 months to mimic the weathering process that occurs in nature. Pieces of wood were used as a control surface.

After a week in the water to establish biofilms on the plastic and wood samples, the investigators extracted DNA from the microbial communities and conducted a metagenomics analysis, comparing the diversity of the microbes that grew on the wood and plastic sample with that of the surrounding water (the planktonic environment).

The microbial communities that developed on the plastic and wood were similar to one another but quite different from those in the water samples. On the wood and plastic samples, species like *Pseudomonas, Acinetobacter,* and *Aeromonas* predominated, with *Pseudomonas* being more abundant on the weathered plastic—a finding the study authors suggest could be linked to the release of organic compounds that encourage the growth of specific bacteria.

The water samples, on the other hand, were dominated by pathogenic species like *Escherichia, Klebsiella, Salmonella*, and *Streptococcus,* which were also found in wood and plastic biofilms but in much lower quantities. The wood and plastic samples also contained more ARGs, and different ARG subtypes, than the water samples. The relative abundance of ARGs was clearly higher in the weathered plastic biofilms than in the other biofilms or the water samples.

In an additional experiment, the investigators found that exposing the plastic, wood, and water samples to sub-inhibitory but clinically relevant antibiotic concentrations—the kind that have been found in studies of wastewater and river sediment—increased the prevalence of their corresponding ARGs. But the different microbial communities in the samples were affected differently by each antibiotic.

Comment: The findings are noteworthy both because of the sheer volume of plastic debris that rivers carry to oceans each year (as much as 2 million metric tons, by some estimates) and the known ability of microbes to colonize plastic once it enters the water. In addition, the investigators note that plastics may facilitate the horizontal transfer of ARGs to pathogenic bacteria. It is too early to determine whether plastics can spread infection-causing, antibiotic-resistant bacteria and to quantify the health risk posed by plastic pollution. In addition, the abundance of opportunistic pathogens and ARGs found in the wood and water samples suggest future studies need to examine the entire river ecosphere as a potential reservoir for resistant pathogens. This study highlights concerns that the "riverine plastisphere" could serve as a reservoir of antibiotic resistance.

Society of Critical Care Medicine and the Infectious Diseases Society of America Guidelines for Evaluating New Fever in Adult Patients in the ICU Crit Care Med 2023; 51:1570-1586

DOI: 10.1097/CCM.0000000000006022

Fever, a frequent early indicator of infection, occurs in 26–88% of adult ICU patients, depending on the definition used and characteristics of the cohort studied. (1) The range of potential etiologies of fever is vast and includes both infectious and noninfectious causes. (2)

The CDC definition of fever in the diagnosis of hospital-acquired infections is a measured temperature of greater than 38°C [100.4 °F]. The Infectious Diseases Society of America (IDSA) has defined fever in individuals greater than 65 years old residing in long-term care facilities as a single oral temperature greater than 37.8°C [100 °F], repeated temperature measurements greater than 37.2°C[99 °F] (oral) or greater than 37.5°C[99.5 °F] (rectal), or an increase from baseline greater than 1.1°C [Clin Infect Dis 2009; 48:149–171] In patients with neutropenia due to chemotherapy, fever is defined by both the IDSA and the National Comprehensive Cancer Network as a single oral temperature measurement greater than or equal to 38.3°C[100.9 °F] or greater than 38.0°C sustained over at least 1 hour [J Natl Compr Canc Netw 2004; 2:390–432] The SCCM and IDSA have previously defined fever in ICU patients as the presence of a single temperature measurement greater than or equal to 38.3°C [Crit Care Med 2008; 36:1330–1349] They used this SCCM/IDSA definition of fever for this guideline.

Highlights

1. Central temperature monitoring methods, including thermistors for pulmonary artery catheters, bladder catheters, or esophageal balloon thermistors, are preferred when these devices are in place or accurate temperature measurements are critical to diagnosis and management. For patients without these devices in place, they suggest using oral or rectal temperatures over other temperature measurement methods that are less reliable (such as axillary or tympanic membrane temperatures, noninvasive temporal artery thermometers, or chemical dot thermometers) (weak recommendation, very low-quality evidence).
2. For critically ill patients with fever, they suggest avoiding routine use of antipyretic medications for the specific purpose of reducing the temperature (weak recommendation, moderate quality evidence).
3. For patients who develop fever during ICU stay, we recommend performing a chest radiograph (best-practice statement).
4. For patients who have recently undergone thoracic, abdominal, or pelvic surgery, we recommend performing CT (in collaboration with the surgical service) as part of a fever workup if an etiology is not readily identified by initial workup (best practice statement)
5. In patients with fever and recent abdominal surgery or in any patient with either abdominal symptoms or suspicion of an abdominal source (e.g., abnormal physical examination/POCUS, increased transaminases, or alkaline phosphatase, and/or bilirubin), they recommend performing a formal bedside diagnostic ultrasound of the abdomen (best-practice statement).

6. For ICU patients with fever without an obvious source and who have a central venous catheter, we recommend simultaneous collection of central venous catheter and peripherally drawn blood cultures to allow calculation of differential time to positivity (Best practice statement)
7. In patients with fever in the ICU in whom central venous catheter cultures are indicated, they recommend sampling at least two lumens (best-practice statement). One study showed that blood cultures should be collected through all catheter lumens to establish a diagnosis of catheter-related bloodstream infection; failure to separately collect blood from each lumen may lead to missed detection of bacteremia. (57)
8. When performing blood cultures in adult ICU patients, they recommend collecting at least two sets of blood cultures (ideally 60mL of blood total) [this is higher than 40mL usually recommended] one after the other, from different anatomical sites, without a time interval between them (best practice statement) Proper filling of blood culture bottles (10mL per bottle) is important; subpar filling can decrease yield.
9. For febrile ICU patients with pyuria and in whom urinary tract infection is suspected, they recommend replacing the urinary catheter and obtaining urine cultures from the newly placed catheter (best-practice statement) [I would add rescreening urine for pyuria and reflex to culture] The panel in the text states “members of the panel considered that the presence of urinary tract symptoms (if ascertainable)/ signs and pyuria (defined as 5–10 WBC/hpf)[I use 10WBC/hpf] on urinalysis should be used to justify urine culture.”
10. There was insufficient evidence to allow a recommendation on performing routine blood testing for viral pathogens in immunocompetent patients in the ICU (e.g., herpesviruses, adenovirus). The review states: “In most adult patients in the ICU, fever is not related to systemic herpesvirus (e.g., herpes simplex virus, varicella zoster virus, Epstein-Barr virus, cytomegalovirus) or adenovirus infection, so blood testing for these viruses with NAATs is not indicated.” Studies have shown asymptomatic CMV reactivation in immunocompetent ICU patients is increasingly recognized, but treatment for CMV in this population does not improve outcomes.
11. If the probability of bacterial infection is deemed low to intermediate in a critically ill patient with a new fever and no clear focus of infection, they suggest measuring procalcitonin (PCT) in addition to bedside clinical evaluation vs bedside clinical evaluation alone (weak recommendation, very low-quality evidence).
12. If the probability of bacterial infection is deemed high in a critically ill patient with a new fever and no clear focus of infection, we suggest not measuring PCT to rule out bacterial infection. (Weak recommendation, very low-quality evidence).
13. If the probability of bacterial infection is deemed low to intermediate in a critically ill patient with a new fever and no clear focus of infection, they suggest measuring serum PCT or CRP to rule out bacterial infection (weak recommendation, very low-quality evidence) [I wish to stress that PCT and CRP can provide information but does not substitute for clinical judgment. PCT has a very good negative predictive value.]

Comment: This is a very useful article to share with our critical care colleagues and provides rationale guidance on evaluation of new fever in the ICU. Fever is common in ICU patients and only ~50% in fact is due to a documented infection.

Safety of early oral ambulatory treatment of adult patients with bloodstream infections discharged from the emergency department Antimicrob Agents Chemother 2023; 67: e00780-23

doi.org/10.1128/aac.00780-23

Febrile illnesses commonly cause adult visits to the emergency department (ED), and the identification of positive blood cultures after discharge home often results in hospital admission for parenteral antibiotics. In a retrospective observational study researchers evaluated the safety of oral antibiotic therapy in ambulatory patients with bloodstream infections identified after ED discharge. Criteria for outpatient management included early responses to prescribed treatment on discharge; use of antibiotic therapy based on available microbiology; no need for source control; and no immunosuppression. S aureus and Candida spp. infections were excluded.

Of 123 patients with bacteremia identified after ED discharge (median age, 65), 103 were managed as outpatients — and among these, 99 remained out of the hospital during their follow-up. Patients had median Pitt score of 0 and median Charlson score of 5, with 40% having cancer and 20% having diabetes mellitus. Sources of febrile infection were mainly urinary (74%) and abdominal (10%). Microbiology consisted primarily of Enterobacterales (80%) and non-fermenting gram-negative bacteria (10%). Empiric antibiotics were prescribed in 92% of febrile bacteremic patients at the initial ED visit, with 91% providing appropriate coverage. Most (83%) received beta-lactam antibiotics. Hospital admission occurred in 4% at 30 days (compared with 3% in nonbacteremic patients) and 14-day mortality was 0% overall.

Comment: This study provides evidence that a + blood culture by itself after a patient is sent home from the ED should not automatically trigger admission for IV therapy. For patients with gram-negative bacteremia, especially if from a urinary source [the majority], a simple phone call to ensure the patient is improving and on an effective antibiotic can keep most patients out of the hospital. I would be more cautious when it comes to patients with gram-positive bacteremia especially S aureus and Candida which were excluded in this study. Other gram-positive organisms such as Streptococcus pneumoniae, Streptococcus agalactiae, Streptococcus anginosus, and Streptococcus dysgalactiae, and enterococcus need to be evaluated on a case-by-case basis. There were imbalances between groups regarding a higher rate of non-focal fever and lower rates of empirical treatments among non-BFP (bacteremic febrile patients). The size was relatively small so the cohort may be underpowered to detect small differences.

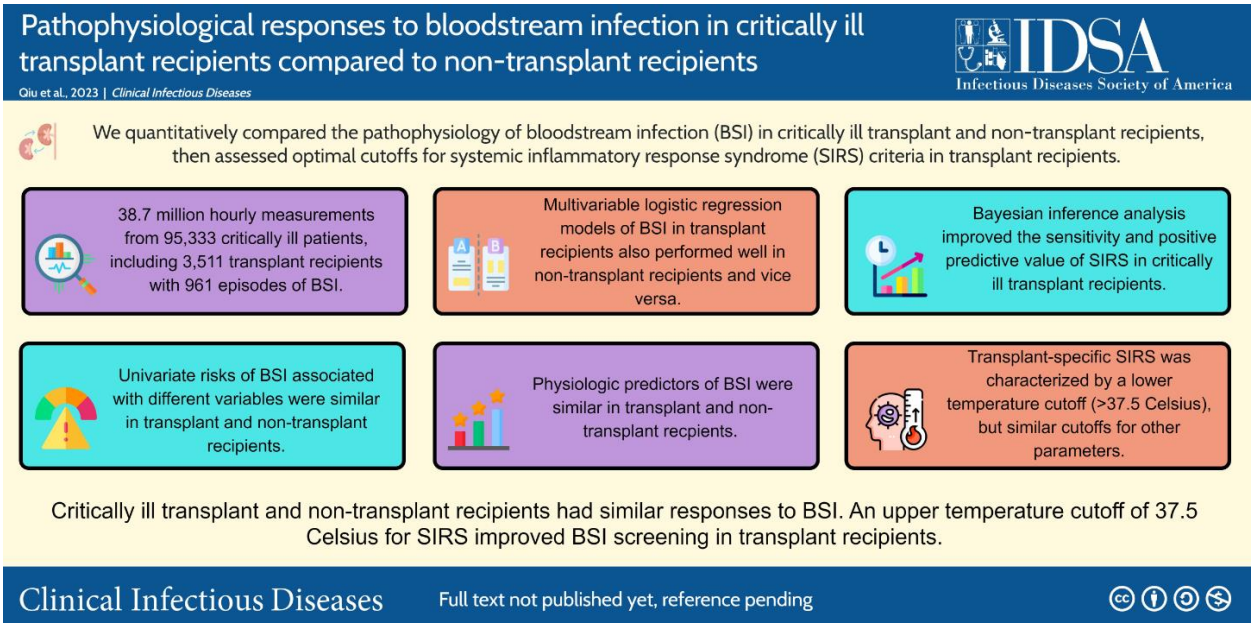
Bottom line: For bacteremic UTI responding and on an effective antibiotic most patients can be managed as an outpatient.

Pathophysiological responses to bloodstream infection in critically ill transplant recipients compared to non-transplant recipients Clin Infect Dis published online October 27, 2023

DOI: 10.1093/cid/ciad662

The investigators aimed to compare responses to BSI in critically ill transplant and non-transplant recipients and to modify systemic inflammatory response syndrome (SIRS) criteria for transplant recipients. They analyzed univariate risks and developed multivariable models of BSI with 27 clinical variables from adult ICUs at two academic centers (UVA and Pitt). They used Bayesian inference to adjust SIRS criteria for transplant recipients.

They analyzed 38.7 million hourly measurements from 41,725 patients at UVA, including 1,897 transplant recipients with 193 episodes of BSI, and 53,608 patients at Pitt, including 1,614 transplant recipients with 768 episodes of BSI. The univariate responses to BSI were comparable in transplant and non-transplant recipients. The area under the receiver operating characteristic curve (AUC) was 0.82 (95% confidence interval [CI], 0.80-0.83) for the model using all UVA patient data and 0.80 (95% CI, 0.76-0.83) when using only transplant recipient data. The UVA all-patient model had an AUC of 0.77 (95%CI, 0.76-0.79) in non-transplant recipients and 0.75 (95% CI, 0.71-0.79) in transplant recipients at Pitt. The relative importance of the 27 predictors was similar in transplant and non-transplant models. An upper temperature of 37.5° C in SIRS criteria improved reclassification performance in transplant recipients.



Comment: Their data suggests that pathophysiologic manifestations of BSI in critically ill transplant recipients are largely similar to non-transplant recipients. An upper temperature of 37.5° C in SIRS criteria improved BSI screening in transplant recipients. They did not have access to the time from transplantation to BSI, which could have implications for the degree of patient immunosuppression and pathophysiological response to infection. Their multivariable analysis grouped all transplant recipients together, which limited their ability to determine differences between transplant and non-transplant recipients and between different types of transplant recipients. They did not have access to immunosuppressive regimens.

Fecal microbiota transplantation promotes reduction of antimicrobial resistance by strain replacement Sc Trans Med 2023; 15: 720 eabo2750

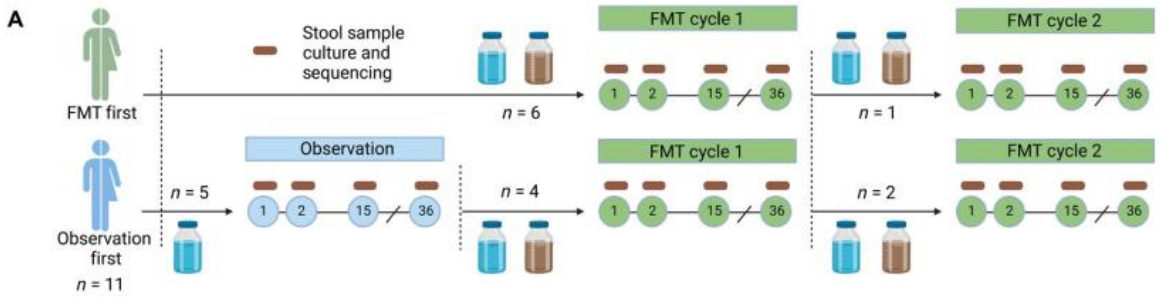
DOI: 10.1126/scitranslmed.abo2750

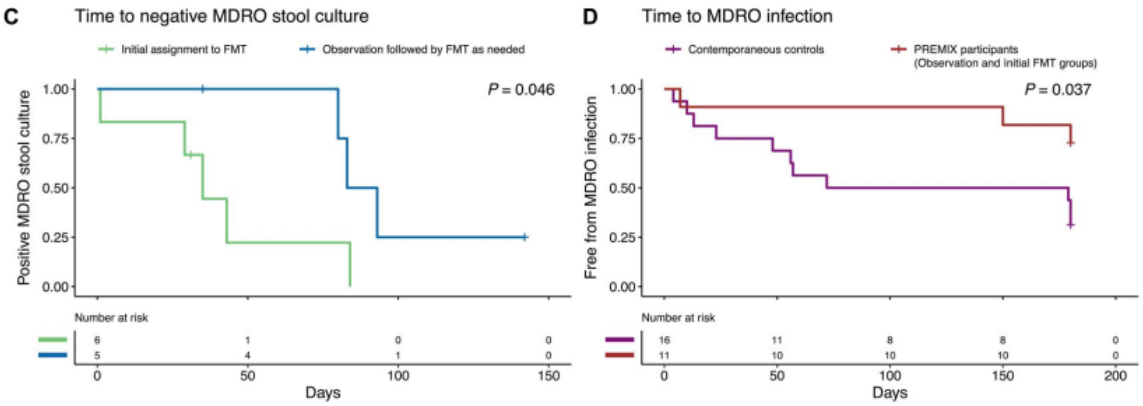
Kidney transplant patients are at high risk for MDRO colonization and infection because they receive prophylactic antibiotics after transplant, which can select for MDROs. Therefore, they are a priority for decolonization because many of the antibiotics used to treat MDRO infections may also be nephrotoxic.

In this phase 1 trial, investigators enrolled and randomized 11 renal transplant recipients (RTRs) to receive FMT—or an observation period followed by delayed FMT if stool cultures were MDRO positive at day 36. Kidney transplant patients are at high risk for MDRO colonization and infection because they receive prophylactic antibiotics after transplant, which can select for MDROs. They are thus a priority for decolonization because many of the antibiotics used to treat MDRO infections are nephrotoxic.

All 11 patients ultimately received at least one dose of FMT, with 9 receiving two treatments who were MDRO positive after one FMT. While no participants in the observation group had spontaneous MDRO decolonization, 4 of 6 participants randomized to the FMT group were MDRO-negative after one dose, and 8 of 9 participants who received all protocol-specified FMTs were MDRO-negative by their last visit. In addition, at 180 days, FMT-treated participants had a longer time to recurrent MDRO infection compared with a control group of renal transplant recipients who did not receive FMT. Post hoc analysis of this cohort did not detect increases in renal transplant rejection after FMT.

Analysis of E coli isolates from a subset of the FMT treatment group found that, rather than simply eradicating the MDRO strains, FMT appeared to promote competition with antibiotic-susceptible E coli strains that were present in the patients prior to FMT, with the susceptible strains replacing the MDRO strains. Susceptible Enterobacterales strains that replaced baseline extended-spectrum β-lactamase–producing strains were not detectable in donor microbiota.





Comment: They conclude that microbiome therapies like FMT may provide a path to utilize bacterial strain competition to eradicate MDRO colonization. This trial also provided evidence that reducing MDRO colonization in RTRs could reduce recurrence of MDRO infections, which has broad potential to improve patient care and public health response and to reduce health care costs in patient groups beyond transplants. Long-term studies are needed to better evaluate the durability of donor strain engraftment and pathogen reduction observed in this study.

Bottom line: While more work needs to be done, I am encouraged by the potential application of FMTs in reducing MDRO colonization and recurrent infections. See next review.

Editor's Choice

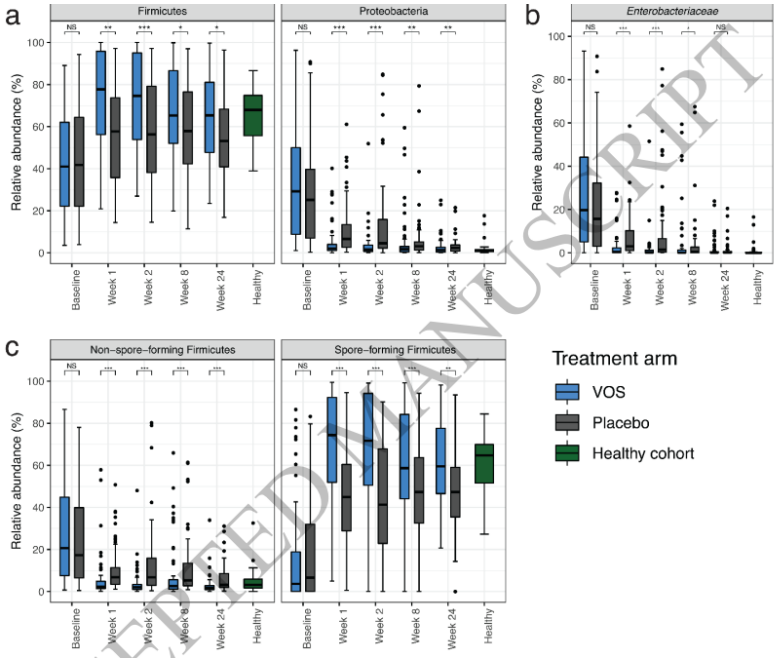
Impact of a purified microbiome therapeutic on abundance of antimicrobial resistance genes in patients with recurrent *Clostridioides difficile* infection. Clin Infect Dis published online October 12, 2023

DOI: 10.1093/cid/ciad636

This is a post hoc proof of concept analysis of the Phase 3 ECOSPOR III trial, assessing impact of a microbiota-based oral therapeutic (fecal microbiota spores, live [VOWSTTM Oral Spores; VOS, formerly SER-109]) compared with placebo, on AR gene (ARG) abundance in patients with recurrent C difficile infection (rCDI). Adults with rCDI were randomized to receive VOS or placebo orally for 3 days following standard-of-care antibiotics. ARG and taxonomic profiles were generated using whole metagenomic sequencing of stool at baseline and Weeks 1, 2, 8, and 24 post-treatment.

Baseline (n=151) and serial post-treatment stool samples collected through 24 weeks (total n=472) from 182 patients (59.9% female; mean age 65.5 years) in ECOSPOR III as well as 68 stool samples obtained at a single timepoint from a healthy cohort were analyzed. Baseline ARG abundance was similar between arms and significantly elevated vs. the healthy cohort. By Week 1, there was a greater decline in ARG abundance in VOS vs. placebo (p=0.003) in association with marked decline of Proteobacteria and repletion of spore-forming Firmicutes, as compared with baseline. They observed abundance of Proteobacteria and non-spore forming

Firmicutes were associated with ARG abundance, while spore-forming Firmicutes abundance was negatively associated.



Comment: Patients with rCDI are at high risk of harboring ARGs [Clin Infect Dis 2016; 62:1479–1486], as demonstrated by the wide spectrum of resistance observed at baseline across both intervention and placebo arms in this Phase 3 trial. In this proof-of-concept post hoc analysis, when compared with placebo, VOS treatment was associated with an accelerated reduction of ARG abundance, as illustrated by a significantly greater reduction in ARGs at early post-treatment timepoints. Furthermore, this effect was likely achieved through microbiome remodeling with broad compositional changes across two phyla that were either dominant (i.e., Proteobacteria) or depleted (i.e., Firmicutes) following antibiotic exposure. At baseline, patients in both arms had evidence of a distinct distribution of resistance mechanisms compared with the healthy cohort. Glycopeptide resistance at baseline was notably elevated in both treatment arms compared with the healthy cohort, which is consistent with the highly prevalent use of PO vancomycin in these study patients treated for rCDI. After VOS administration, ARG abundance was significantly reduced compared with placebo as early as Week 1. In vulnerable patient populations known to be at increased risk of microbial translocation across the GI tract, such temporal differences may be potentially meaningful, as mortality rates are higher with drug-resistant infections. In the disrupted microbiome of patients with rCDI, Proteobacteria, such as Klebsiella, E coli, and Pseudomonas, are unusually abundant compared with the healthy microbiome. [Nature 2012; 489:220–230 30] Thus, the observed reduction in ARGs is likely due to restructuring of the microbiome towards a healthy state where Proteobacteria become a minority population driven by engraftment of spore-forming Firmicutes that are less apt to harbor ARGs. Since this was a post hoc analysis, there may be underlying differences in the patient populations or biases. Since stool samples were not collected between Weeks 2 and 8, they were limited in their ability to discern dynamic changes between VOS and placebo recipients for approximately a six-week period.

Bottom line: Confirmation of the GI as a reservoir for multidrug resistant bacteria amenable to remodeling through microbiome therapeutics, creates a potential new therapeutic option for

combating drug resistance. The hypothesis that microbiome restoration may reduce ARG abundance through microbiome remodeling needs to be tested in a prospective clinical trial.

Editor's Choice

Probiotics, Prebiotics, Lactoferrin, and Combination Products for Prevention of Mortality and Morbidity in Preterm Infants A Systematic Review and Network Meta-Analysis

JAMA Pediatr 2023;177(11):1158-1167.

doi:10.1001/jamapediatrics.2023.3849

Necrotizing enterocolitis (NEC) is a devastating inflammatory disorder of the intestine and among the leading causes of mortality and morbidity in neonatal intensive care units. With an incidence ranging from 2% to 10% in infants born before 32 weeks' gestation and 5% to 22% among those with a birthweight of less than 1000 grams. The condition often develops in the second or third week of life. Modulation of the intestinal microbiome has long been suggested as a potentially effective preventive strategy for NEC and late-onset sepsis (LOS). A wide range of probiotics and synbiotics with different formulations and including different probiotic species have been studied, and although numerous systematic reviews and meta-analyses of RCTs and observational studies have addressed the use of probiotics, prebiotics, or lactoferrin to prevent NEC and LOS, no review has simultaneously addressed the comparative effectiveness of all these agents. Therefore, the authors conducted a systematic review and network meta-analysis (NMA) of RCTs addressing the effectiveness of these interventions in reducing mortality and morbidity in preterm infants.

They included 106 trials involving 25,840 preterm infants and found that multiple-strain probiotics were associated with reductions in all-cause mortality, necrotizing enterocolitis, feeding intolerance, and hospitalization. When combined with oligosaccharides, multiple-strain probiotics were associated with reductions in NEC and feeding intolerance and the best effectiveness for these outcomes but did not have high-certainty evidence for other outcomes.

	Statistically significant difference vs placebo and ≥1 other treatment	Statistically significant difference vs placebo	No statistically significant difference vs placebo
Moderate- or high-certainty evidence	Among the best	Among the intermediate	Among the worst
Low- or very low-certainty evidence	May be among the best	May be among the intermediate	May be among the worst

	RR (95% CI)					MD (95% CI)		
	All-cause mortality	Severe NEC (stage 2 or 3)	Culture-proven sepsis	NEC-related mortality	Feeding intolerance	Days to reach full feeding	Days of hospitalization	Weight, g
MultiPrb	**0.69 (0.56-0.86)**	**0.38 (0.30-0.50)**	**0.84 (0.74-0.95)**	0.55 (0.29-1.04)	**0.61 (0.46-0.80)**	**-2.03 (-3.04 to -1.02)**	**-2.20 (-4.08 to -0.31)**	31.20 (-70.81 to 133.21)
MultiPrb + OLGS	0.65 (0.30-1.41)	**0.13 (0.05-0.37)**	0.72 (0.49-1.07)	0.18 (0.02-1.58)	**0.45 (0.29-0.67)**	-0.98 (-3.10 to 1.13)	-0.23 (-3.31 to -2.86)	NA
SinglePrb	0.85 (0.70-1.04)	**0.61 (0.47-0.80)**	0.86 (0.73-1.00)	0.71 (0.40-1.26)	**0.61 (0.51-0.72)**	**-1.94 (-2.96 to -0.92)**	**-3.31 (-5.05 to -1.58)**	55.69 (-18.76 to 130.13)
MultiPrb + LF	0.70 (0.33-1.49)	**0.05 (0.00-0.79)**	**0.33 (0.14-0.78)**	NA	NA	-0.91 (-4.82 to 3.00)	1.10 (-5.08 to 7.29)	NA
MultiPrb + OLGS	0.34 (0.10-1.15)	**0.31 (0.12-0.84)**	0.68 (0.30-1.54)	1.69 (0.25-11.19)	0.51 (0.18-1.45)	-0.83 (-5.30 to 3.63)	-1.29 (-8.12 to 5.55)	44.37 (-131.05 to 219.78)
Lactoferrin	1.00 (0.80-1.25)	0.86 (0.60-1.25)	**0.74 (0.60-0.93)**	1.13 (0.02-54.72)	**0.39 (0.21-0.71)**	-1.32 (-3.31 to 0.66)	-0.09 (-2.91 to 2.75)	33.77 (-152.65 to 220.20)
MultiPrb + OLGS + LF	2.00 (0.51-7.78)	0.25 (0.02-2.56)	1.48 (0.78-2.81)	0.33 (0.01-8.09)	1.00 (0.02-50.23)	0.00 (-4.58 to 4.58)	3.00 (-5.02 to 11.02)	39.00 (-246.89 to 323.89)
OLGS	0.47 (0.17-1.27)	1.09 (0.62-1.93)	0.82 (0.57-1.17)	0.34 (0.01-7.63)	0.83 (0.47-1.45)	-2.21 (-4.42 to 0.01)	-4.34 (-9.25 to 0.56)	45.87 (-76.41 to 168.14)
MultiPrb + LF	0.67 (0.04-10.32)	0.74 (0.07-8.06)	1.13 (0.38-3.41)	NA	NA	NA	NA	NA

Numbers in bold indicate statistically significant results. LF indicates lactoferrin; MD, mean difference; MultiPrb, multiple-strain probiotics; NA, not available; NEC, necrotizing enterocolitis; OLGS, oligosaccharides (human milk oligosaccharides, fructo-oligosaccharides, and/or galacto-oligosaccharides); RR, risk ratio; SinglePrb, single-strain probiotics.

Comment: In this systematic review and network meta-analysis (NMA) comparing the benefits of probiotics, prebiotics, lactoferrin, and combination products for prevention of mortality and morbidity in preterm infants, they found moderate- to high-certainty evidence that multiple-strain probiotics were associated with reduced mortality (unlike any other intervention) and were among the best interventions associated with important reductions in all-cause mortality, severe NEC, LOS, feeding intolerance, time to reach full feeding, and duration of hospital stay (see figure above). Prebiotics alone likely have little to no benefit. Combination products, including single- and multiple-strain probiotics combined with prebiotics or lactoferrin, were associated with the largest reduction in morbidity and mortality. They did not observe any effect modification for risk of bias, birth weight, gestational age, feeding with breast milk, or delivery type. Variability in probiotic composition (i.e., diverse strains, species, and doses) makes it difficult to identify with certainty the most effective probiotic species or synbiotics products for clinical use. Despite limited evidence and variability in probiotic strains used across trials, they found combinations of 1 or more *Lactobacillus* species and 1 or more *Bifidobacterium* species were superior to single- and other multiple-strain probiotic products.

Bottom line: Moderate- to high-certainty evidence shows multiple-strain probiotics alone or possibly in combination with oligosaccharides to be superior to alternative prophylactic interventions. See FDA alert below

The FDA warned doctors against using probiotics for preterm babies outside of clinical trials.

To help prevent NEC, nearly all neonatal units in Australia and New Zealand give probiotics, as do a majority in several European countries and about 40% in the US. Then last month, American hospitals stopped. Why you may ask?- The FDA had linked an infant's death recently when an infant died after taking a probiotic made by Infinant. The agency found the bacteria invading a preterm baby's bloodstream to be an exact genetic match to those in the hospital's probiotic. It warned doctors about using them in preterm infants without getting agency permission first, and pushed Abbott Laboratories and the other major manufacturer, Infinant Health, to stop selling them. FDA officials and other doctors worry that, without rigorous testing and stringent manufacturing, the products themselves are a health risk. To ensure they safely work in premature babies, the agency has demanded companies conduct studies and manufacture according to pharmaceutical-grade standards. Supporters of probiotics recently sent letters to the FDA. Probiotics supporters say the FDA disregarded the evidence favoring probiotics for preterm babies, saying that they likely save hundreds of infants for every 1. probiotic-caused infection, which they say can be treated with antibiotics. During a meeting with concerned clinicians last week, the FDA said it would take steps to help streamline other testing efforts.

Comment: An analysis of more than 100 studies involving more than 25,000 premature infants, reviewed above in JAMA Pediatrics, found that probiotics were associated with reduced deaths and NEC. Several neonatal units have reported dramatic drops in their NEC rates after introducing probiotics. However, the American Academy of Pediatrics in 2021 called the data on probiotics "conflicting" and didn't recommend them for premature babies. Some neonatologists also have expressed concern because probiotic manufacturers do not have to follow strict drug protocols and batches may vary.

Bottom line: We do need pharmaceutical-grade standards to assure consistent composition of probiotics. I hope the FDA will in fact streamline testing efforts since the evidence suggests probiotics may save lives.

Cefoxitin versus carbapenems as definitive treatment for extended-spectrum β-lactamase-producing Klebsiella pneumoniae bacteremia in intensive care unit: a propensity-matched retrospective analysis Critical Care (2023) 27:418

doi.org/10.1186/s13054-023-04712-2

This was a retrospective single-center study conducted between January 2013 and January 2023 at an 800-bed tertiary care medical center. All consecutive adult patients (age≥18 years) hospitalized in ICU with cefoxitin-susceptible ESBL-KP bloodstream infections (BSIs) were included. Definitive antibiotic therapy was defined as the treatment administered after bacterial identification and antibiotic susceptibility testing, regardless of the initial empirical antibiotic therapy. The choice of definitive antibiotic therapy, either cefoxitin or carbapenem (meropenem or imipenem-cilastatin), was guided by local recommendations, but the final decision was left to the treating physician's discretion. Exclusion criteria were positive blood cultures with multiple bacteria, treatment by another antibiotic, lack of access to clinical records, patient's death within 24 hours of the onset of bacteremia, definitive monotherapy administered for less than 50% of

the total duration of antimicrobial therapy and patient refusal to participate. Susceptible strains were defined by minimum inhibitory concentration (MIC)≤8 mg/L for cefoxitin and MIC ≤2 mg/L for carbapenems; resistant strains by MIC>16 mg/L for cefoxitin, MIC>4 mg/L for imipenem and MIC>8 mg/L for meropenem. [EUCAST]

The primary endpoint was the 30-day clinical success rate defined as a composite endpoint: 30-day survival after inclusion, absence of relapse and no change of antibiotic therapy before the planned end of treatment. Secondary endpoints were (i) all-cause mortality at 7 and 30 days post-inclusion, (ii) relapse of infection, defined as a new ESBL-KP bacteremia between the end of treatment and 30 days, (iii) change of antibiotic therapy before the scheduled end of treatment due to the onset of a new co-infection, or caused by clinical or microbiological failure, (iv) microbiological failure defined as the persistence of ESBL-KP-positive blood culture after two days of definitive antibiotic therapy until the end of treatment and (v) selection of all bacteria resistant to cefoxitin or carbapenems identified in any microbiological sample after 24 h of definitive antibiotic therapy until the end of follow-up. The Propensity Score (PS) was computed using the covariates age, Charlson comorbidity index, year of inclusion, SAPS II score, source of infection, time to effective antibiotic therapy, mechanical ventilation, septic shock, SOFA and Pitt bacteremia scores.

A total of 110 patients with BSIs were enrolled. Sixty-three patients (57%) received definitive antibiotic therapy with cefoxitin, while forty-seven (43%) were treated with carbapenems. 30-day clinical success was not significantly different between patients treated with cefoxitin (57%) and carbapenems (53%, p=0.823). PS-adjusted and PS-matched analysis confirmed these findings. Change of definitive antibiotic therapy was more frequent in the cefoxitin group (17% vs. 0%, p=0.002). No significant differences were observed for the other secondary endpoints. The acquisition of carbapenem-resistant Pseudomonas aeruginosa was significantly higher in patients receiving carbapenem therapy (5% vs. 23%, p=0.007). However, fifteen beta-lactamase AmpC-producing Enterobacterales (12 Enterobacter cloacae and 3 Enterobacter aerogenes) were selected among the cefoxitin-treated patients, compared with only two (1 Enterobacter cloacae and 1 Serratia marcescens) in the carbapenem group (p=0.006). There was no significant difference in the selection of cefoxitin-resistant bacteria, including Klebsiella pneumoniae, between the two groups.

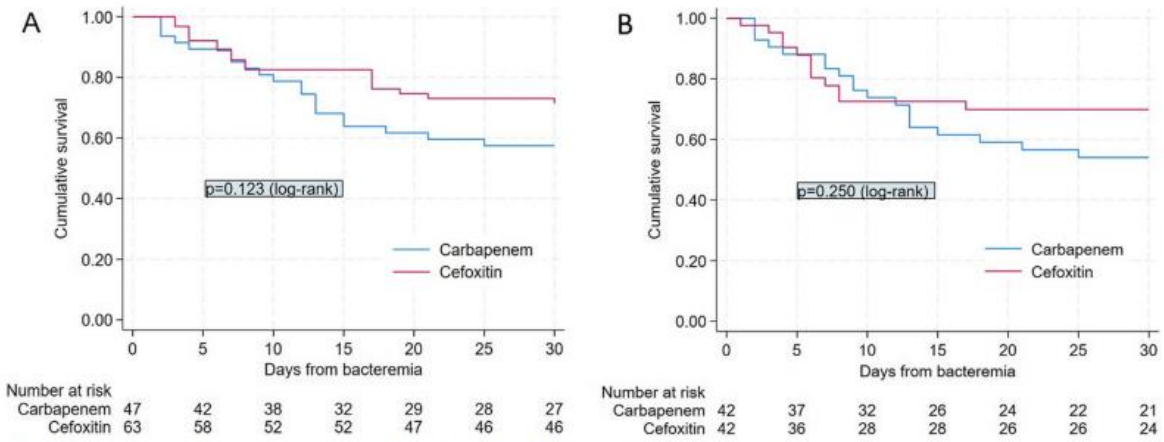


Fig. 2 Kaplan–Meier survival curves for baseline population (**A**) and PS-matched patients (**B**) receiving cefoxitin or carbapenem therapy for extended-spectrum beta-lactamase (ESBL)-producing *Klebsiella pneumoniae*

Comment: Currently IDSA does not recommend the use of cephamycins for the treatment of ESBL infections until more clinical outcomes data are available. This study's main finding, confirmed by PS-matched analysis, shows that there was no statistical difference in 30-day clinical success when cefoxitin was used as definitive antibiotic therapy for ESBL-KP bacteremia, compared with carbapenems. The second interesting finding is that the use of cefoxitin instead of carbapenems reduced the selection of carbapenem-resistant Pseudomonas aeruginosa but may have been selected for more Amp-C Enterobacterales.

Many studies of BSIs have shown that the source of infection is a major prognostic factor in clinical success and mortality. [BMC Infect Dis. 2023; 23:69] Interestingly, 100% of patients with catheter-related bacteremia for whom thrombophlebitis was ruled out (n=20) was cured on cefoxitin with catheter removal. The majority of UTIs were also cured. In contrast, it was difficult to conclude on the efficacy of cefoxitin in bacteremia secondary to pneumonia and intra-abdominal infections, in view of the extreme severity and small numbers of patients in the study. This was a non-randomized retrospective observational study with the inherent shortcomings of these studies. At baseline, the two treatment groups were not comparable on several criteria, with more severe patients overall in the carbapenem group, probably due to an indication bias. Although there were no significant differences in primary and secondary endpoints, using a PS-based matched analysis, they acknowledge that the 95% confidence intervals for propensity-matched outcomes are very wide and include the possibility of harm. Another potential weakness is that cefoxitin was mainly administered on an intermittent basis, whereas several recent studies confirm that continuous administration of large doses of cefoxitin appeared necessary to achieve the recommended beta-lactam PK/PD target in critically ill patients. [Ann Intensive Care. 2022; 12:90; Eur J Clin Microbiol Infect Dis 2021; 40:1393–1397] Lastly, the sample size was small.

Bottom line: Despite the weaknesses of this study, results suggest that cefoxitin antibiotic therapy could be an alternative for ESBL-KP bacteremia in ICU, if the source is UTI and perhaps catheter-related bacteremia without thrombophlebitis. Continuous administration of large doses of cefoxitin is preferred. See next review.

Efficacy and Safety of Cefmetazole for Bacteremia Caused by Extended-Spectrum β-Lactamase–Producing Enterobacterales vs Carbapenems: A Retrospective Study

OFID published online October 7, 2023

doi.org/10.1093/ofid/ofad502

The investigators retrospectively reviewed patients who were treated with cefmetazole (CMZ) or (carbapenems) CPMs for bacteremia caused by ESBL producing Enterobacterales between April 1, 2014 and September 31, 2022 in Japan. The primary outcome measure was 90-day mortality. They also evaluated resistance genes and sequence types of ESBL-producing Enterobacterales.

In total, 156 patients were enrolled in this study. Ninety patients (58%) received CMZ therapy. Patients in the CMZ group were significantly older than those in the CPM group (median [IQR], 79 years [71–86] vs 74 years [64–83]; P = .001). The severity of the Pitt bacteremia score (PBS) of the CMZ group was lower than that in the CPM group (0 [0–2] vs 2 [0–2], P = .042). Six patients (7%) in the CMZ group and 10 (15%) in the CPM group died by day 90 (P = .110).

Charlson Comorbidity Index and prevalence of sequence 131 between the groups were statistically insignificant. The study found the rate of 90-day all-cause mortality was actually lower among patients who received cefmetazole vs carbapenems. In addition, the rate of bacteremia recurrence and 30-day hospital readmission was also lower among patients who received cefmetazole. CTX M15 β-lactamases are the most common type of ESBLs identified.

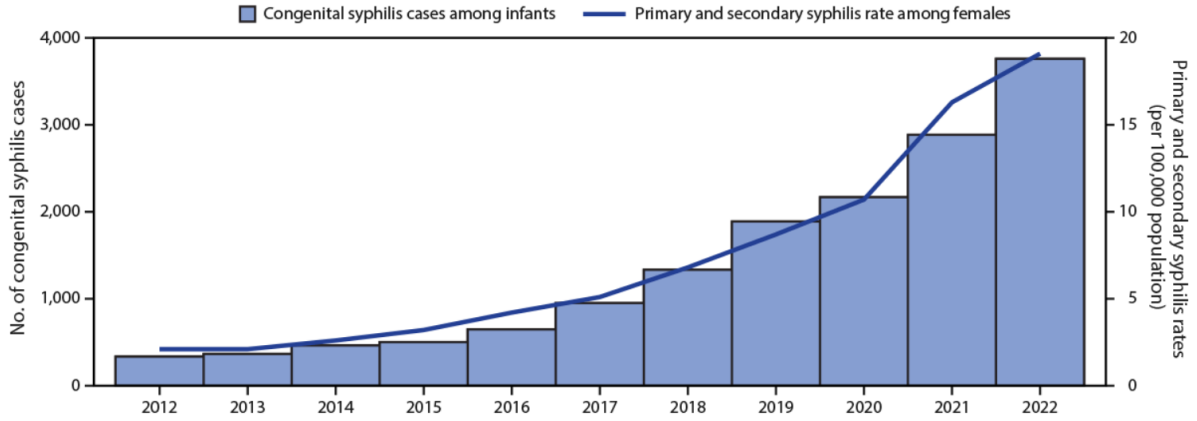
Comment: Cefmetazole is a Cephamycins, like cefoxitin and are classified as a second-generation cephalosporins. Cefmetazole is not commercially available in the US. They are distinct from other second-generation cephalosporins due to the presence of a methoxy group at the seventh position of cephalosporanic acid. They are resistant to hydrolysis by ESBL-producing Enterobacterales [Clin Microbiol Rev 2005; 18:657–86.] and have good activity against ESBL-producing Enterobacterales in vitro. [Diagn Microbiol Infect Dis 2016; 84:322–7] This study had several limitations. First, this was a retrospective study conducted at a single institution. Second, there was a noticeable difference between the groups in the number of patients who were admitted to the Department of Hematology or who had received chemotherapy, as well as in PBS result and receipt of bone marrow transplant. Third, some patients were treated with empiric antibiotics before definitive therapy.

Bottom line: These findings suggest that CMZ is a well-tolerated alternative to CPM for treating bacteremia caused by ESBL-producing Enterobacterales. However, more extensive prospective studies in multiple settings and multicenter randomized trials are required to corroborate these findings.

***Vital Signs*: Missed Opportunities for Preventing Congenital Syphilis — United States, 2022** Vital Signs early release November 7, 2023

Congenital syphilis cases in the US increased 755% during 2012–2021. Syphilis during pregnancy can lead to stillbirth, miscarriage, infant death, and maternal and infant morbidity. In 2022, a total of 3,761 cases of congenital syphilis in the United States were reported to CDC, including 231 (6%) stillbirths and 51 (1%) infant deaths. Lack of timely testing and adequate treatment during pregnancy contributed to 88% of cases of congenital syphilis. Testing and treatment gaps were present in the majority of cases across all races, ethnicities, and US Census Bureau regions.

FIGURE 1. Reported number of cases of congenital syphilis among infants, by year of birth, and rates* of reported cases of primary and secondary syphilis† among females aged 15–44 years, by year — United States, 2012–2022



* Cases per 100,000 population.

Comment: Lack of timely testing and adequate treatment during pregnancy contributed to 88% of congenital syphilis cases in 2022 and represent missed opportunities to prevent maternal syphilis-associated morbidity. Lack of timely testing and adequate treatment contributed to substantial proportions of cases in all geographic areas and in all racial and ethnic groups. Timely testing without evidence of late seroconversion occurred in 58% of cases; however, inadequate treatment occurred in 69% of these cases, and no treatment or nondocumented treatment in 19%. Treatment could be considered inadequate based on inappropriate selection of an antimicrobial agent, dosing, or spacing of doses, as well as an insufficient interval between initiation of treatment and delivery.

Benzathine penicillin G is the only recommended treatment for syphilis during pregnancy; this drug must be administered as an injection by a trained professional as either a single dose or as 3 doses spaced 7–9 days apart, depending on the stage of infection. The success rate of this treatment in preventing congenital syphilis has been reported to be as high as 98%. [Obstet Gynecol 1999; 93:5–8] Because the US is currently facing a shortage of benzathine penicillin G, CDC has encouraged providers and health departments to prioritize benzathine penicillin G for the treatment of syphilis in pregnancy.

Bottom line: Congenital syphilis rates are rapidly increasing in the US and are at the highest level in at least 30 years. This is also true of other STDs. This represents a breakdown in our public health infrastructure. This is a disgraceful crisis accelerated by funding cutbacks and bureaucratic obstacles. It is obvious we have a broken system.

Fall 2023 Hospital Safety Grades from The Leapfrog Group Find Improved Infection Rates Following Major Spike During COVID-19 Pandemic November 6, 2023

The latest data shows that over 85% of hospitals have improved performance on at least one of the three dangerous infections the Hospital Safety Grade accounts for. That includes:

- 19% of hospitals have improved in all three infection measures,
- 66% of hospitals have improved at least one infection measure, and
- 16% of hospitals have continued to worsen or made no improvement.

	04/2016 - 06/2017 Spring '18	10/2016 - 12/2017 Fall '18	04/2017 - 06/2018 Spring '19	10/2017 - 12/2018 Fall '19	04/2018 - 06/2019 Spring '20	10/2018 - 12/2019 Fall '20	01/2019 - 12/2019 Spring '21	04/2019 - 09/2020 Fall '21	10/2019 - 03/2021 Spring '22	10/2020 - 12/2021 Fall '22	04/2021 - 06/2022 Spring '23	10/2021 - 12/2022 Fall '23
MRSA	0.92	0.881	0.881	0.840	0.823	0.791	0.798	0.840	1.032	1.134	1.095	0.927
CAUTI	0.90	0.874	0.831	0.791	0.774	0.724	0.721	0.752	0.849	0.898	0.862	0.735
CLABSI	0.82	0.789	0.765	0.726	0.700	0.669	0.670	0.810	1.047	1.106	1.077	0.888

Comment: The new grades are the first to reflect hospital performance post-pandemic. Nationally, hospitals significantly reduced three HAIs-MRSA, CLABSI and CAUTI—after CLABSI, MRSA and CAUTI reached a 5-year high during the pandemic. In the fall 2022 Safety Grade cycle, hospitals experienced a 35% increase in the average standard infection ratios (SIRs) of CLABSI and MRSA from pre-pandemic levels as well as a 20% increase in CAUTI. This report shows 2/3 of the sites are now reporting a reduction in at least 1 HAI. This is great news for patient safety.

Comparing Practices to Prevent Infectious Diseases Transmission Among Veterans Affairs and Non-Veterans Affairs Hospitals: Results from a National Survey in the United States Am J Infect Control published online November 7, 2023

doi.org/10.1016/j.ajic.2023.10.013

Data was collected via a survey conducted from April 2021 – May 2022 sent to infection preventionists at all VA hospitals (n=127) and a random sample of US non-VA hospitals (n=881) about hospital and infection control program characteristics and various infection transmission focused prevention practices. Respondents were asked about hospital and infection control program characteristics and various infection transmission-focused prevention practices, such

as hand hygiene and contact precautions (e.g., use of gloves and gowns for contact with patients with a known or suspected infection). The overall response rate was 56% for VA hospitals and 47% for non-VA hospitals.

The mean reported hand hygiene compliance rate and percentage of hospitals using direct observation to monitor compliance was 90% among both the VA and non-VA hospitals, and roughly 60% of VA and non-VA hospitals reported use of CHG for daily bathing of intensive care unit patients and around 20% for non-ICU patients.

But a higher percentage of VA versus non-VA hospitals reported using contact precautions with active surveillance culturing for MRSA (56.7% vs 24.4%) and carbapenem-resistant Enterobacterales (CRE) (26.9% vs 13.3%) and for VRE without surveillance culturing (67.7% vs 38.9%). In addition, a higher percentage of VA hospitals (67.6% vs 52.9%) reported using supplemental no-touch disinfection devices to clean rooms used to care for patients with C difficile infection. <70% performed CHG bathing in the ICU.

	Veterans Affairs Hospitals (N = 71)			Non-Veterans Affairs Hospitals* (N = 415)			
Question	**N**	**Freq**	**%**	**N**	**Freq**	**%**	**P-value**
CHG Bathing							
Chlorhexidine gluconate for daily bathing of ICU patients	61	37	60.7%	388	264	68.00%	0.25
Chlorhexidine gluconate for daily bathing of non-ICU patients	62	13	21.0%	399	72	18.00%	0.58

Comment: The use of contact precautions for MRSA, VRE, and CRE varied, with VA hospitals generally more likely to deploy contact precaution requirements for all three multidrug-resistant organisms (MDROs). As an integrated system, some infection prevention activities are implemented nationally across VA hospitals, such as the MRSA Prevention Initiative. [JAMA Netw Open. 2021;4(3)] Recently updated practice recommendations from several professional organizations include MRSA contact precautions as an essential practice, with some flexibility based on MRSA rates and the effectiveness of other infection control prevention practices. [Infect Control Hosp Epidemiol 2023; 44:s71-s99] This topic was reviewed in the November 2023 issue of ID Watch. The low percentage of CHG bathing especially in the ICU was surprising and disappointing especially since both the 2014 and 2022/3 Compendium has recommended CHG in the ICU to prevents CLABSI as an essential practice with a high level of evidence. [Infect Control Hosp Epidemiol 2023; 44:s31-s47] This result is similar to the NHSN survey on CHG bathing. This reminds me of the IOM report on “Crossing the Quality Chasm.”

There may be differences between hospitals that responded and those that did not. The authors relied on self-report by lead infection preventionists, which may not reflect actual hospital practice. Additionally, the Covid-19 pandemic altered some standard contact precautions requirements given personal protective equipment supply limitations. They did not collect data on the number of hours employees were dedicating to infection prevention and therefore were unable to calculate full-time equivalent (FTE) estimates. Although this survey examines practices it did not collect outcomes of infection prevention practices, therefore, they cannot

comment on whether certain practices resulted in decreased transmission or infection with the targeted organisms.

Direct Gloving vs Hand Hygiene Before Donning Gloves in Adherence to Hospital Infection Control Practices A Cluster Randomized Clinical Trial JAMA Network Open. 2023;6(10):e2336758.

doi:10.1001/jamanetworkopen.2023.36758

The investigators set out to determine if a a strategy of direct gloving compared with performing hand hygiene (HH) before donning nonsterile gloves influences adherence to infection prevention practices among HCWs.

This was a multicenter, cluster randomized clinical trial conducted at 4 academic centers from January 1, 2016, to November 30, 2017. [pre pandemic] Data analysis was completed April 25, 2019. Participants were 3790 HCWs across 13 hospital units. Hospital units were randomly assigned to direct gloving, with HH not required before donning gloves (intervention), or to usual care (HH before donning nonsterile gloves). The primary outcome was adherence to the expected practice at room entry and exit. A random sample of HCWs' gloved hands were imprinted on agar plates at entry to contact precautions rooms. Primary and secondary outcomes between treatment groups were assessed using generalized estimating equations with an unstructured working correlation matrix to adjust for clustering; multivariate analysis using generalized estimating equations was conducted to adjust for covariates, including baseline adherence.

In total, 13 hospital units participated in the trial, and 3790 HCWs were observed. Adherence to expected practice was greater in the 6 units with the direct-gloving intervention than in the 7 usual care units (1297 of 1491 [87%] vs 954 of 2299 [41%]; $P < .001$) even when controlling for baseline hand hygiene rates, unit type, and universal gloving policies (risk ratio [RR], 1.76; 95% CI, 1.58-1.97). Glove use on entry to contact precautions rooms was also higher in the direct-gloving units (1297 of 1491 [87%] vs 1530 of 2299 [67%]; $P = .008$. The intervention had no effect on hand hygiene adherence measured at entry to non–contact precautions rooms (951 of 1315 [72%] for usual care vs 1111 of 1688 [66%] for direct gloving; RR, 1.00 [95% CI, 0.91-1.10]) or at room exit (1587 of 1897 [84%] for usual care vs 1525 of 1785 [85%] for direct gloving; RR, 0.98 [95% CI, 0.91-1.07]). The intervention was associated with increased total bacteria colony counts (adjusted incidence RR, 7.13; 95% CI, 3.95-12.85) and greater detection of pathogenic bacteria (adjusted incidence RR, 10.18; 95% CI, 2.13-44.94) on gloves in the emergency department and reduced colony counts in pediatrics units (adjusted incidence RR, 0.34; 95% CI, 0.19-0.63), with no change in either total colony count (RR0.87 [95% CI, 0.60 to 1.25] for adult intensive care unit; RR, 0.59 [95% CI, 0.31-1.10] for hemodialysis unit) or presence of pathogenic bacteria (RR, 0.93 [95% CI, 0.40-2.14] for adult intensive care unit; RR, 0.55 [95% CI, 0.15-2.04] for hemodialysis unit) in the other units.

Comment: Current guidelines require hand hygiene before donning nonsterile gloves, but evidence to support this requirement is lacking This multicenter, cluster randomized trial including 3790 HCWs across 13 hospital units of 4 academic centers demonstrated a statistically significant 46% increase in adherence to a direct-gloving strategy vs usual care of hand hygiene before donning gloves (87% vs 41% adherence). This cluster randomized clinical

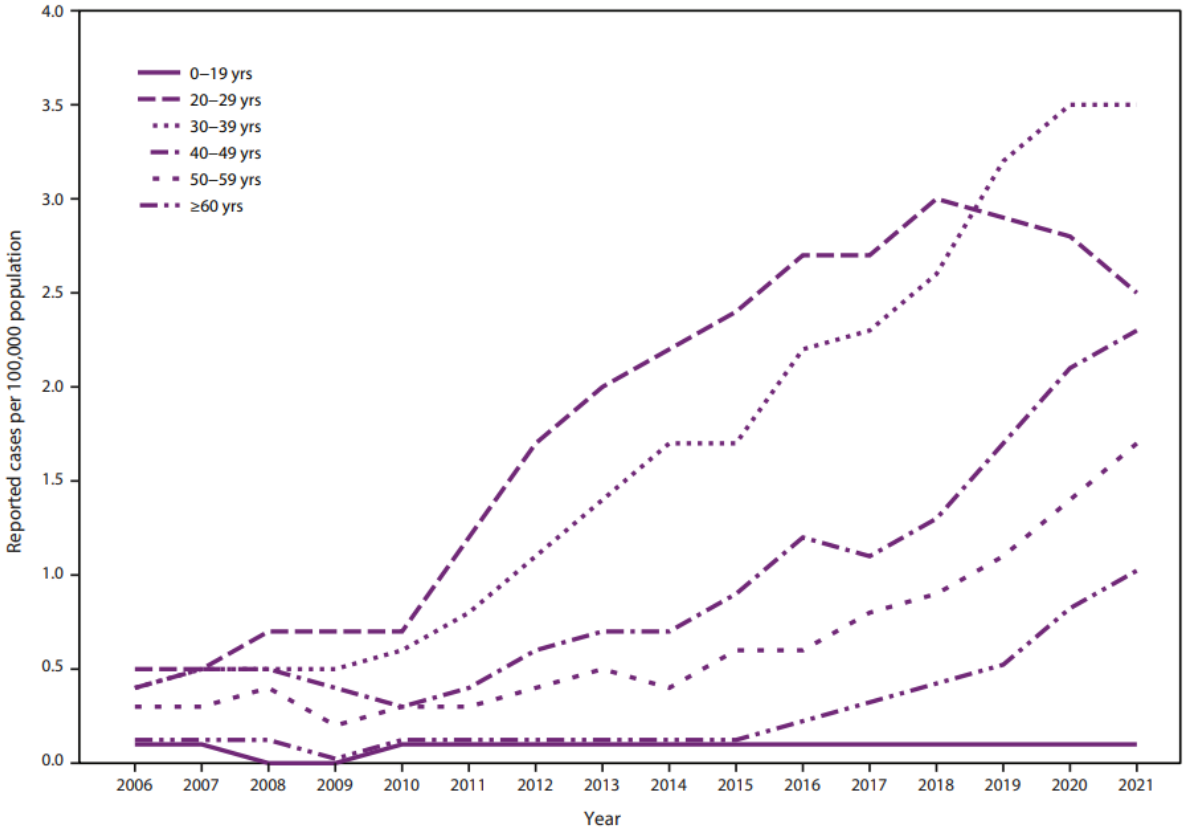
trial demonstrated that a policy endorsing a direct-gloving strategy compared with the current strategy requiring hand hygiene before glove use led to improved adherence with expected practices and increased overall glove use, was accepted by HCWs, and did not increase bacterial contamination of gloves in most clinical areas, except where hand hygiene rates were low (i.e., ED). This study was completed before the Covid-19 pandemic, and practices may be different during vs after the pandemic. This study did not have clinical outcomes.

Bottom line: Nonetheless, the findings from this cluster randomized clinical trial indicate that a direct-gloving strategy without prior hand hygiene should be considered by health care facilities with high levels of HH compliance.

CDC Recommendations for Hepatitis C Testing Among Perinatally Exposed Infants and Children — United States, 2023**;** 72(4):1–19

Because acute HCV infection can lead to chronic infection, this has resulted in increasing rates of HCV infections during pregnancy. Approximately 6%–7% of perinatally exposed (i.e., exposed during pregnancy or delivery) infants and children will acquire HCV infection. Curative direct-acting antiviral therapy is approved by the FDA for persons aged ≥3 years. However, many perinatally infected children are not tested or linked to care. In 2020, because of continued increases in HCV infections in the US, CDC released universal screening recommendations for adults, which included recommendations for screening for pregnant persons during each pregnancy [MMWR Recomm Rep 2020;69[No. RR-2]:1–17]. This report introduces four new CDC recommendations: 1) HCV testing of all perinatally exposed infants with a nucleic acid test (NAT) for detection of HCV RNA at age 2–6 months; 2) consultation with a health care provider with expertise in pediatric hepatitis C management for all infants and children with detectable HCV RNA; 3) perinatally exposed infants and children with an undetectable HCV RNA result at or after age 2 months do not require further follow-up unless clinically warranted; and 4) a NAT for HCV RNA is recommended for perinatally exposed infants and children aged 7–17 months who previously have not been tested, and a hepatitis C virus antibody (anti-HCV) test followed by a reflex NAT for HCV RNA (when anti-HCV is reactive) is recommended for perinatally exposed children aged ≥18 months who previously have not been tested. The CDC stresses proper identification of perinatally infected children, referral to care, and curative treatment are critical to achieving the goal of hepatitis C elimination.

FIGURE 1. Rates* of laboratory confirmed acute hepatitis C virus infection,† by age group — United States, 2006–2021§,¶



Comment: During 2010–2021, HCV infections increased in the US, consequences of which include cirrhosis, liver cancer, and death. Rates of acute infections more than tripled among reproductive-aged persons during this time (from 0.8 to 2.5 per 100,000 population among persons aged 20–29 years and from 0.6 to 3.5 among persons aged 30–39 years). Because more pregnant persons with HCV infection are identified through universal screening, more infants and children with identified exposure will seek care at various stages. Using a testing strategy of highly sensitive and specific NATs for RNA detection among infants and children perinatally exposed to HCV increases the identification of children with HCV infection in whom substantial morbidity and mortality might develop.

Editor's Choice

Ecological diversity profiles of non-vaccine-targeted HPVs after gender-based community vaccination efforts Cell Host & Microbe 31, 1921–1929

doi.org/10.1016/j.chom.2023.10.001

The investigators performed an 8-year follow-up of 33 communities randomized to gender-neutral HPV16/18 vaccination, girls-only HPV16/18 vaccination, and control communities without HPV vaccination. The 1992/93 and 1994 birth cohorts were invited to school years 2007/8 and 2008/9. Follow-up cervico-vaginal sampling at 18 and 22 years of age, 4- and 8-years post-vaccination, respectively, were attended by 11,396 and 5,602 participants. HPV

types 6/11/16/18/31/33/35/39/45/51/52/56/58/59/66/ 68 were genotyped and used for the community-level ecological diversity estimations.

Gender-neutral vaccination communities with a stronger herd immunity than girls-only vaccination communities show a significantly increased HPV a-diversity ($p = 1.1\ 3\ 10^{-8}$) from 4 to 8 years post-vaccination, despite the clearance of the vaccine-targeted HPVs in these communities.

Comment: With gender-neutral vaccination, a 50% vaccination coverage per year cohort was sufficient to nearly eliminate the occurrence of high-oncogenic HPV types targeted by the vaccine. However, when vaccines are administered only to girls, the uptake needs to be extremely high to reach the same results. Therefore, they demonstrated the need to opt for gender-neutral HPV vaccination strategies to realistically meet the WHO-targeted eradication of the oncogenic HPVs. While eradication of HPV16/ 18/31/45 will eliminate most cervical cancers, it is tempting to suggest that an increase of HPV33/35/51/52/56/6638 or the like with increased virulence might cause a risk of HPV-related cancers in the future. [Methods Ecol. Evol. 3, 471–474]

Bottom line: Overall this is another example of the impact of vaccination in preventing disease, in this case HPV and cervical cancer.

HICPAC meeting November 2-3, 2023

Masking

This has been an area of controversy. Using more protective practices and PPE to address new and emerging pathogens of concern the proposed new categories for transmission-based precautions, Special Air Precautions recommends the use of NIOSH-approved fit-tested N95 (or higher-level) respirators as the default option during care of patients with pandemic or emerging respiratory viruses. Other recommended categories to prevent transmission by air include Routine Air, which would have healthcare personnel wear a mask and eye precautions for endemic respiratory pathogens, and Extended Air Precautions, which would be used when providing care to patients with pathogens that can spread efficiently across long distances and over extended times. See chart below.

Table 3. Transmission-Based Precautions to Prevent Transmission by Air

Category	Mask or Respiratory Protection	Eye Protection	AIIR[a]
Routine Air Precautions	Mask	Per Standard Precautions	Not routinely recommended
Special Air Precautions	NIOSH-approved® N95 (or higher-level) respirator	Yes	Not routinely recommended
Extended Air Precautions	NIOSH-approved® N95 (or higher-level) respirator	Per Standard Precautions	Yes

a. AIIR = Airborne Infection Isolation Room for containment of air in a designated space

Routine Air Precautions are focused on reducing transmission of common, often endemic, respiratory pathogens that spread predominantly over short distances based on observed patterns of transmission, and for which individuals and their communities are likely to have some degree of immunity.

Special Air Precautions are applied to patients with a respiratory pathogen, typically new or emerging, that is not observed or anticipated to spread efficiently over long distances (such as through ventilation systems), for which infection generally leads to more than mild illness, and where immunity (or vaccine) and effective treatment are not available.

Extended Air Precautions are used when providing care to patients with pathogens that are observed to spread efficiently across long distances and over extended times, such that room air needs to be contained (e.g., prevented from moving into the hallway where individuals are not appropriately protected).

There was neither expert consensus, nor sufficient supporting data, to create a definitive and comprehensive list of these procedures (sometimes called “aerosol-generating procedures”) for healthcare settings.

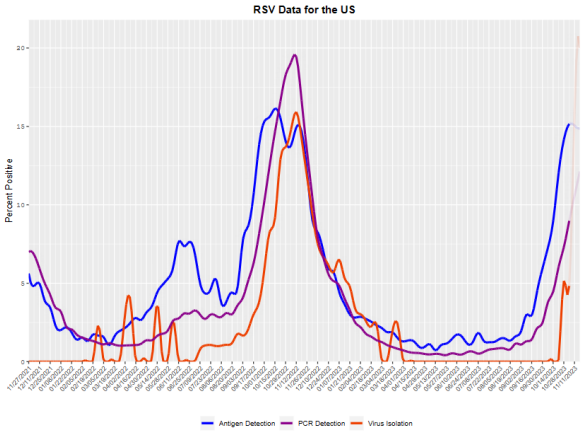
Comment: They also proposed updating the conceptual framework for respiratory pathogen transmission, including a continuum of pathogen transmission by air, rather than the dichotomy of “droplet” versus “airborne” transmission. They added while not required for Routine Air Precautions, HCP may choose voluntarily to wear a NIOSH-approved N95 (or higher-level) respirator, per existing federal regulations. I think this was a compromise since the nurses lobbied for stronger protections. Critics have argued that surgical masks would offer inadequate protection. Zenei Triunfo-Cortez, RN, president of National Nurses United (NNU), called the draft guidance "permissive and weak". NNU feels the draft guidance will only further degrade the already dangerous working conditions of nurses and other healthcare workers. However, a systematic review and meta-analysis presented at the HICPAC meeting found that there was no difference in seasonal respiratory virus infection rates for healthcare workers whether they use N95 or surgical masks during routine patient care.

This draft will be posted in the Federal Register for comment. The workgroup did not make pathogen-specific recommendations for infection control. Drafting of that section will begin after Part 1 is completed, likely Spring 2024.

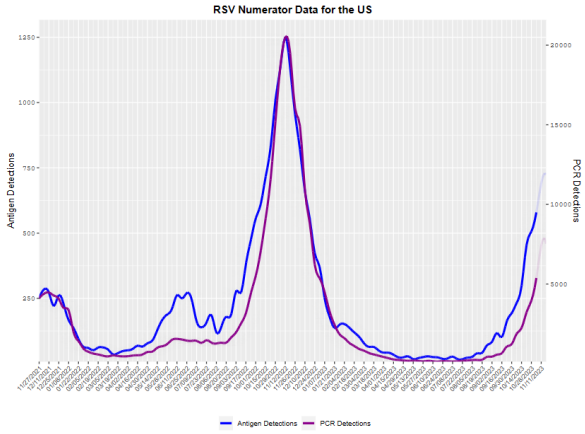
US Viral Respiratory Activity

RSV

Percent Positive

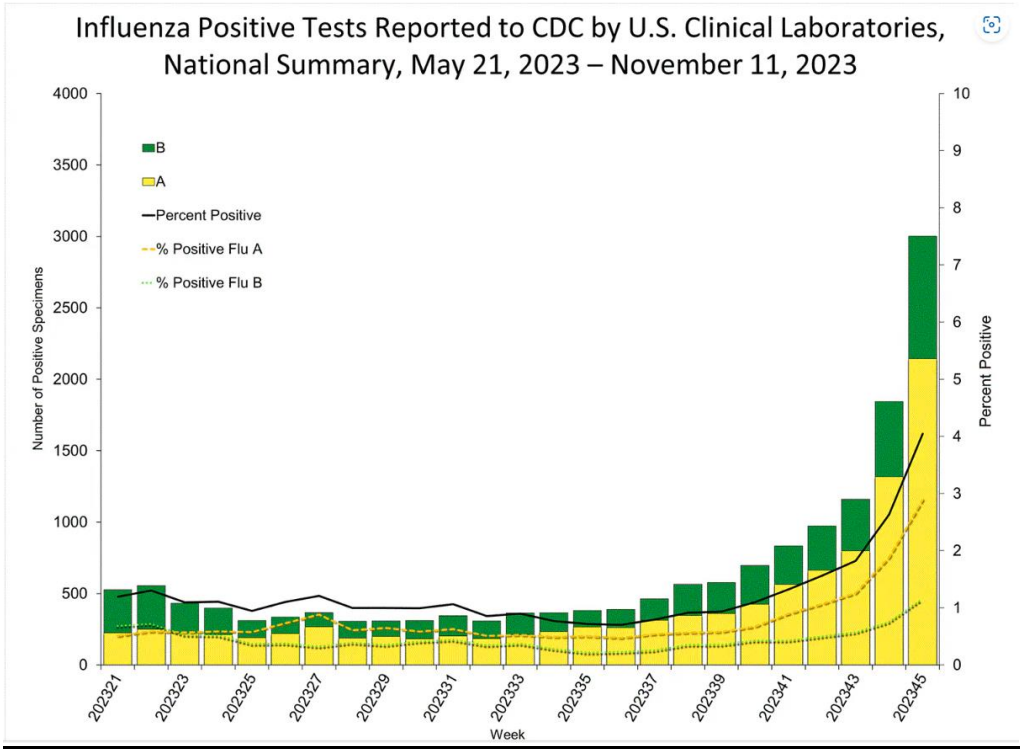


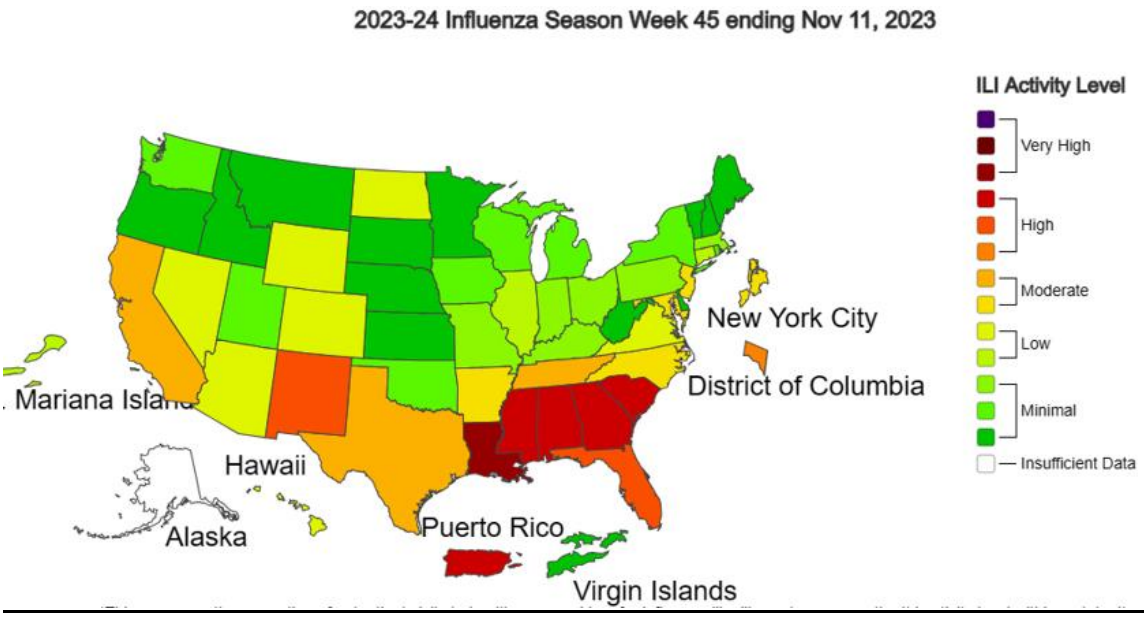
Detections



Comment: Clearly RSV activity and hospitalizations are up in several areas of the US. This is the traditional time RSV activity.

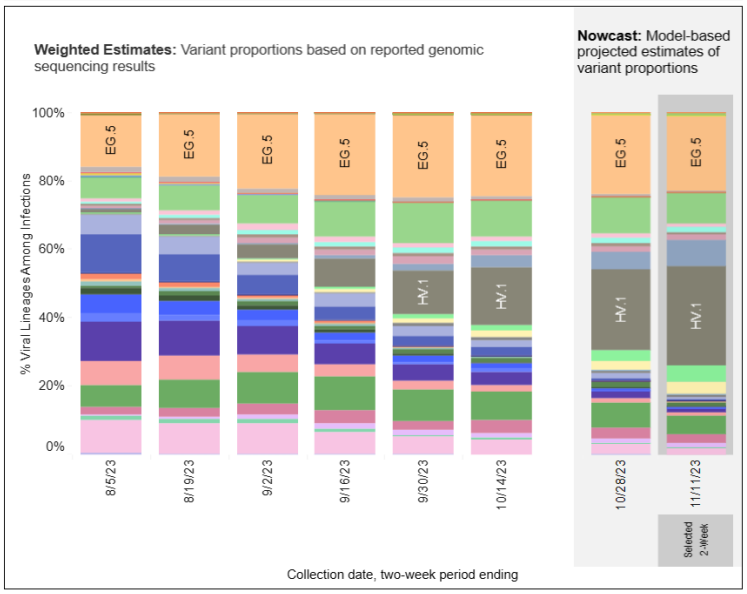
Seasonal Influenza





Comment: Seasonal influenza activity continues to increase in most parts of the country, most notably in the South Central, Southeast, and West Coast regions. The number of weekly flu hospital admissions continues to increase. We are seeing both influenza A (~71% of cases most H1N1) and influenza B (~29% of cases all the Victoria strain). It is not too late to get your influenza vaccinea.

COVID-19



USA

WHO label	Lineage #	%Total	95%PI
Omicron	HV.1	29.0%	26.0-32.1%
	EG.5	21.7%	19.3-24.2%
	FL.1.5.1	9.3%	8.0-10.8%
	HK.3	7.8%	6.2-9.9%
	XBB.1.16.6	5.6%	4.7-6.6%
	JD.1.1	4.6%	3.4-6.1%
	JF.1	3.5%	2.7-4.5%
	XBB.1.16.11	2.5%	2.0-3.2%
	XBB.2.3	1.9%	1.5-2.3%
	GK.1.1	1.6%	1.2-2.3%
	HF.1	1.4%	0.9-2.1%
	XBB.1.16.15	1.4%	1.0-1.9%
	XBB.1.16	1.2%	0.9-1.6%
	XBB.1.5.70	1.2%	0.6-2.2%
	BA.2	1.0%	0.5-2.1%
	GE.1	0.9%	0.6-1.3%
	XBB.1.16.1	0.8%	0.6-1.1%
	XBB	0.8%	0.6-1.0%
	GK.2	0.6%	0.5-0.9%
	EG.6.1	0.5%	0.3-0.7%
	XBB.1.5	0.3%	0.2-0.4%
	XBB.1.9.1	0.3%	0.2-0.4%
	XBB.1.42.2	0.2%	0.1-0.3%
	XBB.1.5.68	0.2%	0.1-0.3%
	XBB.1.9.2	0.2%	0.1-0.2%
	XBB.1.5.72	0.2%	0.1-0.2%
	CH.1.1	0.2%	0.1-0.3%
	XBB.2.3.8	0.1%	0.0-0.2%
	XBB.1.5.10	0.1%	0.0-0.1%
	XBB.1.5.59	0.0%	0.0-0.1%
	FD.1.1	0.0%	0.0-0.0%
	XBB.1.5.1	0.0%	0.0-0.0%
	FE.1.1	0.0%	0.0-0.0%
	EU.1.1	0.0%	0.0-0.0%
Other	Other*	1.1%	0.6-2.0%

Comment: Covid-19 activity overall slightly up, but not surging. HV.1 and EG.5 account for over 50% of variants as of the second week in November. Both variants are from the XBB lineage. Vaccination rates for updated vaccine remain <20%. This dashboard was not updated this past Friday due to the Thanksgiving holiday.

COVID-19

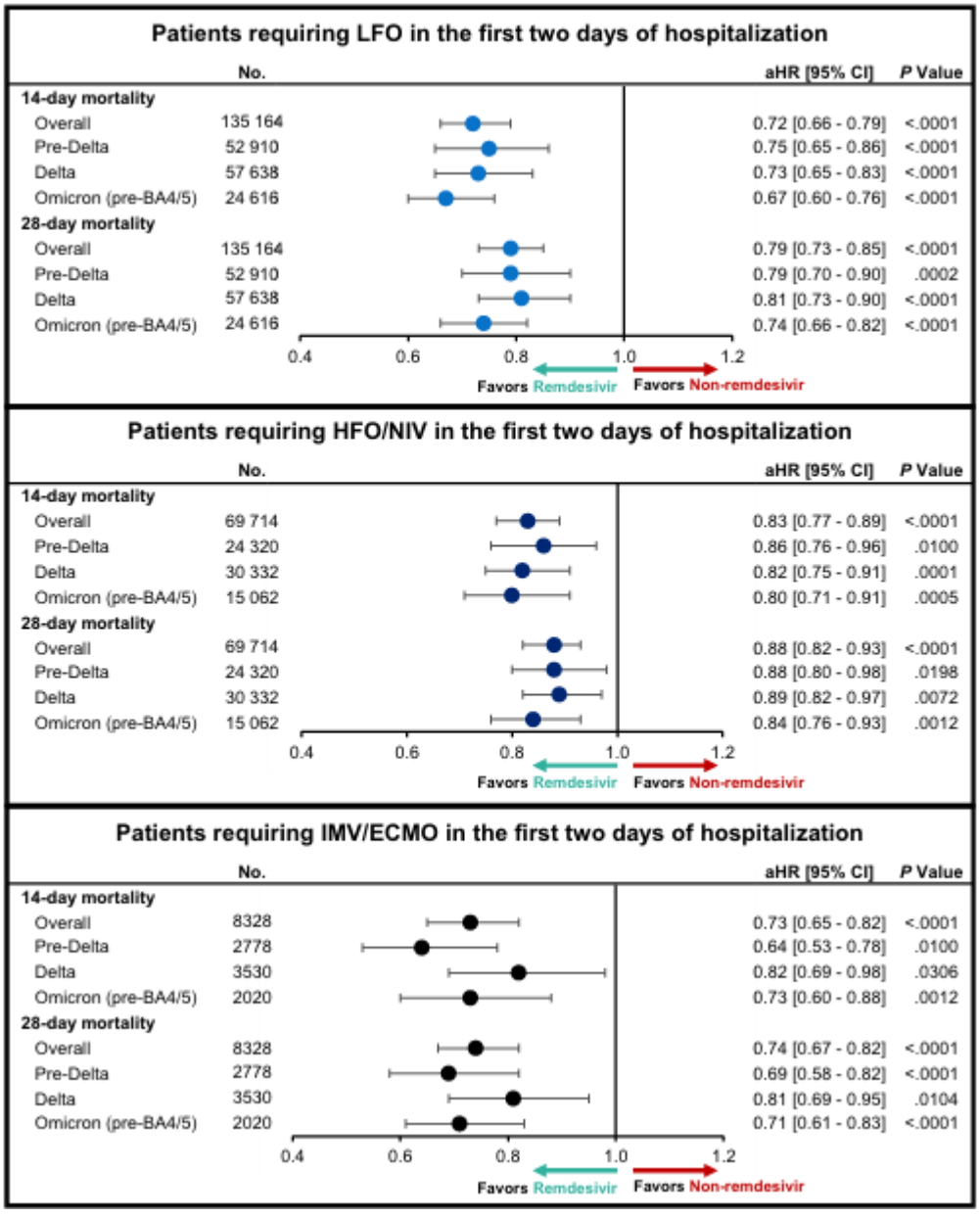
Remdesivir Is Associated With Reduced Mortality in COVID-19 Patients Requiring Supplemental Oxygen Including Invasive Mechanical Ventilation Across SARS-CoV-2 Variants OFID published online September 22, 2023

https://doi.org/10.1093/ofid/ofad482

Patients hospitalized for Covid-19 between December 2020 and April 2022 and administered remdesivir upon admission were 1:1 propensity score matched to patients not administered remdesivir during their Covid-19 hospitalization were included. Analyses were stratified by supplemental oxygen requirement upon admission and VOC(variant of concern) period. Cox proportional hazards models were used to derive adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for 14- and 28-day mortality.

Patients treated with remdesivir (67,582 LFO, 34,857 HFO/NIV, and 4164 IMV/ECMO) were matched to non- remdesivir patients. Unadjusted mortality rates were significantly lower for remdesivir-treated patients at 14 days (LFO: 6.4% vs. 8.8%; HFO/NIV: 16.8% vs. 19.4%;

IMV/ECMO: 27.8% vs. 35.3%) and 28 days (LFO: 9.8% vs. 12.3%; HFO/NIV: 25.8% vs. 28.3%; IMV/ECMO: 41.4% vs. 50.6%). After adjustment, remdesivir treatment was associated with a statistically significant reduction in in-hospital mortality at 14 days (LFO: aHR, 0.72; 95% CI, 0.66–0.79; HFO/NIV: aHR, 0.83; 95% CI, 0.77–0.89; IMV/ECMO: aHR, 0.73; 95% CI, 0.65–0.82) and 28 days (LFO: aHR, 0.79; 95% CI, 0.73–0.85; HFO/NIV: aHR, 0.88; 95% CI, 0.82–0.93; IMV/ECMO: aHR, 0.74; 95% CI, 0.67–0.82) compared with non-remdesivir treatment. Lower risk of mortality among remdesivir-treated patients was observed across VOC periods.



Comment: Remdesivir treatment is associated with significantly reduced mortality among patients hospitalized for Covid- 19 requiring supplemental oxygen upon admission, including those requiring HFO/NIV or IMV/ECMO with severe or critical disease, across VOC periods. Remdesivir was associated with reduced mortality across VOC periods but was most pronounced during the Omicron wave. [prior studies were done with ancestral strain, alpha and

delta] Randomized controlled trial data have confirmed the effectiveness of early remdesivir administration in reducing time to recovery and mortality among Covid-19 patients in outpatient settings, in hospitalized patients not requiring ventilation, and in patients requiring. The effectiveness of remdesivir in patients requiring HFO, NIV, IMV, or ECMO has been more uncertain, in part related to the smaller proportion of critically ill patients enrolled in the trials. For patients requiring IMV/ECMO, the ACTT-1[N Eng J Med 2020; 383:1813–26] and SOLIDARITY[Lancet 2022; 399:1941–53] trials did not detect a significant effect of remdesivir on patients with Covid-19 who required ventilation at baseline; however, neither trial was designed or powered for subgroup analysis to evaluate the effectiveness of remdesivir among patients requiring ventilation (invasive or noninvasive). In the previous PINC AI Healthcare Database study, a significant reduction in mortality was observed in remdesivir- treated patients compared with non-remdesivir patients (14-day aHR, 0.70; 95% CI, 0.58–0.84; 28-day aHR, 0.81; 95% CI, 0.69–0.94) among a subgroup of 2592 patients requiring IMV/ECMO between August and November 2020. [Clin Infect Dis 2022; 75: e450–8] The primary limitation of this and other comparative effectiveness studies is the potential for residual confounding and subsequent indication bias. To minimize the risk of confounding by indication, propensity score methods and covariate adjustments were employed using an extensive list of clinically relevant covariates. In addition, this data set did not permit determination of prehospital care such as antivirals or other therapeutics administered before hospitalization, which may have led to residual confounding. Data on vaccinations was not available in this database either. The authors conclude that based on the current evidence, remdesivir should be administered as soon as possible in patients hospitalized for Covid-19 to prevent progression to severe or critical disease.

Bottom line: The results of this analysis, especially in IMV/ECMO may warrant a revision of current practice guidelines if confirmed by other studies. See WHO guideline updates below.

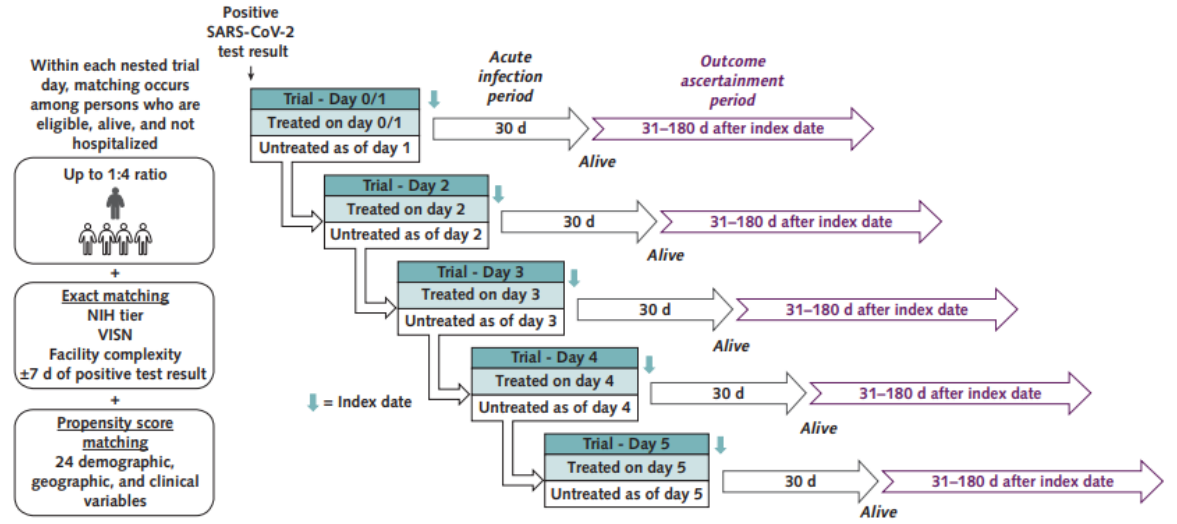
Effectiveness of Nirmatrelvir–Ritonavir Against the Development of Post–COVID-19 Conditions Among U.S. Veterans Ann Intern Med published online October 31, 2023

doi:10.7326/M23-1394

The purpose of this study was to measure the effectiveness of outpatient treatment of Covid-19 with nirmatrelvir–ritonavir in preventing PCCs (post–Covid-19 conditions). The investigators conducted a retrospective target trial emulation study comparing matched cohorts receiving nirmatrelvir–ritonavir versus no treatment. Nonhospitalized veterans in VHA care who were at risk for severe Covid-19 and tested positive for SARS-CoV-2 during January through July 2022 were included. Cumulative incidence of 31 potential PCCs at 31 to 180 days after treatment or a matched index date, including cardiac, pulmonary, renal, thromboembolic, gastrointestinal, neurologic, mental health, musculoskeletal, endocrine, and general conditions and symptoms were recorded.

As expected, eighty-six percent of the participants were male, with a median age of 66 years, and 17.5% were unvaccinated. Baseline characteristics were well balanced between participants treated with nirmatrelvir–ritonavir and matched untreated comparators. No differences were observed between participants treated with nirmatrelvir–ritonavir (n = 9593)

and their matched untreated comparators in the incidence of most PCCs examined individually or grouped by organ system, except for lower combined risk for venous thromboembolism and pulmonary embolism (subhazard ratio, 0.65 [95% CI, 0.44 to 0.97]; cumulative incidence difference, 0.29 percentage points [CI, 0.52 to 0.05 percentage points]).



Comment: Out of 31 potential PCCs, only combined thromboembolic events seemed to be reduced by nirmatrelvir–ritonavir. RCTs [N Engl J Med. 2022; 386:1397-1408; Lancet. 2023; 401:281-293] and observational studies [Lancet Infect Dis. 2023; 23:696-705; Clin Infect Dis. 2023;76: e342-e349] support beneficial effects of nirmatrelvir–ritonavir and, to a lesser extent, molnupiravir against hospitalization and/or death during the first 30 days after Covid-19 illness. Using an emulation trial design based on VA data, they previously reported that compared with no treatment, both nirmatrelvir–ritonavir and molnupiravir seemed to reduce the risk for death 31 to 180 days after infection. [Ann Intern Med. 2023; 176:807-816] Their results differ from those of a VA study by Xie and colleagues that reported that treatment with nirmatrelvir-ritonavir was associated with lower risk for 10 out of 13 PCCs.[JAMA Intern Med. 2023;183:554-564] Several factors may have accounted for differences in their findings, including data sources, period of study, eligibility criteria, and study methods. To enhance ascertainment of antiviral treatment, PCC outcomes, and key baseline covariates (including Covid-19 vaccination), the investigators combined VHA EHR, Community Care, and CMS– Medicare data, whereas Xie and colleagues used VHA EHR data alone. Xie and colleagues also included patients experiencing reinfection, whereas the investigators in this study focused on primary infections, although similar benefits from nirmatrelvir–ritonavir were observed in patients with reinfection versus primary infection. Mirroring the design of the EPICHR study [N Engl J Med. 2022; 386:1397-1408], the investigators excluded persons who were hospitalized on the date they tested positive (day 0) or the following day (day 1), which as expected resulted in a higher proportion of untreated patients excluded due to hospitalization on days 0 or 1 than treated persons. Xie and colleagues did not exclude persons who were hospitalized on or the day after their test-positive date and did not assign a paired index date to untreated comparators, which may have allowed sicker patients to be allocated to the untreated group, resulting in spurious associations between treatment and lower risk for PCCs. They could not ascertain symptom burden or date of symptom onset accurately using EHR data. Patients treated with nirmatrelvir–ritonavir might have been more likely to be symptomatic on their treatment date than their matched untreated

comparators on their assigned paired index date. Symptoms are inaccurately captured and may not reflect symptoms that were present as of the index date. PCCs as captured by ICD-10 codes may not accurately reflect the negative, long-term consequences of Covid-19.

Bottom line: Their results suggest that considerations about PCCs may not be an important factor in Covid-19 treatment decisions, but this requires further study.

Nirmatrelvir/ritonavir use in pregnant women with SARS-CoV-2 Omicron infection: a target trial emulation Nat Med published online November 1, 2023

doi.org/10.1038/s41591-023-02674-0

This target trial emulation study aims to address this gap by evaluating the use of nirmatrelvir/ritonavir in non-hospitalized pregnant women with symptomatic SARS-CoV-2 Omicron variant infection. Among patients diagnosed between 16th March 2022 and 5th February 2023, exposure was defined as outpatient nirmatrelvir/ritonavir treatment within five days of symptom onset or Covid-19 diagnosis. Primary outcomes were maternal morbidity and mortality index (MMMI), all-cause maternal death, and Covid-19-related hospitalization, while secondary outcomes were individual components of MMMI, preterm birth, stillbirth, neonatal death, and caesarean section. One-to-ten propensity-score matching was conducted between nirmatrelvir/ritonavir users and non-users; followed by cloning, censoring, and weighting.

Overall, 211 pregnant women on nirmatrelvir/ritonavir and 1,998 non-users were included. Nirmatrelvir/ritonavir treatment was associated with reduced 28-day MMMI risk (absolute risk reduction [ARR] = 1.47%, 95%CI = 0.21%-2.34%); but not 28-day COVID-19-related hospitalization (ARR = -0.09%, 95%CI = -1.08%-0.71%). Nirmatrelvir/ritonavir treatment was also associated with reduced risks of caesarean section (ARR = 1.58%, 95%CI = 0.85%-2.39%); and preterm birth (ARR = 2.70%, 95%CI = 0.98%-5.31%). No events of maternal or neonatal death or stillbirth were recorded.

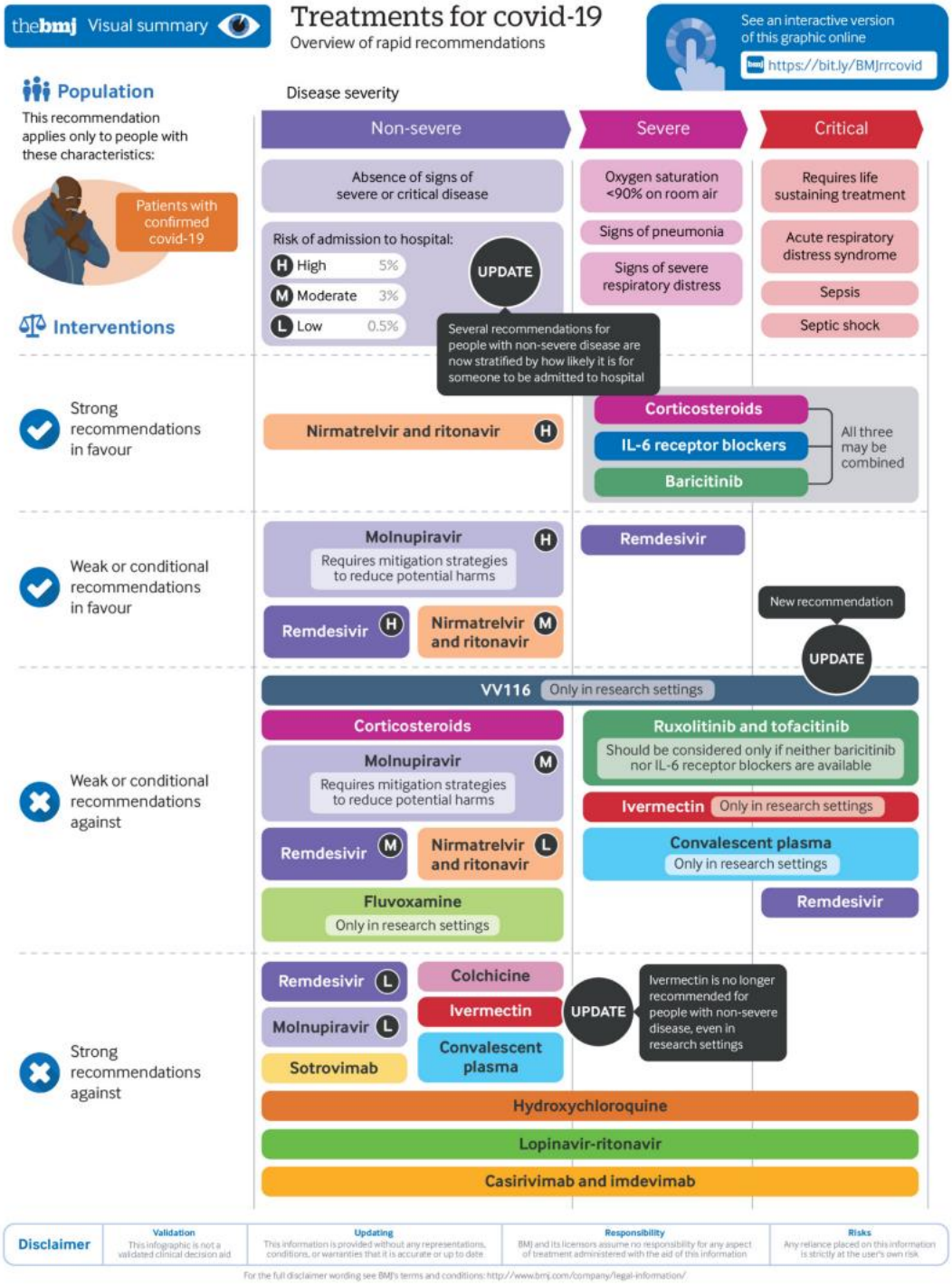
Comment: The findings suggest nirmatrelvir/ritonavir is an effective and safe treatment in symptomatic pregnant women with SARS-CoV-2 Omicron variant infection.

A living WHO guideline on drugs for Covid-19 BMJ published online November 10, 2023

doi.org/10.1136/bmj.m3379

Here is what is new: The guideline development group (GDG) defined 1.5% as a new threshold for an important reduction in risk of hospitalization in patients with non-severe Covid-19. Combined with updated baseline risk estimates, this resulted in stratification into patients at low, moderate, and high risk for hospitalization. A new recommendation was added for moderate risk of hospitalization for nirmatrelvir/ritonavir, and for moderate and low risk of hospitalization for molnupiravir and remdesivir. The new recommendation advised against use of remdesivir and molnupiravir for patients with non-severe Covid-19 at moderate and low risk of hospital admission (treatment is suggested for patients at high risk of admission).

New pharmacokinetic evidence was included for nirmatrelvir/ritonavir and molnupiravir, supporting existing recommendations for patients at high risk of hospitalization. New was a strong recommendation against the use of ivermectin for patients with non-severe Covid-19. A new recommendation was made against the antiviral agent VV116 for patients with non-severe and with severe or critical illness outside of randomized clinical trials based on one RCT comparing the drug with nirmatrelvir/ritonavir.



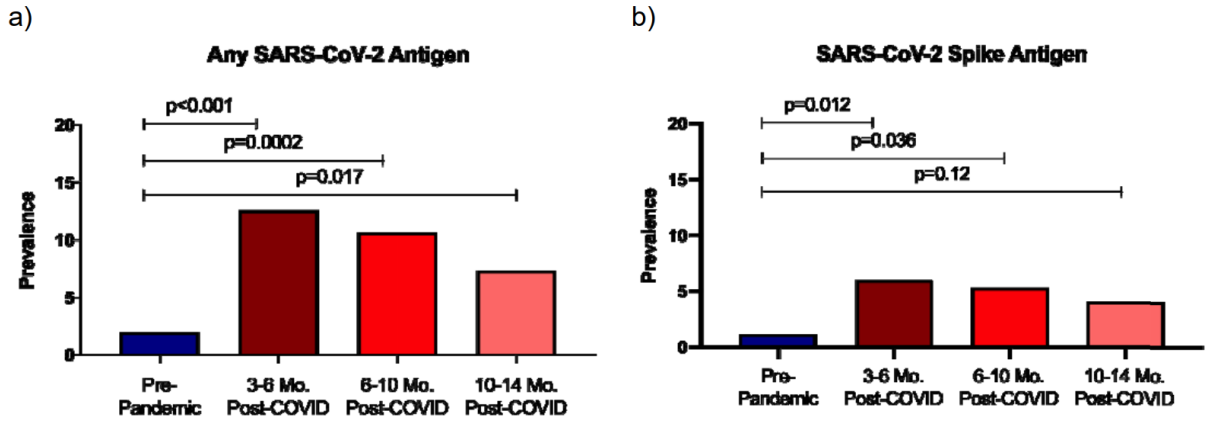
Comment: The new recommendations reflect changes in the virulence and transmissibility of circulating SARS-CoV-2 variants and sub-variants, along with changes in immunity related to global vaccinations and or natural immunity, which have led to lower baseline risks of severe illness and death for most patients with non-severe Covid-19.

Plasma-based antigen persistence in the post-acute phase of SARS-CoV-2 infection medRxiv published online October 26, 2023

doi.org/10.1101/2023.10.24.23297114

Using single molecule array (Simoa) assays for SARS-CoV-2 spike, S1, and nucleocapsid antigen in plasma from 171 pandemic-era individuals in the post-acute phase of SARS-CoV-2 infection and 250 pre-pandemic control samples, they compared prevalence of antigen detection. They used logistic regression models and prevalence ratios (PRs) to assess the relationship between demographic and disease factors and antigen persistence.

Compared to the proportion of antigen positivity in the pre-pandemic controls (2%), detection of any SARS-CoV-2 antigen was more frequent across all post-acute Covid-19-time bins (3-6 months:12.6%, p<0.001; 6-10 months, 10.7%, p=0.0002; 10-14 months, 7.5%, p=0.017). These differences were driven by spike protein for up to 14 months and nucleocapsid in the first 6 months after infection. The co-occurrence of multiple antigens at a single timepoint was uncommon. Hospitalization for acute Covid-19 (versus not hospitalized) and worse self-reported health during acute Covid-19 among those not hospitalized (versus more benign illness) were associated with higher prevalence of post-acute antigen detection (PR 1.86, p=0.03; PR 3.5, p=0.07, respectively) in the pandemic era.



Comment: Early in the pandemic, prolonged nasopharyngeal and/or gastrointestinal shedding of presumably non- infectious virus was observed in some individuals for 90 days or more, often despite clinical recovery. [Nature Reviews Microbiology 2023; 21:147-161] More recently, evidence has suggested that SARS-CoV-2 protein and/or RNA can be detected beyond the acute phase of illness in a subset of individuals. [Nat Immunol 2023. DOI: 10.1038/s41590-023-01601-2]

The findings in this paper provide evidence that SARS-CoV-2 antigens can persist beyond the period of acute illness in plasma. The observation that more than 10% of plasma samples for

over a year following initial SARS-CoV-2 infection contain detectable viral antigen, which could be potentially immunogenic, has significant implications given the sheer number of people infected with SARS-CoV-2 to date. The proportion of antigen positivity was lower in this study than in a prior report using this assay. [Clin Infect Dis 2023;76(3): e487-e490] The lower prevalence detected in this study may be because they enrolled individuals in the post-acute phase regardless of illness severity or the presence of post-acute symptoms. The finding that the virus can evolve over months in immunocompromised individuals suggests that persistent infection may be possible. In addition, they found antigen detection to be sporadic in individuals in whom it was present. It is possible that small variations over time could result in periods during which antigen is less detectable using current assays or antigen release from tissue reservoirs may in fact be intermittent, driven by host factors that have not yet been determined but might include differential release from tissues based on other factors.

Bottom line: More is needed to determine whether these antigens have a causal role in post-acute sequelae of SARS-CoV-2 infection (PASC). This article has not been peered reviewed.

Editor's Choice

SARS-CoV-2 Virologic Rebound With Nirmatrelvir–Ritonavir Therapy An Observational Study

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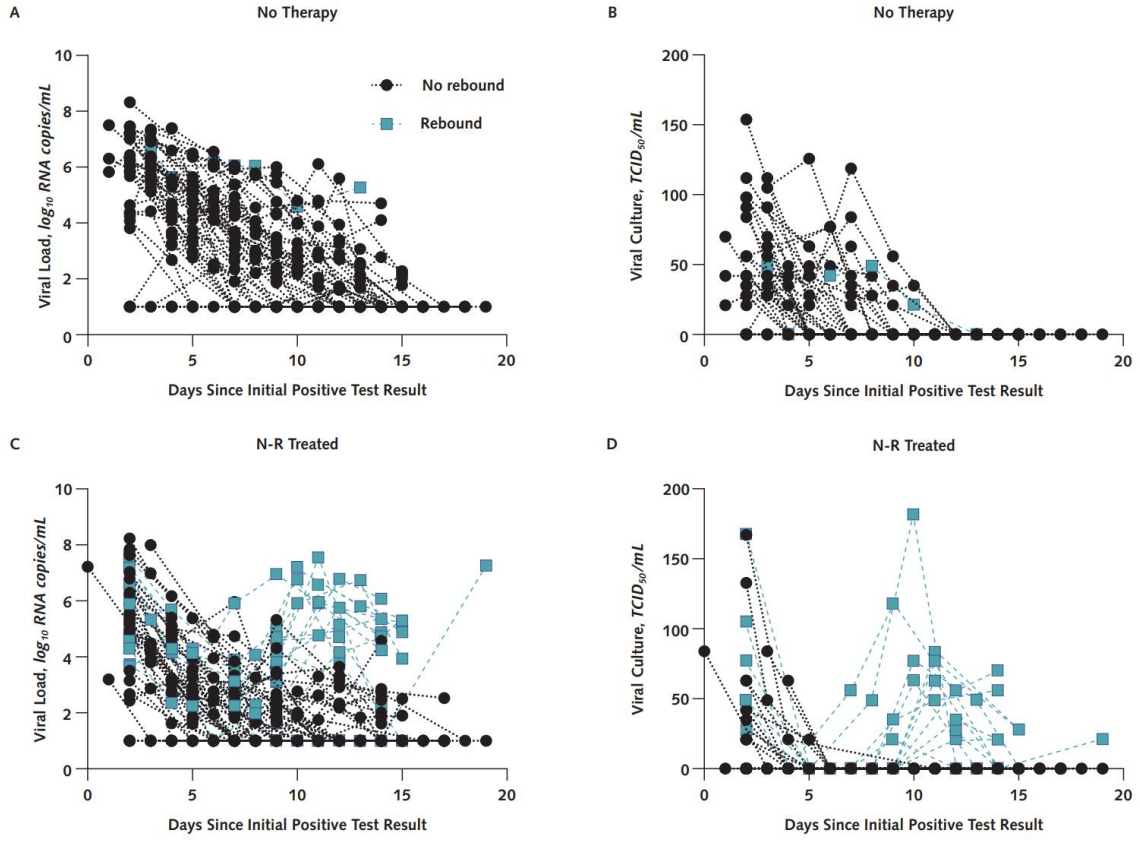
In this study, the investigators estimated the effect of nirmatrelvir-ritonavir (N-R) use on the frequency and duration of virological rebound (VR) in ambulatory persons. Secondary aims included estimating the validity of symptom reporting to detect VR and exploring the emergence of drug resistance mutations after VR. Participants and data for this analysis were drawn from POSITIVES (Post-vaccination Viral Characteristics Study), a prospective observational cohort study that enrolls persons with acute Covid-19 for longitudinal assessment of quantitative viral load, viral culture, and symptom data collection. The parent study provided data for the study of Covid-19 variants, host immunity, vaccination, therapeutics, and viral dynamics. Persons who are potentially eligible for recruitment into the POSITIVES cohort are identified from an automated list of persons with a positive test result and/or a prescription for a Covid-19 therapeutic. The 2 strategies of interest in this study were receipt of 5 days of N-R therapy and no receipt of therapy for Covid-19. They assigned eligible participants to the N-R group if they initiated N-R within 5 days of their first positive result on a Covid-19 diagnostic test and to the no-therapy group if they did not initiate any Covid-19 therapy within 5 days of their first positive result. The primary outcome of interest was VR within 20 days of the participant's initial positive test result, which we defined as either 1) a positive SARS-CoV-2 viral culture result after a prior negative result, or 2) sustained elevated viral load characterized by the combination of a nadir viral load below 4.0 log10 copies/mL followed by an increase in viral load that was at least 1.0 log10 copies/mL above the nadir, and 2 consecutive viral load results of 4.0 log10 copies/mL or higher. They selected this primary outcome as a surrogate for putative transmission risk, based on prior data relating transmission risk and replication-competent virus with viral loads of 4.0 log10 copies/ mL or higher. [Elife. 2021;10] For the secondary outcome, they restricted viral load measurements to days 5, 10, and 14 (all ±1 day) and defined VR as a viral load at days 10 and

14 of at least 2.7 log10 copies/mL and at least 0.5 log10 copies/mL greater than the result at day 5.

Compared with untreated persons (n=55), those taking N-R (n=72) were older, received more Covid-19 vaccinations, and more commonly had immunosuppression. Fifteen participants (20.8%) taking N-R had VR versus 1 (1.8%) who was untreated (absolute difference, 19.0 percentage points [95% CI, 9.0 to 29.0 percentage points]; P = 0.001). All persons with VR had a positive viral culture result after a prior negative result. In multivariable models, only N-R use was associated with VR (adjusted odds ratio, 10.02 [CI, 1.13 to 88.74]; P = 0.038). Virologic rebound was more common among those who started therapy within 2 days of symptom onset (26.3%) than among those who started 2 or more days after symptom onset (0%) (P = 0.030). Among participants receiving N-R, those who had VR had prolonged shedding of replication competent virus compared with those who did not have VR (median, 14 vs. 3 days). Eight of 16 participants (50% [CI, 25% to 75%]) with VR also reported symptom rebound; 2 were completely asymptomatic. No post-VR resistance mutations were detected.



Comment: Frequent monitoring by both PCR and viral culture during the acute stages of Covid-19 showed that VR with shedding of replication-competent virus occurred in approximately 20% of persons taking N-R and 2% of those who did not. Virologic rebound remained more common with N-R use after stratification by demographic and clinical characteristics, such as vaccination and immunosuppression status. Moreover, the VR phenomenon was associated with a substantial prolongation of shedding of replication-competent virus (median, 14 vs. 3 days). It is still important to remember that for moderate- to high-risk patients, the clinical benefits associated with N-R use, including protection from hospitalization and death, are well

established. [Clin Infect Dis. 2023;76: e537-e539] These data support the possibility of an N-R–specific VR phenomenon, which substantially increases the duration of shedding of replication-competent virus and has implications for post–N-R monitoring and isolation recommendations. The investigators in this study found a higher incidence of VR with N-R use than prior studies. If they had restricted their analysis to 3 time points based on viral load, as was done in prior trials, [N Engl J Med. 2022;387:1047-1049] they detected a 2.4% rate of VR, which is similar to the rate in prior studies, but notably missed 80% of VR events. This suggests that the discrepancy between the incidence of VR found in this study and that described in prior studies may result from differences in frequency of sampling and use of culture methods to detect VR. Symptoms should not be relied on to detect or exclude VR. Two persons with VR had a complete absence of symptoms during the VR period, and fewer than half with VR had symptom rebound. In contrast, the majority of those who did have symptom rebound did not experience VR. Thus, strategies that use antigen testing to identify persons treated with N-R who develop VR and consequent prolonged shedding of viable virus would be most effective if they were deployed independent of symptom rebound.

This study was limited by its observational design, with expected differences between those taking N-R and untreated persons based on treatment guidelines for N-R, and its relatively small sample size. Finally, they used viral culture as a surrogate for transmission risk but did not measure contagiousness or transmission events directly.

Bottom line: Larger samples, with more balanced groups, will be needed to assess the causal relationship more thoroughly.