Infectious Diseases Watch

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General Infectious Diseases

Doxycycline versus cephalexin treatment of presumed streptococcal skin and soft tissue infection among adults presenting to the emergency department

Antimicrob Agents Chemother published online January 3, 2024

doi: 10.1128/aac.01282-23

This is a retrospective single-center cohort study involving 100 patients presenting to the ED with new nonpurulent cellulitis and treated as outpatients with <14 days of oral doxycycline or cephalexin. They assessed clinical failure (requirement for hospital admission or change in antibiotic prescription [including need for parenteral therapy] within 14 days of diagnosis). At this center, S pyogenes isolates showed 82% tetracycline susceptibility. Patients were excluded for the following: polymicrobial infection, surgical wound, immersion injury, chronic lesion (>3 months), additional systemic antibiotic with S. pyogenes activity, deep-seated infection, significant immunocompromise, or pregnancy/breastfeeding.

In analysis of outcomes among 50 doxycycline recipients and 50 propensity-matched cephalexin recipients (median age, 46; mean BMI, 29 kg/m^2, antibiotic duration, 7–10 days, diabetes mellitus in 12% and 24% of recipients, respectively), fever was documented in only 1 patient, and only 4% had leukocytosis. The 14-day clinical failure rate was 6% in each group, with only 3 patients requiring hospitalization.

Comment: First this is a small study with mild nonpurulent cellulitis (suggests most are Strep). The population is generally younger uncomplicated patients prescribed either doxycycline or cephalexin. The study was not powered to detect a specific difference in antibiotic effectiveness. Doxycycline has certain advantages which include reduced risk of C diff infection and anti-inflammatory effects. For severe nonpurulent infections cephalosporins provide more reliable strep coverage.

Bottom line: These results provide support for the use of doxycycline for uncomplicated mild non purulent cellulitis. Larger prospective clinical investigations to evaluate the potential role for doxycycline as an alternative treatment option for cellulitis are needed.

Comparative Effectiveness of First-Line and Alternative Antibiotic Regimens in Hospitalized Patients With Nonsevere Community-Acquired Pneumonia Chest 2024; 165:68-78

doi.org/10.1016/j.chest.2023.08.008

The American Thoracic Society and Infectious Diseases Society of America's (ATS/IDSA) most recent guideline on treating hospitalized patients with community-acquired pneumonia (CAP) recommends combination therapy with a β-lactam plus a macrolide or monotherapy with a respiratory fluoroquinolone [Am J Respir Crit Care Med 2019; 200: e45] Substituting doxycycline for a macrolide also is an option in some clinical settings (e.g., prolonged PR interval). Empirical coverage for S aureus or P aeruginosa is recommended for patients with risk factors or history of these pathogens.

In a retrospective study of 23,500 patients from 19 Canadian hospitals, investigators assessed whether mortality differed when various antibiotic regimens were used in patients hospitalized with CAP; patients who were admitted to intensive care or with diagnoses of aspiration pneumonia were excluded. Patients received a β-lactam plus a macrolide (40%), a β-lactam alone (39%), a respiratory fluoroquinolone alone (19%), or a β-lactam plus doxycycline (2%).

In analyses adjusted extensively for potentially confounding factors, outcomes were similar for all the antibiotic regimens except for β-lactam alone. When compared with the β-lactam-plus-macrolide combination, the β-lactam-alone regimen was associated with significantly longer time to clinical stability and borderline-significant 1.5% higher in-hospital mortality.

Comment: This large observational study supports recent guidelines for treating inpatients with CAP. This study reinforces that β-lactams should not be used alone. Although evidence is not as robust for doxycycline in place of a macrolide in combination with a β-lactam, there are other studies that show doxycycline is a viable alternative and is associated with a lower risk of C. difficile. [Clin Infect Dis 2018; 66:514–22] In fact, in this study, the β-lactam/doxycycline group had the lowest risk for C difficile colitis. Even though they adjusted for many prognostic factors using propensity scores and overlap weighting, there could still be residual confounders.

Bottom line: β-lactam plus a macrolide, FQ alone, and β-lactam plus doxycycline had similar outcomes and can be considered effective regimens for nonsevere CAP.

Editor's Choice

Incidence and risk factors for subsequent infections among rectal carriers with carbapenem-resistant Klebsiella pneumoniae: a systematic review and meta-analysis J Hosp Infect 2024; 145:11e21

doi.org/10.1016/j.jhin.2023.12.002

The PubMed, Web of Science, and Cochrane Library databases were searched for relevant articles published between December 1998 and June 2023. Pooled estimates with a 95% confidence interval (CI) were calculated for the incidence rate, whereas pooled odds ratios

(ORs) were calculated for the risk factors for which the OR was reported in three or more studies.

Fourteen studies were included in the review with 5483 patients for the assessment of incidence, whereas seven of these studies with 2170 patients were included for the analysis of risk factors. In the meta-analysis, the incidence of CRKp infections after colonization was 23.2% (17.9-28.5). Additionally, three independent risk factors for subsequent CRKp infections were identified as admission to the intensive care unit (ICU) (2.59; 95% CI: 1.64-4.11), invasive procedures (2.53; 95% CI: 1.59-4.03), and multi-site colonization (6.24; 95% CI: 2.38-16.33).

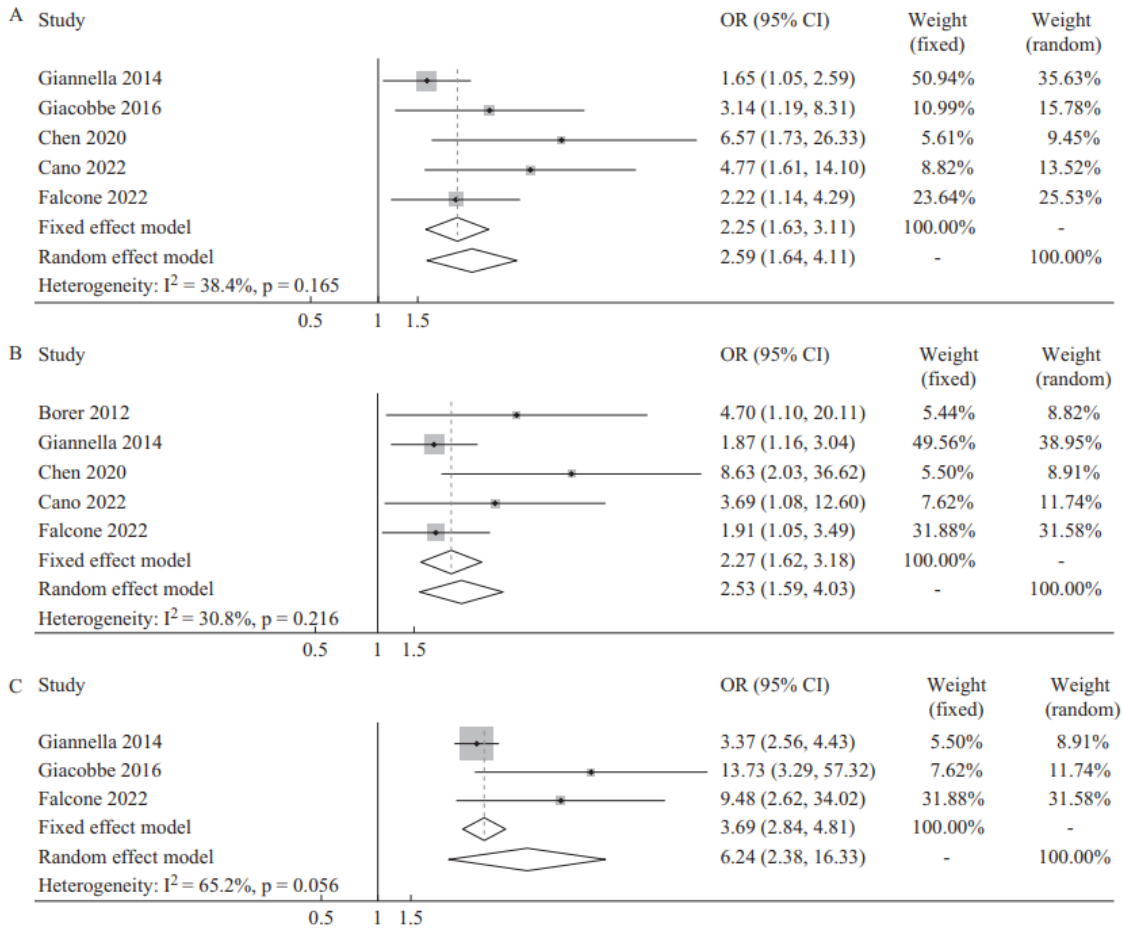


Figure 3. Forest plot of the risk factors for carbapenem-resistant *K. pneumoniae* (CRKp) infections in rectal carriers. (A) Admission to intensive care unit. (B) Invasive procedures. (C) Multi-site colonization with CRKp.

This review reveals the incidence of CRKp infections in rectal carriers in different countries, emphasizing the role of rectal colonization with CRKp as an important source of nosocomial infections. Significantly, the risk factors indicated in this review can assist clinicians in identifying CRKp carriers with an elevated risk of subsequent infections, thereby enabling further measures to be taken to prevent nosocomial infections.

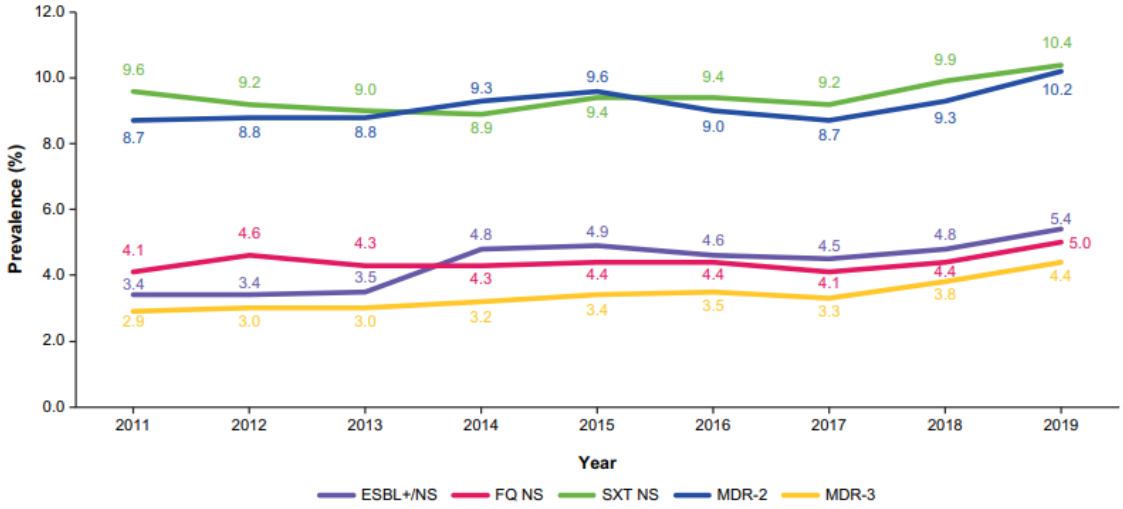
Bottom line: This study confirms the risk of GI colonization for gram-negative MDROs and subsequent infection. We need better tools to proactively identify carriers and develop interventions such as FMTs. [Sc Trans Med 2023; 15: 720 eabo2750]

Prevalence, regional distribution, and trends of antimicrobial resistance among female outpatients with urine Klebsiella spp. isolates: a multicenter evaluation in the United States between 2011 and 2019 Antimicrobial Resistance & Infection Control 2024 13:21

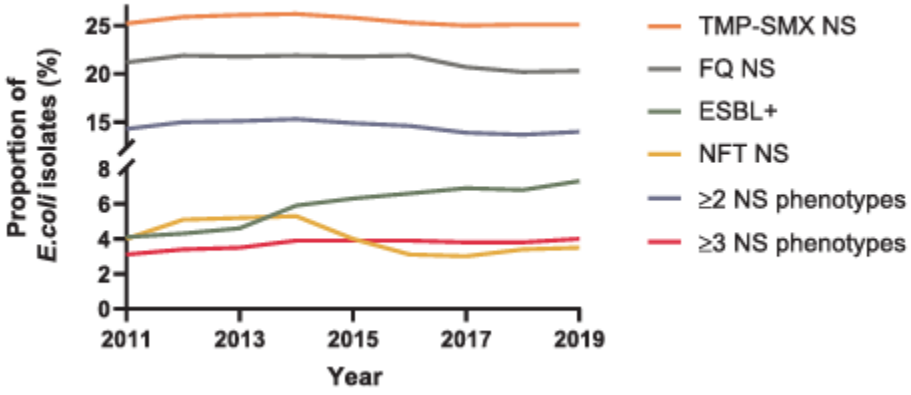
doi.org/10.1186/s13756-024-01372-x

This was a retrospective cohort study to assess the prevalence and geographic distribution of antimicrobial resistance among Klebsiella species and antimicrobial resistance trends for K. pneumoniae in the US (2011–2019). K pneumoniae and K. oxytoca urine isolates (30-day, non-duplicate) among female outpatients (aged≥12 years) with presumed uUTI(uncomplicated) at 304 centers in the US were classified by resistance phenotype(s): not susceptible to nitrofurantoin, trimethoprim/sulfamethoxazole, or fluoroquinolone, extended-spectrum β-lactamase-positive/not susceptible; and multidrug-resistant based on≥2 and≥3 resistance phenotypes. Antimicrobial resistance prevalence by census division and age, as well as antimicrobial resistance trends over time for Klebsiella species, were assessed using generalized estimating equations.

270,552 Klebsiella species isolates were evaluated (250,719 K. pneumoniae; 19,833 K. oxytoca). The most frequent resistance phenotypes in 2019 were nitrofurantoin not susceptible (Klebsiella species: 54.0%; K. pneumoniae: 57.3%; K. oxytoca: 15.1%) and trimethoprim/sulfamethoxazole not susceptible (Klebsiella species: 10.4%; K. pneumoniae: 10.6%; K. oxytoca: 8.6%). Extended-spectrum β-lactamase-positive/not susceptible (NS) prevalence was 5.4%, 5.3%, and 6.8%, respectively. K. pneumoniae resistance phenotype prevalence varied (p <0.0001) geographically and by age and increased over time (except for the nitrofurantoin NS phenotype, which was stable and>50% throughout).



Comment: E coli is still the most common cause of community-acquired uUTIs, and previous work has determined the prevalence and geographic distribution of AMR among E. coli in the US. [BMC Infect Dis. 2022; 22:194]. One such study demonstrated a high prevalence of non-susceptibility to trimethoprim/sulfamethoxazole (SXT; 25.4%) and fluoroquinolones (FQs; 21.1%) among E. coli isolates [Clin Infect Dis. 2021;73:1992–9]. Further, the study showed an increasing trend of extended-spectrum β-lactamase (ESBL)-producing E. coli isolates over recent years, with relative average yearly increases of 7.7%. Nitrofurantoin resistance was <4%). See below



This current publication studied a large sample of K. pneumoniae isolates from US outpatients over nine years and provides valuable insights into prevalence of AMR among urine isolates in the outpatient setting. The rapid spread of pathogens with the ESBL+ phenotype is of global concern, as effective empiric oral therapeutic options are limited and the burden of AMR in acute care settings is increasing. In this study, the model-estimated overall prevalence of ESBL+/NS K. pneumoniae isolates over the 2011–2019 study period was 4.6% (across all census divisions), with a relative annual increase in prevalence of 5.4% over this same period. The data in this study are comparable to previous studies of ESBL+ prevalence in the US. [Int J Antimicrob Agents. 2022; 59:106535; Ann Emerg Med. 2021; 77:32–43] The study includes potential variability in susceptibility testing due to reliance on different local laboratory practices. The lack of information on specific laboratory practices within census divisions precluded more localized resistance data. The study period also included various changes in the minimum inhibitory concentration (MIC) breakpoints and interpretive criteria from the CLSI for cefazolin, cefepime, levofloxacin, and ciprofloxacin; when these changes were implemented by individual laboratories involved in the study is unknown.

Bottom line: Awareness of AMR patterns among outpatient Klebsiella spp. uropathogens, particularly K. pneumoniae, is important to help guide physicians in the optimal empiric treatment of uUTI. This large study confirms high nitrofurantoin resistance and increasing AMR trends among urinary K. pneumoniae and K. oxytoca isolates from female outpatients in the US. This is important to consider when updating clinical practice guidelines for the treatment of uUTI, such as those published by IDSA in 2011, which recommend NTF as a first-line treatment for uUTI. [Clin Infect Dis. 2011;52: e103–20.27] However, E coli is still the most common pathogen for uUTI where NTF is still very active.

Effectiveness of Prophylactic Oral and/or Vaginal Probiotic Supplementation in the Prevention of Recurrent Urinary Tract Infections: A Randomized, Double-Blind, Placebo-Controlled Trial Clin Infect Dis published online December 12, 2023

doi.org/10.1093/cid/ciad766

This double-blind, placebo-controlled study enrolled 174 premenopausal women with a history of recurrent UTIs and randomized them to 1 of the 4 treatment groups: placebo (G1, oral placebo + vaginal placebo), oral probiotic (G2, oral lactic acid bacteria and bifidobacteria + vaginal placebo), vaginal probiotic (G3, oral placebo + vaginal lactobacilli), and probiotic combination (oral lactic acid bacteria and bifidobacteria + vaginal lactobacilli), for 4 months. Participants were followed up for symptomatic UTIs for 1 year. The primary end points were the number of symptomatic UTIs at 4 months, the proportion of participants with at least 1 symptomatic UTI, and the time to the first symptomatic UTI.

Results. The incidence of UTI at 4 months in G1, G2, G3, and G4 was 70.4%, 61.3%, 40.9%, and 31.8%, respectively. The mean number of symptomatic UTI recurrences at 4 months was significantly lower ($P < .05$) in G3 (1.06) and G4 (1.07) compared with G1 (2.1) and G2 (1.63). Further, the time to first symptomatic UTI (days) was significantly longer ($P < .05$) in G3 (123.8) and G4 (141.8) compared with G1 (69.3) and G2 (71.9). Probiotic supplementations were well tolerated with no serious adverse events.

The vaginal microbiota assessments by RT-PCR revealed a significant increase in the vaginal *E coli* relative count at 4 months in G1, whereas G3 and G4 showed significantly lower counts. Moreover, within-group analysis in G3 and G4 demonstrated a significant reduction in the counts of the chief UTI pathogens, namely, *E. coli*, *K pneumoniae*, and *P mirabilis*, and a significant increase in lactobacilli and bifidobacteria counts after treatment at 4 months. The post-intervention vaginal lactobacilli count was significantly higher only in G4 when compared with the other groups ($P = .008$;)

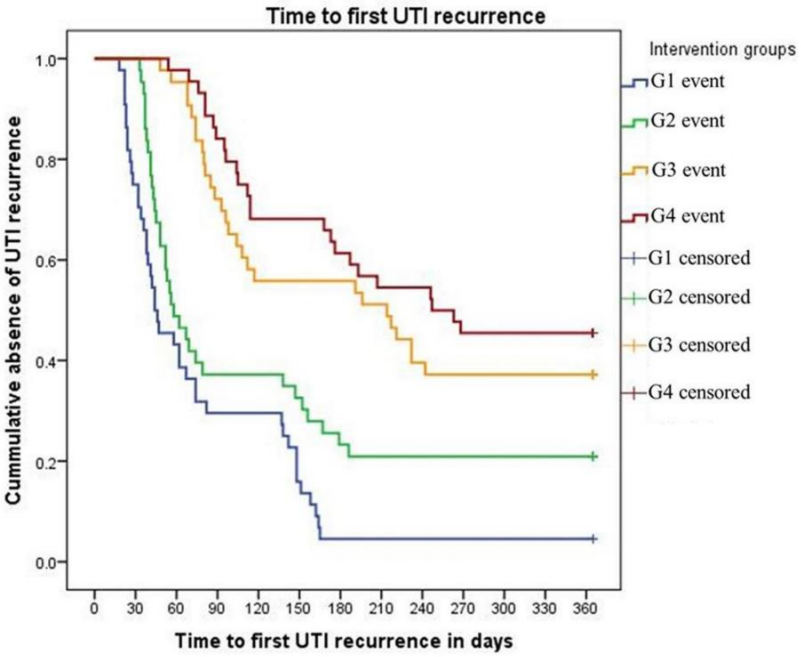


Figure 2. Kaplan–Meier analysis plot of time to first UTI recurrence in 12 months in the treatment groups. G1 used oral placebo + vaginal placebo; G2 used oral probiotic + vaginal placebo; G3 used oral placebo + vaginal probiotic; and G4 used oral probiotic + vaginal probiotic. $P < .05$ (compared with G1 in the post hoc test). $P < .05$ (compared with G2 in the log-rank pair-wise test). Abbreviations: G, group; UTI, urinary tract infection.

Comment: The study revealed a significantly lower incidence, lower number of recurrent UTI episodes, and longer mean time to first episode of symptomatic UTI recurrence with a vaginal probiotic alone or in combination with the oral probiotic mix, thus showing a promising role of probiotics in the management of recurrent UTIs in premenopausal women. Probiotics avert or stop the ascension of uropathogens into the bladder through various mechanisms, including interference with pathogen adhesion, biofilm formation, invasion and growth, expression of virulence factors, and modulation of the host's defenses to fight infections. [Indian J Med Microbiol 2017; 35:347–54] The lactobacilli strains in the intravaginal probiotic formulation are known to produce antiinfective agents, including hydrogen peroxide. The probiotic bacteria adhere at high levels to human epithelial cells, displacing vaginal pathogens [J Appl Microbiol 2002; 93:884–93] Sample size was modest, and direct comparison of probiotics to prophylactic antibiotics for the prevention of recurrent UTIs was not performed. This study may not be generalizability in postmenopausal women who are naturally at a higher risk for recurrent UTIs.

Bottom line: This study suggests that probiotics could be a promising option for the management of recurrent UTIs in premenopausal women especially with a vaginal probiotic alone or in combination with the oral probiotic mix.

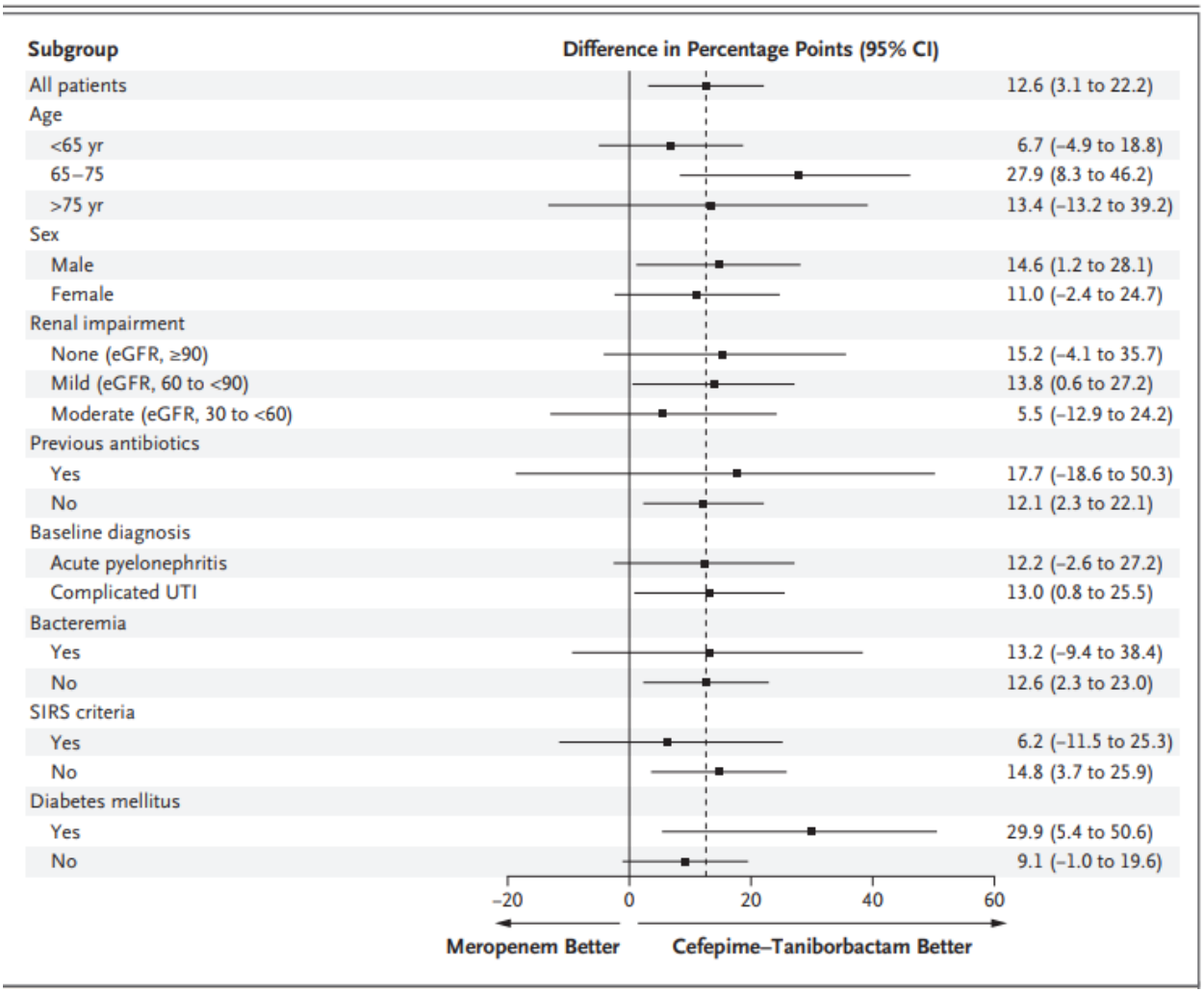
Editor's Choice

Cefepime–Taniborbactam in Complicated Urinary Tract Infection N Engl J Med 2024;390:611-22

DOI: 10.1056/NEJMoa2304748

Cefepime–taniborbactam is an investigational β-lactam and β-lactamase inhibitor combination with activity against Enterobacterales species and P. aeruginosa expressing serine- and metallo-β-lactamases. This is a phase 3, double-blind, randomized trial. They assigned hospitalized adults with complicated urinary tract infection (UTI), including acute pyelonephritis, in a 2:1 ratio to receive intravenous cefepime–taniborbactam (2.5 g) or meropenem (1 g) every 8 hours for 7 days; this duration could be extended up to 14 days in case of bacteremia. Oral step-down therapy was not permitted. Patients were excluded if they had received antibacterial drug therapy for complicated UTI for more than 24 hours before randomization, had an infection with a meropenem-resistant pathogen. Also excluded were patients with an estimated glomerular filtration rate of less than 30 ml per minute per 1.73 m2 of body-surface area or who had prostatitis, perinephric or renal abscess, severe hepatic impairment, or hypersensitivity to any β-lactam antibiotic or who had undergone renal transplantation. Randomization was performed before the availability of baseline culture results. The primary outcome was both microbiologic and clinical success (composite success) on trial days 19 to 23 in the microbiologic intention-to-treat (microITT) population (patients who had a qualifying gram-negative pathogen against which both study drugs were active). A prespecified superiority analysis of the primary outcome was performed after confirmation of noninferiority.

Of the 661 patients who underwent randomization, 436 (66.0%) were included in the microITT population. The mean age of the patients was 56.2 years, and 38.1% were 65 years of age or older. In the microITT population, 57.8% of the patients had complicated UTI, 42.2% had acute pyelonephritis, and 13.1% had bacteremia. Composite success occurred in 207 of 293 patients (70.6%) in the cefepime–taniborbactam group and in 83 of 143 patients (58.0%) in the meropenem group. Cefepime–taniborbactam was superior to meropenem regarding the primary outcome (treatment difference, 12.6 percentage points; 95% confidence interval, 3.1 to 22.2; P=0.009). Differences in treatment response were sustained at late follow-up (trial days 28 to 35), when cefepime–taniborbactam had higher composite success and clinical success. Adverse events occurred in 35.5% and 29.0% of patients in the cefepime–taniborbactam group and the meropenem group, respectively, with headache, diarrhea, constipation, hypertension, and nausea the most frequently reported; the frequency of serious adverse events was similar in the two groups.



Comment: Taniborbactam is a bicyclic boronate β-lactamase inhibitor with potent, selective, direct inhibitory activity against Ambler class A, B, C, and D enzymes, including prevalent serine and metallo-β-lactamases.[J Med Chem 2020; 63:2789-80] The cefepime– taniborbactam combination is active in vitro against most isolates of carbapenem-resistant Enterobacterales species, multidrug-resistant Pseudomonas aeruginosa, and Enterobacterales species and P. aeruginosa organisms that are resistant to both ceftolozane–tazobactam and ceftazidime–avibactam. However, in a recent report it was shown that New Delhi MBL-9 (NDM-9) escapes the inhibitory action of taniborbactam by a single amino acid substitution with respect to New Delhi MBL-1 (NDM-1), the most widely disseminated MBL. [Antimicrob Agents Chemother 2024; 68: 10.1128/aac.01168-23] The FDA will review approval of Cefepime–taniborbactam in the coming weeks. As with any new drug we will need to monitor the development of resistance over time.

Bottom line: Cefepime–taniborbactam was shown to be a potential treatment option for patients with complicated UTI and acute pyelonephritis caused by Enterobacterales species and *P. aeruginosa*, including antimicrobial resistant strains.

Oral gepotidacin versus nitrofurantoin in patients with uncomplicated urinary tract infection (EAGLE-2 and EAGLE-3): two randomised, controlled, double-blind, double-dummy, phase 3, non-inferiority trials Lancet published online February 8, 2024

doi.org/10.1016/ S0140-6736(23)02196-7

Gepotidacin is a novel, bactericidal, first-in-class triazaacenaphthylene antibiotic that inhibits bacterial DNA replication by a distinct mechanism of action and a unique binding site, providing well balanced inhibition of two type II topoisomerase enzymes. The investigators aimed to compare the efficacy and safety of oral gepotidacin with that of nitrofurantoin in adolescent and adult female individuals with uncomplicated urinary tract infections.

EAGLE-2 and EAGLE-3 were phase 3, randomized, multicenter, double-blind, double-dummy, non-inferiority (10% margin) trials, in which patients were enrolled at 219 centers worldwide. Patients assigned female at birth, nonpregnant, aged 12 years or older, weighing 40 kg or more, with two or more symptoms of dysuria, frequency, urgency, or lower abdominal pain, and with evidence of urinary nitrite, pyuria, or both were eligible for inclusion. Patients were randomly assigned (1:1) centrally by interactive response technology to receive oral gepotidacin (1500 mg twice daily for 5 days) or oral nitrofurantoin (100 mg twice daily for 5 days), with randomization stratified by age category and history of recurrent uncomplicated urinary tract infections. Patients, investigators, and the sponsor study team were masked to treatment assignment. The primary endpoint, therapeutic response (success or failure) at test-of-cure (i.e., day 10–13), was evaluated in randomly assigned patients with nitrofurantoin-susceptible qualifying uropathogens ($\geq 10^5$ CFU per mL) and who received at least one dose of study treatment. Therapeutic success was defined as combined clinical success (i.e., complete symptom resolution) and microbiological success (i.e., reduction of qualifying uropathogens to $<10^3$ CFU/mL) without other systemic antimicrobial use. Safety analyses included patients who were randomly assigned and who received at least one dose of study treatment.

Studies were undertaken from October 17, 2019, to November 30, 2022 (EAGLE-2), and from April 23, 2020, to December 1, 2022 (EAGLE-3). 1680 patients in EAGLE-2 and 1731 patients in EAGLE-3 were screened for eligibility, of whom 1531 and 1605 were randomly assigned, respectively (767 in the gepotidacin group and 764 in the nitrofurantoin group in EAGLE-2, and 805 in the gepotidacin group and 800 in the nitrofurantoin group in EAGLE-3). After an interim analysis, which was prospectively agreed as a protocol amendment, both studies were stopped for efficacy. In EAGLE-2, 162 (50.6%) of 320 patients assigned gepotidacin and 135 (47.0%) of 287 patients assigned nitrofurantoin had therapeutic success (adjusted difference 4.3%, 95% CI –3.6 to 12.1). In EAGLE-3, 162 (58.5%) of 277 patients assigned gepotidacin and 115 (43.6%) of 264 patients assigned nitrofurantoin had therapeutic success (adjusted difference 14.6%, 95% CI 6.4 to 22.8). Gepotidacin was non-inferior to nitrofurantoin in both studies and superior to nitrofurantoin in EAGLE-3. In both studies, the most common reason for microbiological failure at test-of-cure with gepotidacin was unable to determine outcome (i.e., missing urine culture result or receipt of other systemic antimicrobials before the visit), whereas microbiological failure with nitrofurantoin was predominantly due to microbiological recurrence (i.e., baseline qualifying uropathogen $\geq 10^3$ CFU/mL at test-of cure having been $<10^3$ CFU/mL at

previous visit; in 49 [17.1%] of 287 patients in EAGLE-2 and in 51 [19.3%] of 264 patients in EAGLE-3). The most common adverse event with gepotidacin was diarrhea (observed in 111 [14%] of 766 patients in EAGLE-2 and in 147 [18%] of 804 patients in EAGLE-3), whereas the most common adverse event with nitrofurantoin was nausea (in 29 [4%] of 760 patients in EAGLE-2 and in 35 [4%] of 798 patients in EAGLE-3). Cases were mostly mild or moderate. No life-threatening or fatal events occurred. E coli represented 90% of urinary pathogens.

Gepotidacin demonstrates potent in vitro activity against a number of common bacterial pathogens. See table below from J Antimicrob Chemother 2023; 78: 1137–1142

Table 1. MIC data for gepotidacin[a]

Organism	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Range
MRSA	0.25	0.5	≤0.06 to 1
MSSA	0.5	0.5	0.12 to 2
S. pneumoniae	0.12	0.25	0.03 to 1
S. pyogenes	0.25	0.25	0.03 to 0.5
H. influenzae	0.5	1	≤0.015 to 8
M. catarrhalis	≤0.06	≤0.06	≤0.06 to 0.12
E. coli	2	2	≤0.03 to >32
Shigella spp.	0.5	1	not provided
C. perfringens	0.12	0.5	not provided
N. gonorrhoeae	0.25	0.5	≤0.015 to 1

Gepotidacin has shown efficacy against Yersinia pestis in a primate animal model. In vitro studies show promise against mycoplasma and ureaplasma infections, including drug-resistant Mycoplasma genitalium. In vitro and in vivo animal models have shown activity of gepotidacin against mycobacterial pathogens, including Mycobacterium tuberculosis and drug-resistant nontuberculous mycobacteria. A recent report demonstrated good activity against Stenotrophomonas maltophilia, an increasingly recognized nosocomial pathogen that is often resistant to multiple antibiotics.

Overall, the results of the EAGLE-2 and EAGLE-3 trials provide strong evidence that Gepotidacin is an effective and safe oral antibiotic for the treatment of uncomplicated urinary tract infections. Gepotidacin has the potential to be a valuable new treatment, which is particularly promising for patients who are resistant to other antibiotics or who are intolerant to first-line treatments. Mutations in both enzymes would likely be necessary for resistance to occur, thus raising hopes that the drug will be able to maintain long-term effectiveness. Gepotidacin appears to have activity against resistant GC. Some limitations to EAGLE-2 and EAGLE-3, including the inclusion criterion recommended by the FDA and EMA and the use of a clinical scoring tool for symptoms that might not be truly representative of clinical practice. Additionally, the population studied was largely White, with low representation of other ethnicities.

Bottom line: Gepotidacin may be a promising new treatment for uUTI, GC, mycoplasma, and ureaplasma.

Oral β-Lactams, Fluoroquinolones, or Trimethoprim-Sulfamethoxazole for Definitive Treatment of Uncomplicated *Escherichia coli* or *Klebsiella* Species Bacteremia From a Urinary Tract Source OFID published online December 27, 2023

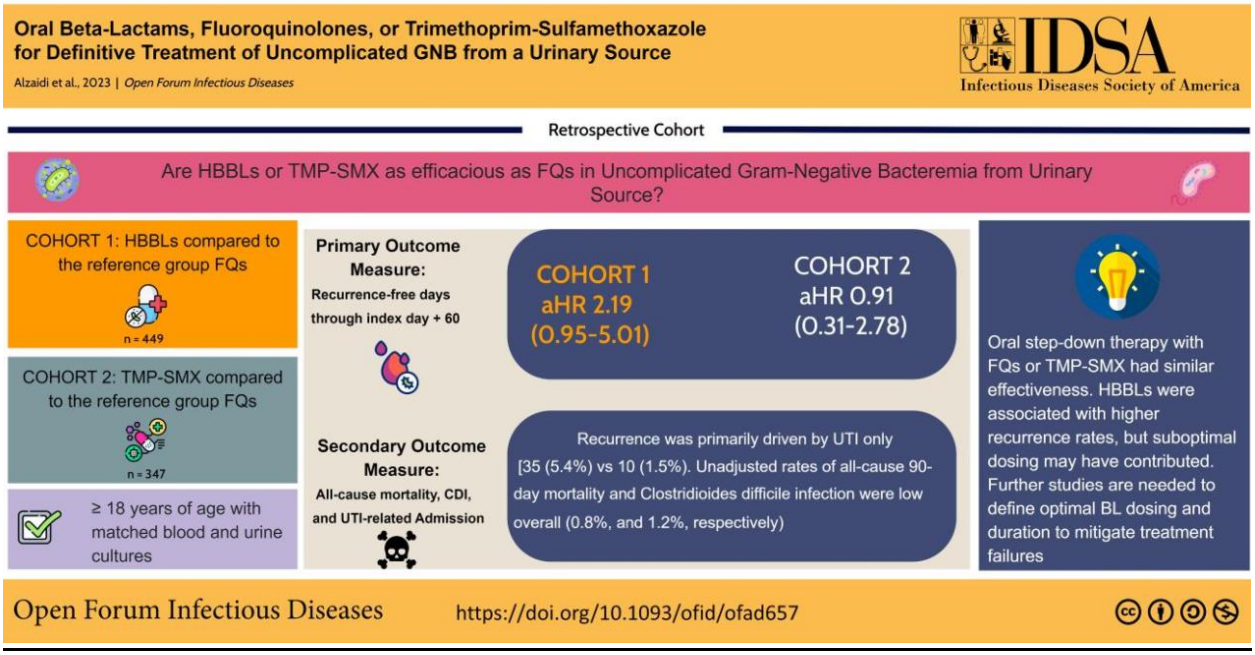
doi.org/10.1093/ofid/ofad657

This was a multicenter observational cohort study, simulated a 3-arm registry trial using causal inference methods to compare the effectiveness of FQs, TMP-SMX, or high bioavailability β-lactams (HBBLs) for gram-negative bloodstream infections oral step-down therapy. The study included adults treated between January 2016 and December 2022 for uncomplicated *E coli* or *Klebsiella* species bacteremia of urinary tract origin who were who were transitioned to an oral regimen after ≤4 days of effective intravenous antibiotics. The study took place in the Intermountain Health integrated network. Data related to hospital course, demographics, laboratory values, and microbiology were extracted electronically from the enterprise data warehouse, whereas comorbid conditions, imaging, severity of illness, antibiotic treatment, recurrent infection, readmissions, and mortality data were abstracted manually from the electronic medical record (EMR) by trained record reviewers. They excluded the following patients: those with concomitant infections (besides GN-BSIs/urinary tract infections [UTIs]) during the index visit, polymicrobial cultures, hospital-onset bacteremia, non– urinary tract source of bacteremia (e.g., prostatitis, epididymoorchitis), or complicated UTIs (defined as benign prostatic hypertrophy, bladder or prostate cancer, urinary obstruction/ retention, hydronephrosis, kidney or bladder stones, neurogenic bladder, chronic urinary incontinence, indwelling or intermittent urinary catheterization, renal abscess, or altered urologic anatomy—e.g., stent, tube, sling, urostomy, cystocele, fistula, or stricture). They also excluded patients who died in the hospital, were discharged to hospice care, transferred to a non-Intermountain facility, were lost to follow-up after discharge, were pregnant, or were immunocompromised (human immunodeficiency virus/AIDS with CD4 cell count <200/μL, neutropenia with an absolute neutrophil count <500/μL, or receiving any of the following medications at the time of admission: antirejection medications after transplantation, chemotherapy, tumor necrosis factor α inhibitors, disease-modifying antirheumatic drugs, or maintenance steroids with equivalent prednisone dose ≥20 mg), and received an oral antibiotic to which the blood or urine isolate was not susceptible,. Patients were classified at the time of enrollment into 1 of 3 comparator groups based on the definitive oral antibiotic they received: FQs (levofloxacin and ciprofloxacin); TMPSMX; or HBBLs (amoxicillin, amoxicillin-clavulanate, and cephalexin). [recommended dose ciprofloxacin, 750 mg orally every 12 hours; levofloxacin, 750 mg orally every 24 hours; TMP-SMX, 5 mg/kg orally every 12 hours (e.g., approximately 2 double-strength tablets every 12 hours for a 70-kg patient); amoxicillin, 1000 mg orally every 8 hour; amoxicillin–clavulanic acid, 875–1000 mg orally every 8 hours; and cephalexin, 1000 mg orally every 6 hours] However, oral antibiotic dosing and duration was per prescriber choice. For sensitivity analyses, they also evaluated a fourth group of low-bioavailability BLs (LBBLs; cefdinir and cefuroxime). The primary outcome was recurrence-free days through index day +60. Recurrence was defined as positive blood or urine culture for the same organism. Secondary outcomes included all-cause mortality, *C difficile* infection, and UTI-related readmission. Propensity weighting was used to balance characteristics between groups. 60-day recurrence was compared using a multinomial Cox proportional hazards model with probability of treatment weighting.

Of 2571 patients screened, 648 (25%) were included. Their median age (interquartile range) was 67 (45–78) years, and only 103 (16%) were male. Characteristics were well balanced

between groups. Compared with FQs, TMP-SMX had similar effectiveness (adjusted hazard ratio, 0.91 [95% confidence interval, .30–2.78]), and HBBLs had a higher risk of recurrence (2.19 [.95–5.01]), although this difference was not statistically significant. Most HBBLs (70%) were not optimally dosed for bacteremia. A total antibiotic duration ≤8 days was associated with a higher recurrence rate in select patients with risk factors for failure.

They did not observe any significant difference in effectiveness between FQs and TMP-SMX in preventing 60-day recurrence. This is notable, given that most TMP-SMX–treated patients received lower-than-recommended doses (i.e., 1 double-strength tablet every 12 hours instead of 2). Their modeling suggested that when TMP-SMX is used as step-down therapy, a total antibiotic duration >8 days may be associated with lower recurrence rates than shorter courses (≤8 days), although the difference was not statistically significant.



Comment: They also observed a lower risk of recurrence when FQ stepdown regimens were prescribed in longer durations (>8 days). This finding should be interpreted with caution given the efficacy of short-course FQs demonstrated in multiple randomized trials [Lancet 2012; 380:484–90; Clin Infect Dis 2019; 69:1091–8], but it does raise a question about real-world factors that may influence FQ effectiveness. In post hoc analyses, they identified several potential contributors to higher recurrence rates that were more prevalent among patients receiving short-course FQ, including history of recurrent UTIs, history of kidney stones, suboptimal dosing, interactions with multivalent cations, and comorbid conditions. Patients with nonmodifiable risk factors (e.g., history of recurrent UTI or kidney stones [if kidney stone was present] they were excluded and other comorbid conditions) could be excluded from the definition of “uncomplicated” short-course FQ therapy is reasonable for patients without these factors (i.e., those with truly uncomplicated GN-BSI), particularly if dosing is optimized and drug interactions avoided.

Conversely, they found that HBBL step-down was associated with >2-fold higher recurrence than FQs, regardless of duration. These findings are similar to those of Punjabi et al [Open Forum Infect Dis 2019; 6: ofz364], where β-lactams had 2-fold higher odds of recurrence than

FQ/TMP-SMX (with a median of 3–5 days of intravenous therapy before oral step-down). It is worth noting that the recurrence rate among HBBLs in this study was low overall (8%) even though the majority of patients receiving HBBLS received lower-than-recommended dosing. While further study is needed to define optimal HBBL dosing/duration and optimal days of intravenous therapy before oral HBBL step-down, high-dose HBBLs might still be reasonable in some patients (e.g., to avoid IV catheter placement and outpatient intravenous antibiotics). However, the data in this study suggests that FQs or TMP-SMX should be preferred as oral step-down therapy for GN-BSI if susceptible.

The investigators were unable to distinguish between recurrence versus new infection during retrospective review, were unable to control for provider-level or facility-level variability owing to sample size, and most patients received a total treatment duration of 10–14 days; thus, they were unable to draw strong conclusions regarding shorter durations by antibiotic class. Their ability to evaluate HBBL effectiveness was limited by current susceptibility testing practices, including lack of granular MICs, use of surrogate intravenous antibiotics to infer susceptibility of oral agents, and lack of systemic susceptibility breakpoints for oral β-lactams. Our unexpected findings of lower recurrence rates with LBBLs compared with HBBLs might also have been affected by these issues [lower MICs], which should all be considered in future studies. In February 2024 ID Watch [JAMA Network Open. 2024;7(1): e2352314] investigators showed IV to PO step down is as effective and possibly safer if we have an appropriately active PO alternative. In that study oral β-lactams were given in almost 2/3 of cases.

Bottom line: FQs and TMP-SMX had similar effectiveness in this real-world data set. HBBLs were associated with higher recurrence rates but suboptimal dosing may have contributed to these results. Nonetheless their findings suggest that FQs and TMP-SMX may be preferred options for susceptible isolates, but further study is needed to define optimal dosing and duration for β-lactams.

Impact of a deep learning sepsis prediction model on quality of care and survival

npj Digital Medicine 2024; 7:14

doi.org/10.1038/s41746-023-00986-6

The objective of this study was to assess the impact of a deep-learning model (COMPOSER) for the early prediction of sepsis on patient outcomes. They completed a before-and-after quasi-experimental study at two distinct EDs within the UC San Diego Health System integrating COMPOSER into their EHR (Epic). [NPJ Digit Med.2021; 4, 134] They included 6217 adult septic patients from 1/1/2021 through 4/30/2023. that met the Sepsis-3 consensus sepsis definition. The exposure tested was a nurse-facing Best Practice Advisory (BPA) triggered by COMPOSER. In-hospital mortality, sepsis bundle compliance, 72-h change in sequential organ failure assessment (SOFA) score following sepsis onset, ICU-free days, and the number of ICU encounters were evaluated in the preintervention period (705 days) and the post-intervention period (145 days). The causal impact analysis was performed using a Bayesian structural time-series approach with confounder adjustments to assess the significance of the exposure at the 95% confidence level.

The deployment of COMPOSER was significantly associated with a 1.9% absolute reduction (17% relative decrease) in in-hospital sepsis mortality (95% CI, 0.3%–3.5%), a 5.0% absolute increase (10% relative increase) in sepsis bundle compliance (95% CI, 2.4%–8.0%), and a 4%

(95% CI, 1.1%–7.1%) reduction in 72-h SOFA change after sepsis onset in causal inference analysis. This study suggests the deployment of COMPOSER for early prediction of sepsis was associated with a significant reduction in mortality in addition to a significant increase in sepsis bundle compliance.

Comment: Existing algorithms within electronic health records (EHRs) have demonstrated relatively poor positive predictive value (PPV) and may contribute to provider mistrust of predictive models. [JAMA Intern. Med. 2023;183, 611–612]. Of note, false positive alerts from such models often lead to alarm fatigue and provider burnout/mistrust. Older models designed to detect sepsis were largely based on clinical criteria (i.e., SIRS criteria, hypotension, or a combination of these). These models were associated with occasional improvement in quality metrics (i.e., increased rates of lactate orders or time to antibiotics) but did not improve patient-centered outcomes and had poor PPV. [J. Hosp. Med. 2015;10, 396–402]

More recently, several studies have implemented sophisticated models at various hospitals showing benefits to patients. Shimaburuko et al. conducted a small, randomized trial of 142 patients in the ICU using a machine-learning algorithm to predict severe sepsis and found a decrease in in-hospital mortality and length of stay in the intervention group, although this study was limited to patients either in the hospital wards or intensive care units. [BMJ Open Respir. Res. 2017;4, e000234] Adams et al. recently provided a prospective analysis of the TREWS model at five hospital systems in which they demonstrated a significant decrease in mortality, organ failure, and length of stay in hospitalized patients when the sepsis alert was confirmed by a provider. [Nat. Med. 2022; 28, 1455–1460] A commonly used predictive model, the Epic Sepsis Score (ESS), has not demonstrated consistent improvement in patient-centered outcomes. Investigations at the University of Michigan highlighted a substantial drop in test characteristics (sensitivity, specificity, PPV) of the ESS at their institution from what was reported by Epic, as well as an unacceptably high rate of false positives. [JAMA Intern Med. 2021; 181:1065-1070] In current, they chose to have the nurses receive the alert and determine if escalation to the provider was appropriate. I think this is wise since they can determine if the alert is due to sepsis. The study was not randomized and thus their findings do not allow causal association. Their study was conducted at two EDs in a large academic center that has a major interest in sepsis and clinical informatics. Although they had a large sample size and a diverse population of patients (racial, ethnic, socioeconomic status, etc.), they acknowledge the need for external validation in other healthcare settings. (e.g., community hospitals) The intervention has important immediate benefits raising awareness and helping to prioritize the care of a specific group of patients. They did not evaluate the impact of this alert on patients who ultimately did not have sepsis, such as the potential adverse effects of inappropriate use of antibiotics and healthcare costs associated with this.

Bottom line: This quasi-experimental design study conducted at two academic EDs demonstrate that the implementation of a real-time deep-learning model to predict sepsis was associated with a significant increase in bundle compliance, a significant reduction in in-hospital mortality, less organ dysfunction at 72 h, and improved timeliness to antibiotics when nurses notified the physician of a potential septic patient. External validation is needed. See next review.

Artificial Intelligence for Early Sepsis Detection A Word of Caution Am J Respir Crit Care Med 2023; 207:853–854

DOI: 10.1164/rccm.202212-2284VP

The need for early sepsis detection has incentivized researchers and companies worldwide to leverage advanced analytical tools, including artificial intelligence (AI), to develop automated systems that provide timely alerts and make physicians aware of imminent sepsis. In the past few years, we have seen the first real world evaluations of these tools and their potential to help improve patient outcomes. The authors of this publication argue that results to date warrant caution. (see below)

Text Box 1. Artificial Intelligence for Early Sepsis Detection: A Word of Caution

- Artificial intelligence (AI) tools already impact sepsis care.
- Up to now, no large-scale, randomized controlled trial–level evidence demonstrates the clinical benefits of AI-based alerts for patients with sepsis.
- Sepsis alerts may trigger the unnecessary use of antibiotics.
- The proprietary nature of many AI tools can make independent validation challenging.
- Caution should be exercised when using early sepsis detection tools.

In 2021, investigators set out to validate the Epic Sepsis Model (ESM), an algorithm for detecting sepsis implemented and used by hundreds of hospitals. [JAMA Intern Med 2021;181: 1065–1070] During the validation, the ESM had poor discrimination (area under the curve [AUC] of only 0.63) and calibration, far worse than the initially reported AUC of 0.76 to 0.83. Physicians needed to evaluate 109 patients to detect 1 case of sepsis earlier than without the ESM. More recently, a prospective study evaluated the impact of using the Targeted Real-time Early Warning System (TREWS) to improve patient outcomes. [Nat Med 2022; 28:1455–1460] Investigators have been developing and fine-tuning the TREWS for years, reaching an AUC of 0.97 for detecting sepsis and flagging 82% of cases. TREWS was then deployed in five hospitals as part of a multisite study of patient outcomes after using the alert. Impressively, the TREWS retained adoption rates of 89% throughout this study. In a retrospective analysis of 6,877 actionable sepsis cases with alerts, the 4,220 cases in which the alert was confirmed within 3 hours had a significantly reduced mortality rate (adjusted relative reduction of 18.7%) compared with the 2,657 controls in which the alert was not confirmed within 3 hours. [Nat Med 2022; 28:1455–1460] Although these results indeed are promising, they seem preliminary. A significant concern lies within the control group, which is highly heterogeneous and may have included many patients without sepsis. Despite the sophisticated adjustments for potential confounding, the study's observational nature and electronic health record–based sepsis identification make it hard to investigate the actual benefits of TREWS in sepsis outcomes. Furthermore, the investigation did not consider the patients with TREWS alerts who did not have sepsis (over 30,000). As they point out, an alert in this group may have had harmful effects, such as the overuse of diagnostics and antimicrobial therapy. The ESM and the TREWS, like many other AI-based sepsis tools, are proprietary algorithms making independent validations nearly impossible.

Comment: Sepsis alerts triggering one-size-fits-all protocols may lead to substantial overuse of antibiotics, with profound implications, and may cause pressure on physicians to evaluate many patients to detect one sepsis patient early. [JAMA 2018; 320:1433–1434] Sepsis is highly heterogeneous and variable presentation makes it hard to establish a prompt and accurate

diagnosis which is why until we have better tools, a human must always review the output to see if the trigger makes sense. We need RCT-level evidence to unequivocally show that using these alerts will have a positive net benefit for the patient.

Bottom line: AI in the future may offer a valuable tool in the early detection of sepsis, but for all the reasons listed above we need better tools and RCT evidence.

Editor's Choice

Development and Validation of the Phoenix Criteria for Pediatric Sepsis and Septic Shock JAMA published online January 21, 2024

JAMA. doi:10.1001/jama.2024.0196

Introduction

Pediatric-specific sepsis criteria were subsequently developed by an expert panel during the International Pediatric Sepsis Consensus Conference (IPSCC) and published in 2005. [Pediatr Crit Care Med. 2005; 6:2-8] Similar to adult definitions (Sepsis-1&2), pediatric sepsis was defined by 2 or more SIRS criteria in the setting of confirmed or suspected infection, with severe sepsis denoting sepsis complicated by organ failure, and septic shock indicating sepsis with severe cardiovascular dysfunction. Acknowledging differences in pediatric physiology, the IPSCC definitions diverged from adult criteria to require at least 1 SIRS criteria be abnormal temperature or white blood cell count and to use age-specific SIRS criteria.

The adult sepsis definitions underwent a third update in 2016 (Sepsis-3), which departed from the SIRS-based definition. [JAMA. 2016; 315:801-810] Sepsis was redefined as life-threatening acute organ dysfunction secondary to a dysregulated host response to infection. SIRS was no longer part of the definition. In 2019, the Society of Critical Care Medicine appointed an international, multiprofessional task force to update the pediatric sepsis criteria.

Validation of the Phoenix Criteria

The development of the Phoenix criteria was a multicenter, international, retrospective cohort study in 10 health systems in the US, Colombia, Bangladesh, China, and Kenya. Data were collected from emergency and inpatient encounters for children (aged <18 years) from 2010 to 2019. Stacked regression models to predict mortality in children with suspected infection were derived and validated using the best-performing organ dysfunction subscores from 8 existing scores. The criteria were selected through a modified Delphi consensus process and informed by several task force– led studies. The final model was then translated into an integer-based score used to establish binary criteria for sepsis and septic shock. The primary outcome for all analyses was in-hospital mortality. Model- and integer-based score performance measures included the area under the precision recall curve (AUPRC; primary) and area under the receiver operating characteristic curve (AUROC; secondary). For binary criteria, primary performance measures were positive predictive value and sensitivity.

The Phoenix sepsis criteria defines sepsis as life-threatening organ dysfunction of the respiratory, cardiovascular, coagulation, and/or neurological systems, demonstrated by a Phoenix Sepsis Score of at least 2, in the setting of confirmed or suspected infection. Septic

shock was defined as sepsis with at least 1point in the cardiovascular category (blood lactate ≥5 mmol/L [≥45.05 mg/dL], hypotension for age, or vasoactive use). These thresholds were selected based on group consensus, requiring more than 80% agreement among more than 80% of the task force.

Table 2. The Phoenix Sepsis Score[a]

	0 Points	1 Point	2 Points	3 Points
Respiratory (0-3 points)				
	Pao_2:FIo_2 ≥400 *or* Spo_2:FIo_2 ≥292[b]	Pao_2:FIo_2 <400 and any respiratory support[c] *or* Spo_2:FIo_2 <292 and any respiratory support[c]	Pao_2:FIo_2 100-200 and IMV *or* Spo_2:FIo_2 148-220 and IMV	Pao_2:FIo_2 <100 and IMV *or* Spo_2:FIo_2 <148 and IMV
Cardiovascular (0-6 points)				
		1 point each (up to 3) for:	**2 points each (up to 6) for:**	
	No vasoactive medications[d]	1 Vasoactive medication[d]	≥2 Vasoactive medications[d]	
	Lactate <5 mmol/L[e]	Lactate 5-10.9 mmol/L[e]	Lactate ≥11 mmol/L[e]	
Mean arterial pressure by age, mm Hg[f,g]				
<1 mo	>30	17-30	<17	
1 to 11 mo	>38	25-38	<25	
1 to <2 y	>43	31-43	<31	
2 to <5 y	>44	32-44	<32	
5 to <12 y	>48	36-48	<36	
12 to 17 y	>51	38-51	<38	
Coagulation (0-2 points)[h]				
		1 point each (maximum of 2 points) for:		
	Platelets ≥100 × 10^3/μL	Platelets <100 × 10^3/μL		
	International normalized ratio ≤1.3	International normalized ratio >1.3		
	D-dimer ≤2 mg/L FEU	D-dimer >2 mg/L FEU		
	Fibrinogen ≥100 mg/dL	Fibrinogen <100 mg/dL		
Neurologic (0-2 points)[i]				
	Glasgow Coma Scale score >10[j]; pupils reactive	Glasgow Coma Scale score ≤10[j]	Fixed pupils bilaterally	

Table. Comparison of Phoenix Pediatric Sepsis Criteria With International Pediatric Sepsis Consensus Conference Criteria

	International Pediatric Sepsis Consensus Conference criteria	Phoenix pediatric sepsis criteria
Sepsis		
Definition	SIRS in the setting of a suspected or confirmed infection: ≥2 SIRS criteria, of which 1 must be temperature or white blood cell count	Life-threatening organ dysfunction in the setting of suspected or confirmed infection, defined as ≥2 points on the Phoenix Sepsis Score
Criteria	Pediatric SIRS Criteria • Core temperature • White blood cell count • Heart rate • Respiratory rate	Organ dysfunction may include • Respiratory (Pao_2:FIo_2 or Spo_2:FIo_2) • Cardiovascular (vasoactive medications, lactate, age-specific MAP • Coagulation (platelets, INR, D-dimer, fibrinogen) • Neurologic systems (Glasgow Coma Scale)
Severe sepsis		
Definition	Sepsis with at least 1 of the following: cardiovascular organ dysfunction, acute respiratory distress syndrome, or ≥2 other organ dysfunctions.	Term no longer used now that sepsis definition requires organ dysfunction
Criteria	Organ dysfunctions include • Respiratory (Pao_2:FIo_2 ratio, $Paco_2$, FIo_2, mechanical ventilation) • Neurological (Glasgow Coma Scale) • Hematologic (platelet count, INR) • Kidney (serum creatinine) • Hepatic (bilirubin, alanine aminotransferase)	
Septic shock		
Definition	Sepsis and cardiovascular organ dysfunction[a]	Sepsis with ≥1 point in the cardiovascular system[b]

Among the 172,984 children with suspected infection in the first 24 hours (development set; 1.2% mortality), a 4-organ-system model performed best. The integer version of that model, the Phoenix Sepsis Score, had AUPRCs of 0.23 to 0.38 (95% CI range, 0.20-0.39) and AUROCs of 0.71 to 0.92 (95% CI range, 0.70-0.92) to predict mortality in the validation sets. Using a Phoenix Sepsis Score of 2 points or higher in children with suspected infection as criteria for sepsis and sepsis plus 1 or more cardiovascular point as criteria for septic shock resulted in a higher positive predictive value and higher or similar sensitivity compared with the 2005 International Pediatric Sepsis Consensus Conference (IPSCC) criteria across differently resourced settings.

Comment: The novel Phoenix sepsis criteria, which were derived and validated using data from higher- and lower-resource settings, had improved performance for the diagnosis of pediatric sepsis and septic shock compared with the existing IPSCC criteria. The Phoenix criteria were developed and validated among children with proven or suspected infection. However, recognizing and confirming infection remains a challenge, with up to a third of patients diagnosed with sepsis having a noninfectious illness in hindsight. The SIRS criteria may remain useful for assessing the presence of infection. While Sepsis-3 in adults requires at least 2 new SOFA points, Phoenix scoring does not specify that organ dysfunction must be new. Chronic organ dysfunction may indicate increased risk of mortality but be less predictive to response to treatments for sepsis. Surprisingly kidney dysfunction (which is included in the IPSCC definition of severe sepsis and associated with mortality in prior studies of pediatric sepsis) was not included in the Phoenix criteria. This study only considered data from the first 24 hours of presentation. Therefore, additional validation, particularly for hospital onset sepsis, is needed.

Bottom line: Although not perfect the Phoenix sepsis criteria identify children with life threatening organ dysfunction in the setting of infection. This sepsis definition is supported by a robust body of research and an important improvement to prior definitions. This new definition will support improvements in the management, research, and outcomes of children with sepsis worldwide.

Job Flows Into and Out of Health Care Before and After the COVID-19 Pandemic

JAMA Health Forum. 2024;5(1):e234964.

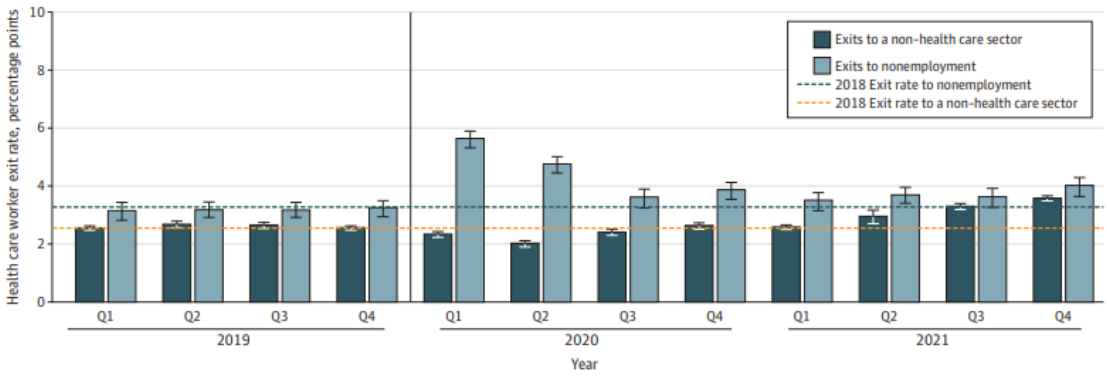
doi:10.1001/jamahealthforum.2023.4964

This is a cohort study which used US Census Bureau state unemployment insurance data on job-to-job flows in the continental US to construct state-level quarterly exit and entry rates for the health care industry from January 2018 through December 2021 (Arkansas, Mississippi, and Tennessee were omitted due to missing data). An event study design was used to compute quarterly mean adjusted rates of job exit from and entry into the health care sector as defined by the North American Industry Classification System. Data were examined from January to June 2023. The main outcomes were the mean adjusted health care worker exit and entry rates in each quarter by state and by worker demographics (age, gender, race and ethnicity, and education level).

In quarter 1 of 2020, there were approximately 18.8 million people (14.6 million females [77.6%]) working in the health care sector in their sample. The exit rate for health care workers increased at the onset of the pandemic, from a baseline quarterly mean of 5.9 percentage points in 2018 to 8.0 (95% CI, 7.7-8.3) percentage points in quarter 1 of 2020. Exit rates remained higher than baseline levels through quarter 4 of 2021, when the health care exit rate was 7.7 (95% CI, 7.4-7.9) percentage points higher than the 2018 baseline. In quarter 1 of

2020, the increase in health care worker exit rates was dominated by an increase in workers exiting to nonemployment (78% increase compared with baseline); in contrast, by quarter 4 of 2021, the exit rate was dominated by workers exiting to employment in non–health care sectors (38% increase compared with baseline). Entry rates into health care also increased in the postpandemic period, from 6.2 percentage points at baseline to 7.7 percentage points (95% CI, 7.4-7.9 percentage points) in the last quarter of 2021, suggesting increased turnover of health care staff. Compared with prepandemic job flows, the share of workers exiting health care after the pandemic who were female was disproportionately larger, and the shares of workers entering health care who were female or Black was disproportionately smaller.

Figure 2. Adjusted Mean Exit Rates From the Health Care Sector Over Time by Exit Type



Comment: This cohort study found a significant increase in health care worker turnover after the Covid-19 pandemic. In particular, they found that even though overall employment levels broadly stabilized in the health care sector by the end of 2020, health care worker exit rates remained elevated above 2018 baseline levels through the end of 2021. The increase in health care workforce turnover may pose substantial costs for both organizations and patients, as it implies potentially disrupted continuity of care and fewer staff with industry- and firm-specific experience. Increasing evidence has suggested that staff dissatisfaction and staff turnover in health care settings can have unfavorable implications for patient care even without staffing shortages. Limitations of the present study include that they were not able to identify the reason for a job flow from the data set, in particular whether a job flow occurred because of reasons relating to the firm (i.e., closures and layoffs) or to the worker (i.e., quitting, burnout); thus, they were unable to separately consider these 2 different types of job flows in the analysis.

Bottom line: Results of this cohort study suggest a substantial and persistent increase in health care workforce turnover after the pandemic, which may have long-lasting implications for workers' willingness to remain in health care jobs.

State-of-the-Art Review: Use of Antimicrobials at the End of Life Clin Infect Dis published online February 1, 2024

doi.org/10.1093/cid/ciad735

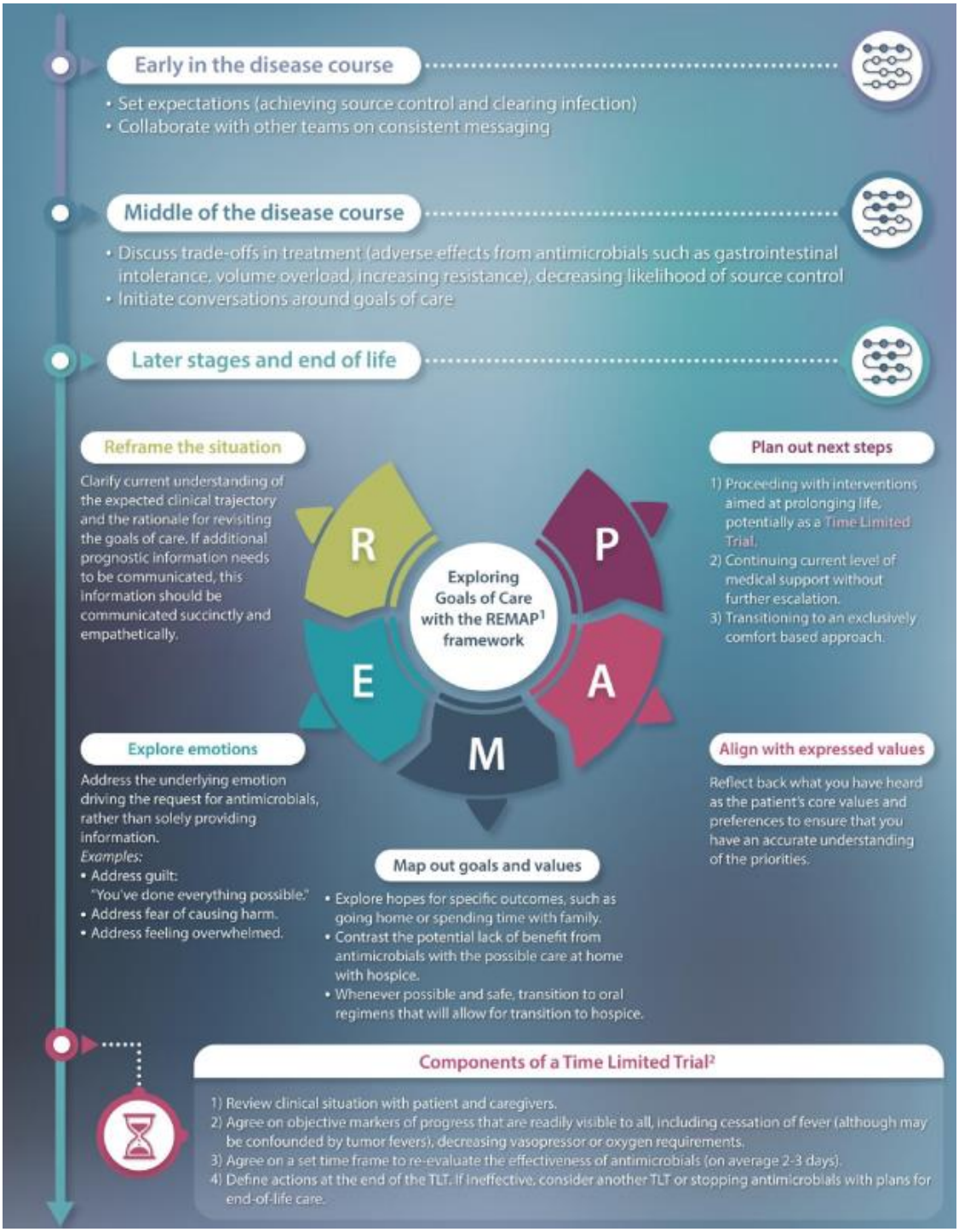
Patients near the end-of-life are prone to infection due to the prevalence of immunosuppression, multiple comorbidies, cognitive impairment, and device utilization. Consequently, exposure to

antimicrobials is common during palliative care. Among hospitalized patients experiencing cancer-related death, 87% received antimicrobials during hospitalization, and over one-third of these patients received antimicrobial therapy following transition to comfort care. [Am J Hosp Palliat Care 2012; 29:599–603] Among nursing home residents with advanced dementia, more than 40% received antimicrobials in the 2 weeks prior to death.[Arch Intern Med 2008;168:357–362] Remarkably, 27% of hospice patients received ≥ 1 antimicrobial during the last week of life, and over 1 in 5 patients discharged to hospice were continued on antimicrobials.[Antimicrob Agents Chemother 2014;58:5473–5477]

In this article the authors outline stepwise changes in the patient's clinical condition, suggest approaches to conversations with the patient and her family, and discuss potential ethical conflicts affecting the ID physician[and other HCWs], including antimicrobial stewardship. Highlights:

- Decisions around antimicrobials in an end-of-life setting may be driven by emotions rather than practical needs.
- An estimated 1 out of 7 ICU patients is in need of a palliative care consultation. [Am J Respir Crit Care Med 2014; 189:428-436]
- At the end of life, goals of life prolongation and symptom control (comfort) may, at times, be in conflict. Antimicrobials can ameliorate some symptoms (such as fever or dysuria) but might complicate or prevent the transition of the dying process to the home environment, where many of these symptoms may be better managed with other treatments such as antipyretics or opioids. May prolong pain and suffering.
- Communication challenges between patients and their various medical teams are at the heart of the use of antimicrobials at the end of life. Shared decision making involves providing clear, accurate, and unbiased medical evidence about risks and benefits of all reasonable options; understanding a patient's goals and treatment preferences; and integrating this information into a clear clinical recommendation.
    - it is important for the clinician to listen to the family's concerns, identify and attend to the emotions underlying those concerns, and then use clinical expertise to recommend the medical interventions that are likely to achieve the desired goals.
- The ID physician is well positioned to further explore goals of care as they pertain to the clinical situation, using the REMAP (Reframe, Expect Emotion, Map Out Patient Goals, Align with Goals, Propose a Plan) framework. See figure below.
- Options in the setting of end-of-life care:
    - proceeding with interventions aimed at prolonging life to the greatest extent possible
    - continuing the current level of medical support without further escalating treatments in the setting of clinical decline
    - transitioning to an exclusively comfort-focused approach, adding treatments to promote comfort and discontinuing interventions that do not directly contribute to comfort.
- Refusing or discontinuing treatments may evoke feelings of guilt for patients, caregivers, and medical teams. Despite the lack of cause and effect, families may feel that discontinuing antimicrobials at the end of life may hasten the dying process.
- Nearly all clinicians will be confronted by the phrase to "do everything."
    - "do everything" should prompt further probing. Exploratory questions should seek to identify underlying emotions, such as fear of giving up.

    - In some cases, however, the request to “do everything” carries a qualifier: “Do everything you think is reasonable”, “do everything so we don’t give up too soon.”
- For hospitalized patients transitioning to comfort care, they recommend considering stopping antimicrobials prior to discharge as antimicrobials have been shown to increase hospital length of stay, taking away valuable time a patient could be spending with family at home. [Am J Hosp Palliat Care 2020; 37:27-33]



Comment: This article supports the role of the ID physician in discussions around end-of-life care. The article provides multiple suggestions to improve complex communication skills, including navigating difficult emotions around end-of-life care, can be used to better direct shared decision making and assist with antibiotic stewardship. Ongoing collaborative discussions between ID and palliative care teams should allow for more meaningful conversations with patients at each phase of their evolving condition. I also recommend a recent article titled "Frontiers in antimicrobial stewardship: antimicrobial use during end-of-life care." [Antimicrob Steward Healthcare Epidemiol 2023, 3, e164, 1–3]

Bottom line: Antimicrobial stewardship during end-of-life care is an emerging opportunity. Understanding how antimicrobials are used in palliative care focusing on management of symptoms, emotional support, and assistance with decision-making – offers new opportunities to optimize effectiveness of antimicrobial stewardship.

Selection of Antibiotics as Prophylaxis for Close Contacts of Patients with Meningococcal Disease in Areas with Ciprofloxacin Resistance — United States, 2024 MMWR 2024 / 73(5);99–103

The guidelines note that while antibiotic resistance in *N meningitidis* has been uncommon in the US, 29 cases of invasive meningococcal disease caused by ciprofloxacin-resistant strains were reported from 2019 to 2021, distributed across the US but with clusters identified in some geographic areas. Ciprofloxacin is one of the recommended first-line options for treating patients and for prophylaxis for their close contacts, who are at increased risk of acquiring the disease. To date, no instances of prophylaxis failure associated with ciprofloxacin resistance has been reported. But because of the high mortality risk of invasive meningococcal disease and the potential for prophylaxis failure, the CDC says the threshold for changing the antibiotic prophylaxis recommendation is low.

Under the new guidelines, the CDC recommends other antibiotics be considered if, over a rolling 12-month period, two or more invasive meningococcal disease cases caused by ciprofloxacin-resistant strains are reported in a local catchment area and 20% or more of the invasive meningococcal disease cases in that area are caused by ciprofloxacin-resistant strains.

Other recommended options for prophylaxis include rifampin, ceftriaxone, and azithromycin. The CDC says local health departments have flexibility in guidance implementation.

Bottom line: The challenge for local clinicians does your local health department have the ciprofloxacin resistance information to make an informed decision on prophylaxis.

Characteristics and Prognosis Factors of Pneumocystis jirovecii Pneumonia According to Underlying Disease A Retrospective Multicenter Study Chest published online January 10, 2024

doi.org/10.1016/j.chest.2024.01.015

Pneumocystis jirovecii pneumonia (PJP) is a common, often severe, complication in individuals who are immunocompromised as a result of HIV infection, solid organ transplantation, or treatment for hematologic malignancies or immune-mediated inflammatory diseases (IMID). However, the influences of these underlying conditions on the characteristics and outcomes of PJP have not been recently reviewed.

French researchers conducted a retrospective analysis involving 481 patients with proven or probable PJP seen at three centers from 2011 through 2021. Immunocompromising conditions included hematologic malignancy (25%), HIV infection (24%), solid organ transplantation (21%), immune-mediated inflammatory disease (18%), and solid tumors (12%). Mean CD4 T-cell counts were decreased at the time of PJP diagnosis but were significantly higher in patients who were HIV negative compared with those who were HIV positive (292/mm^3 vs. 64/mm^3). Only 10% of patients had received PJP prophylaxis prior to diagnosis.

Overall, 90-day mortality was 26% (lowest among patients with HIV infection [10%] and highest among those with IMID [37%] or solid tumors [48%]). In multivariate analysis, parameters independently associated with 90-day mortality were solid tumor disease (OR, 5.7), long-term corticosteroid therapy especially for a prednisone daily dose of >10 mg/day (OR, 2.3) and SOFA score at admission (OR, 1.6). Patients with IMIDs, particularly those exposed to long-term corticosteroid therapy, exhibit the most unfavorable prognosis compared with other immunocompromised conditions.

Comment: Despite the retrospective observational method, the results highlight several points. First the prognosis of PJP varies depending on the underlying immunocompromising condition. Second the CD4 counts may be less reliable as a PJP-risk predictor in HIV-negative immunocompromising individuals. PJP prophylaxis is underutilized. Long-term steroids represent a major risk factor for PJP.

Bottom line: These findings emphasize the necessity of considering PJP prophylaxis for patients with IMIDs especially if on long-terms steroids.

Using Insurance Claims Data to Estimate Blastomycosis Incidence, Vermont, USA, 2011–2020 Emerg Infect Dis 2024 Feb; 30:372.

doi.org/10.3201/eid3002.230825

Blastomycosis has traditionally been thought of as a disease of the upper midwestern and southern U.S., a designation based on sporadic cases, outbreaks, and data from the five states that mandate reporting. Recent observations indicate that blastomycosis may be more common in the northeastern U.S. than realized.

To assess the epidemiology of blastomycosis in Vermont, investigators for CDC and the Vermont Department of Health used ICD-10 data from commercial insurance claims in a retrospective cohort analysis of all patients with a diagnosis of blastomycosis from 2011–2020. Among the 114 patients identified (59% male; median age, 55 years), 30% required hospitalization and 4 deaths were attributable to blastomycosis. The highest disease incidence was in north-central Vermont. Statewide, mean estimated annual incidence was 1.8 cases/100,000 persons — higher than that in 4 of the 5 states that mandated reporting from 1987–2017 (and exceeding all 5 states in 2019).

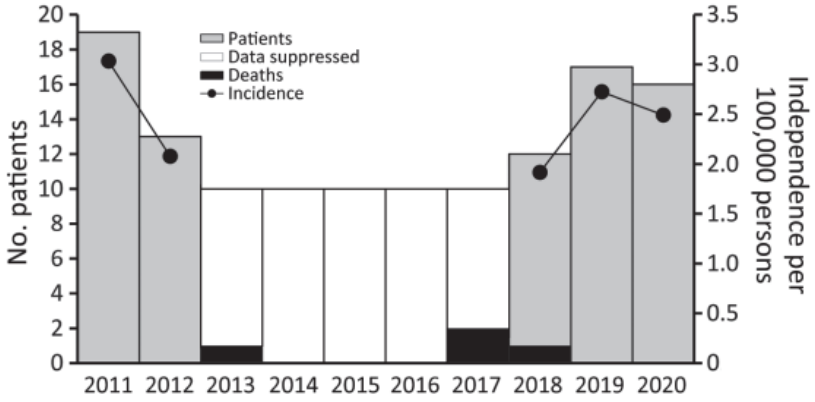


Figure 1. Numbers of patients with blastomycosis, attributable deaths per year, and annual incidence (cases/100,000 population) in Vermont, USA, 2011–2020. Results are suppressed for years with ≤10 patients, in accordance with the Green Mountain Care Board data use agreement for the Vermont Health Care Uniform Reporting and Evaluation System.

Comment: Although Vermont has historically not been considered an area with high relative incidence of blastomycosis, an estimated mean annual incidence of 1.8 case-patients/100,00 population suggests otherwise. That incidence is greater than the mean annual incidences during 1987–2017 in 4 of 5 states that mandate reporting of blastomycosis (Arkansas, Louisiana, Michigan, and Minnesota, but not Wisconsin) (2); incidence in Vermont was greater than in all 5 of those states in 2019 (3). Missouri (10), Mississippi (11), and Illinois (12), also located within known endemic areas, reported mean annual incidences of 0.2–1.3/100,000 population for differing intervals during 1979–2018. Consistent with other published studies, these results demonstrate that blastomycosis was more common in adults and male patients. [Emerg Infect Dis. 2021; 27:999–1006] Like hyperendemic regions of Wisconsin, Vermont is rich in acidic spodosol soil, which is thought to support Blastomyces spp. Growth. The diagnosis of blastomycosis is commonly delayed or missed in clinical practice because of low clinical suspicion and nonspecific symptoms.

Bottom line: Clinicians should consider blastomycosis in patients with compatible signs and symptoms. Standardized surveillance could also improve our understanding of exposures, risk factors, and clinical outcomes.

Impact of Blood Culture Contamination (BCC) on Antibiotic Use, Resource Utilization, and Clinical Outcomes: A Retrospective Cohort Study in Dutch and US Hospitals OFID published online December 12, 2023

doi.org/10.1093/ofid/ofad644

This retrospective observational study examined adults admitted to 2 hospitals in the Netherlands and 5 hospitals in the US undergoing ≥2 blood culture (BC) sets. Exclusion criteria included neutropenia, no hospital admission, or death within 48 hours of hospitalization. The impact of BCC on clinical outcomes—overall inpatient days of antibiotic therapy, test utilization, length of stay, and mortality—was determined via a multivariable regression model.

An overall 22,927 patient admissions were evaluated: 650 (4.1%) and 339 (4.8%) with BCC and 11,437 (71.8%) and 4648 (66.3%) with negative BC results from the Netherlands and the US, respectively. Dutch and US patients with BCC had a mean ± SE 1.74 ± 0.27 (P < .001) and 1.58 ± 0.45 (P < .001) more days of antibiotic therapy than patients with negative BC results. They also had 0.6 ± 0.1 (P < .001) more BCs drawn. Dutch but not US patients with BCC had longer hospital stays (3.36 days; P < .001). There was no difference in mortality between groups in either cohort. Antibiotic use remained higher in US but not Dutch patients with BCC in a subanalysis limited to BC obtained within the first 24 hours of admission.

Table 4. Multivariate Analysis: Outcomes of Patients With BCC vs Negative BC

	Adjusted Analysis, [a] β (SE)			
Outcome	AUMC	*P* Value [b]	JHMHS	*P* Value [b]
Antibiotics, d	−0.068 (0.18)	.708	6.000 (0.107)	**<.001**
IV vancomycin, d	0.028 (0.02)	.204	3.260 (0.001)	**<.001**
No. of BC	−0.016 (0.04)	.700	0.512 (0.112)	**<.001**
No. of images	0.842 (0.13)	**<.001**	4.866 (0.142)	**<.001**
No. of peripheral IV insertions	0.409 (0.14)	**.003**	0.189 (0.009)	**<.001**

Data are based on results of BC collected in the first 24 hours of admission. AUMC, n = 9069 (BCC, n = 422; negative BC, n = 8647). JHMHS, n = 2033 (BCC, n = 127; negative BC, n = 1906).

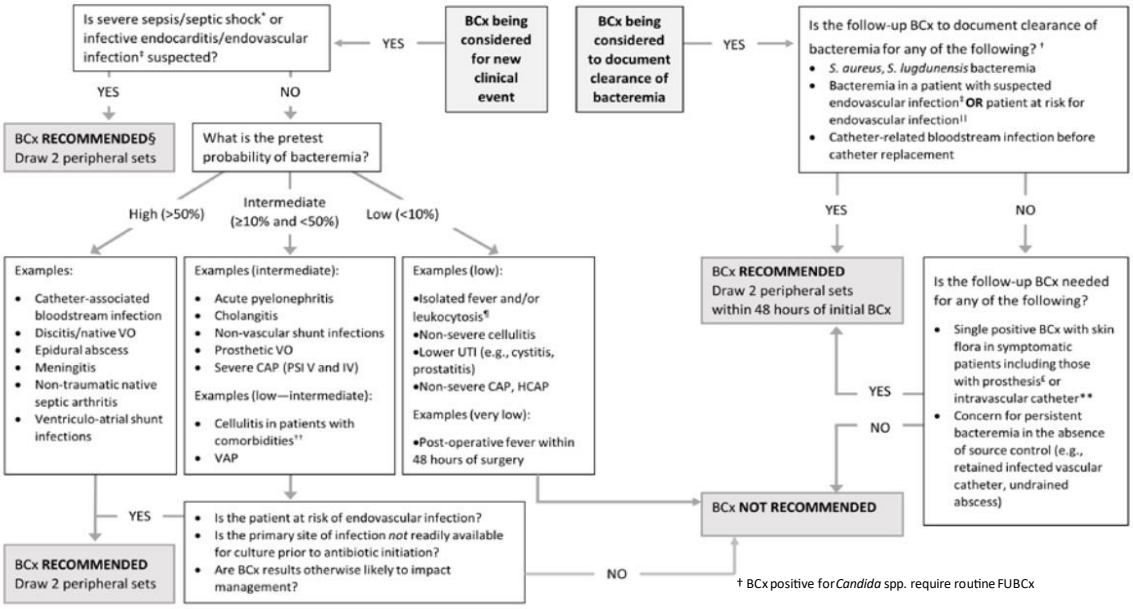
Abbreviations: AUMC, Amsterdam University Medical Centers; BC, blood culture; BCC, blood culture contamination; IV, intravenous; JHMHS, The Johns Hopkins Medicine Health System.

[a]Adjusted for age, sex, Charlson Comorbidity Index, and intensive care unit length of stay.

[b]Bold indicates *P* < .05.

Comment: They found that patients with BCC had higher overall inpatient antibiotic use and health care resource utilization as compared with patients with negative BC results after adjusting for age, sex, CCI, and ICU length of stay. Previous studies showed that patients with BCC received approximately 5 to 7 additional days of antibiotics than patients with negative BC results. [J Clin Microbiol 1998; 36:1923–6] Studies have shown that implementation of rapid diagnostic testing for bacteremia coupled with review of positive BC by antibiotic stewardship programs may lead to fewer patients exposed and shorter exposure to unnecessary antibiotics of patients with BCC. [Clin Microbiol Infect 2018; 24:1339. e7–12] There is an urgent need to improve BC-ordering practices. Publications have shown that approximately 30% of BCs can be reduced safely in the emergency department setting in the Netherlands through the use of a prediction tool that uses easily available electronic medical record data [EBioMedicine 2022; 82:104176], as well as in the inpatient setting in the US through the use of an algorithm with indications on when to draw BCs based on the probability of bacteremia according to the

presenting signs and symptoms. [J Clin Microbiol 2020; 58: e01053-2015] see below



J Clin Microbiol 2020; 58:e01053-20.

BCC has received renewed attention with a new recommended threshold by the Clinical and Laboratory Standards Institute (BCC<1%). [Clinical and Laboratory Standards Institute. CLSI M47: principles and procedures for blood culture] This study only included inpatient antibiotic use because outpatient antibiotic use data were not available for all patients. The US and Dutch cohorts differed in comorbidities and admitting diagnoses—for example, more patients in the US had a history of diabetes and pacemaker implantation, and more US patients were admitted for sepsis.

Blood culture contamination among inpatients is associated with increased use of unnecessary antibiotics. They showed that the mean number of additional days of antibiotic therapy was higher for inpatients with contaminated vs negative blood cultures in both the US cohort and the Netherlands cohort (1.58 and 1.74 days, respectively; P <.001).

Bottom line: Every hospital should initiate blood culture diagnostic stewardship to improve detection and turn-around time and at the same time eliminate unnecessary blood cultures which can lead to increased contamination rates and unnecessary antibiotics.

External Validation of the 2023 Duke - International Society for Cardiovascular Infectious Diseases Diagnostic Criteria for Infective Endocarditis

Clin Infect Dis published online February 8, 2024

DOI: 10.1093/cid/ciae033

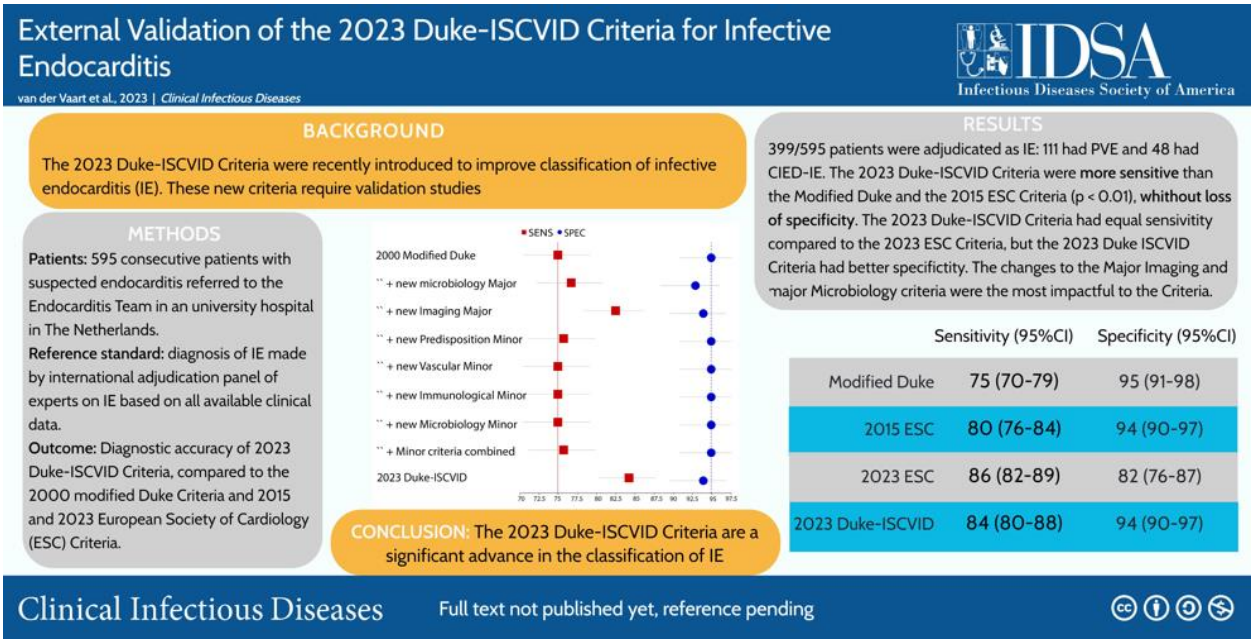
The 2023 Duke-International Society of Cardiovascular Infectious Diseases (ISCVID) Criteria for IE were introduced to improve classification of infective endocarditis (IE) for research and clinical purposes. [Clin Infect Dis 2023; 774:518–26]

CRITERIA	Change
PATHOLOGIC CRITERIA	
Microorganism identification	Microorganisms identified in appropriate sample by PCR, amplicon or metagenomic sequencing, or in situ hybridization
MAJOR CLINICAL CRITERIA	
Microbiology	
Blood cultures	Removed requirements for timing and separate venipunctures for blood cultures.
Definition of typical organisms	Added typical pathogens: 1) *S. lugdunensis*; *E. faecalis;* all streptococci except *S. pneumoniae* and *S. pyogenes*; *Granulicatella* spp.; *Abiotrophia* spp.; and *Gemella* spp. 2) Organisms to be considered "typical" IE pathogens in the setting of intracardiac prosthetic material: coagulase negative staphylococci, *Corynebacterium striatum; C. jeikeium, Serratia marcescens, Pseudomonas aeruginosa, Cutibacterium acnes,* nontuberculous mycobacteria, and *Candida* spp.
Other microbiologic tests	Added new Major Criteria for fastidious pathogens: 1) PCR or amplicon/metagenomic sequencing identifies *C. burnetii, Bartonella* spp., or *T. whipplei* from blood; or 2) IFA ≥1:800 for IgG antibodies identifies *B. henselae* or *B. quintana.*
Imaging	
Echocardiography	Similar to earlier versions. Cornerstone of imaging criterion.
Cardiac computed tomography	Added new Major Criterion. Findings equivalent to echocardiography.
[18F]FDG PET/CT	Added new Major Criterion. Findings for native valve, cardiac device, or prosthetic valve >3 mo after cardiac surgery are equivalent to echocardiography.
Surgical	Added new Major Criterion. Intraoperative inspection constitutes Major Criterion in absence of Major Criterion by cardiac imaging or histopathology.
MINOR CLINICAL CRITERIA	
Predisposition	Added transcatheter valve implant/repair, endovascular CIED, and prior diagnosis of IE.
Fever	Unchanged.
Vascular phenomena	Added splenic and cerebral abscess.
Immunologic phenomena	Added definition for immune complex mediated glomerulonephritis.
Microbiological	Added PCR or amplicon/metagenomic sequencing evidence of typical pathogen.
Imaging	Added PET/CT evidence <3 mo of cardiac surgery.
Physical examination	New auscultation of regurgitant murmur when echocardiography is unavailable.

Abbreviations: [18F] FDG PET CT, positron emission computed tomography with 18F-fluorodeoxyglucose; CIED, cardiac implantable electronic device; IFA, immunofluorescence assay; PCR, polymerase chain reaction.

This study set out to provide external validation. The investigators studied consecutive patients with suspected IE referred to the IE Team at Amsterdam University Medical Center (October 2016-March 2021). An international expert panel independently reviewed case summaries and assigned a final diagnosis of "IE" or "Not IE", which served as the reference standard, to which the "Definite" Duke-ISCVID classifications were compared. They also evaluated accuracy when excluding cardiac surgery and pathology data ("Clinical Criteria"). Lastly, they compared the 2023 Duke-ISCVID to the 2000 Modified Duke Criteria and the 2015 and 2023 European Society of Cardiology (ESC) Criteria.

595 consecutive patients with suspected IE were included: 399 (67%) were adjudicated as IE; 111 (19%) had prosthetic valve IE and 48 (8%) had cardiac implantable electronic device IE. The 2023 Duke-ISCVID Criteria were more sensitive than either the Modified Duke or 2015 ESC Criteria (84.2% vs 74.9% and 80% respectively, $p < 0.001$) without significant loss of specificity. The 2023 Duke-ISCVID Criteria were similarly sensitive but more specific than the 2023 ESC Criteria (94% vs 82%, $p < 0.001$). The same pattern was seen for the Clinical Criteria (excluding surgery/pathology results). The 2023 Duke-ISCVID Criteria represents a significant advance in the diagnostic classification of patients with suspected IE.



Comment: New modifications in the 2023 Duke-ISCVID Criteria related to 'Major Microbiological' and 'Imaging' criteria were most impactful. However, this is done in only a single referral center. Second, the prevalence of people with IVDA in this cohort was low. Third, the usage of PET/CT was relatively high, which will not be generalizable to many healthcare settings.

Bottom line: This study demonstrated that the 2023 Duke-ISCVID Criteria improves the diagnostic classification of patients with suspected IE. Pending validations in other cohorts, we should begin use the 2023 Duke-ISCVID for the diagnosis of IE.

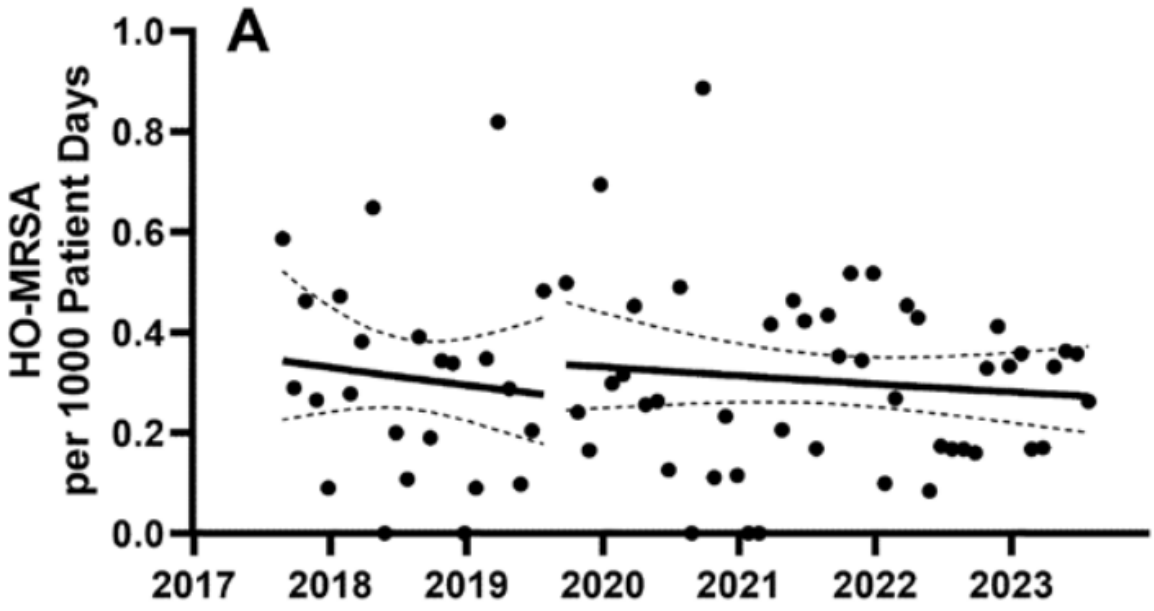
Discontinuation of Contact Precautions (CP) for Methicillin-resistant Staphylococcus aureus in a Pediatric Healthcare System J Pediatric Infect Dis Soc published online January 3, 2024

doi.org/10.1093/jpids/piae001

The investigators conducted a retrospective before-and-after quasi experimental study encompassing all patients hospitalized at a pediatric healthcare system from September 1, 2017, through August 31, 2023. CP for MRSA were discontinued in all locations except the neonatal intensive care unit at a 3-hospital pediatric healthcare system in September 2019. CP were maintained together with active surveillance testing for multidrug-resistant organisms (MDROs) via anterior nasal, axillary, and rectal swabs on NICU admission. All hospitalized patients underwent surveillance for LabID healthcare facility-onset MRSA infections. Analysis was done using interrupted time series (ITS) from September 2017 through August 2023 and aggregate before and-after rate ratios.

There were 234 incidents of healthcare facility-onset MRSA infections during 766,020 patient days of surveillance. After discontinuation of CP for MRSA there was no change in the ITS slope (0.06, 95% CI: −0.35 to 0.47, P = .78) or intercept (0.21, 95% CI: −0.36 to 0.78, P = .47) of the

LabID healthcare facility-onset MRSA infection incidence density rate. Additionally, there was no change in the aggregate incidence density rate of these MRSA LabID events (aggregate rate ratio = 0.98, 95% CI: 0.74 to 1.28). MRSA nasal colonization among patients being screened before cardiac surgery did not change (aggregate rate ratio = 0.94, 95% CI: 0.60 to 1.48). The prevalence rate of contact isolation days decreased by 14.0%. The facility-wide HO-MRSA and CO-MRSA admission prevalence rates did not change in the ITS analysis. Horizontal infection prevention practices such as hand hygiene and CLABSI prevention bundle measures showed high levels of adherence.



Comment: Discontinuation of CP for pediatric patients with MRSA was not associated with increased MRSA infection over 4 years. They attempted to evaluate the possibility of an increase in silent MRSA transmissions after discontinuation of CP by looking at the CO-MRSA admission prevalence and the precardiac surgery MRSA screening prevalence. However, these analyses do not exclude the possibility that silent transmission during admission could have led to increased colonization in other patients or clinically significant infections following hospital discharge. I did not see if they utilized CHG bathing as an additional horizontal infection prevention measure.

Their experience supports considering discontinuation of CP for MRSA in similar pediatric healthcare settings in the context of good adherence to horizontal infection prevention measures. These findings are consistent with the successful experiences described following the implementation of similar changes at hospitals caring for adult patients. [Am J Infect Control 2020; 48:1466–1473; Infect Control Hosp Epidemiol 2022; 43:1595–1602] The 2022 updated Compendium of Strategies to Prevent HAIs in Acute Care Hospitals still recommends CP but mention many of the studies demonstrating success have also had several horizontal strategies in place, including CHG bathing. The update suggests that facilities that choose to discontinue the use of CP for MRSA-colonized or MRSA-infected patients should perform an MRSA risk assessment based on internal infection rates and local epidemiology. Facilities must have

excellent infection prevention policies and documented adherence to standard precautions. [Infect Control Hosp Epidemiol 2023; 44: S71-99]

Bottom line: Discontinuing CP for MRSA in pediatrics except NICU may be possible if the facility has low rates of MRSA and has an excellent infection prevention team with good adherence to standard precautions.

Safety and Efficacy of Midline vs Peripherally Inserted Central Catheters Among Adults Receiving IV Therapy A Randomized Clinical Trial JAMA Network Open. 2024;7(2): e2355716.

doi:10.1001/jamanetworkopen.2023.55716

This was a parallel, 2-group, open-label, RCT conducted from October 2018 to February 2022 at a single academic tertiary care center. Adult inpatients and outpatients were consecutively randomized. Patients were randomized in a 1:1 ratio to either the MC group or the PICC control group. The primary outcome was catheter-related bloodstream infection (CRBSI). Secondary outcomes were symptomatic catheter-related thrombosis and catheter failure, including mechanical cause, phlebitis, infiltration, pain in relation to drug or fluid administration, and leaking from the puncture site.

A total of 304 patients (mean [SD] age, 64.6 [13.5] years; 130 [42.8%] female) were included in the analysis, and 152 patients were allocated to each catheter group. The incidence of CRBSI was low, with 0 in the MC group and only 1 in the PICC control group (P > .99). The MC group had a higher catheter-related complication rate (20 [13.2%] vs 11 [7.2%]), and an IRR of 2.37 (95% CI, 1.12- 5.02; P = .02) for complications compared with the PICC control group. In a post hoc analysis stratified by catheter dwell time, no significant difference in complication rate (IRR, 1.16; 95% CI, 0.50-2.68; P = .73) was found between the 2 groups for catheters used less than 16 days.

Comment: In this RCT with patients who received medium- to long-term intravenous therapy, the incidence of CRBSI was low, with no difference between MCs and PICCs. The use of MCs resulted in a higher incidence of catheter-related complications compared with use of PICCs. In a recent systematic review higher rates of thrombosis and lower rates of infection were reported among patients who received midline catheters compared with PICCs. [Open Forum Infect Dis. 2023;10(2): ofad02] Most of the studies, however, were observational. In the current study we do not know which infusions were delivered or classified as peripherally compatible in the study. How many patients left the hospital with their assigned device is unknown; thus, it is difficult to extrapolate these data to the home setting or care outside of the hospital. However, this trial was a head-to-head study which helped establish the utility of midline catheters for delivering peripherally compatible infusions for durations of 15 or fewer days. The absence of any major complications and lack of difference in rates of minor events during this period suggest that not only are midline catheters safe but they may be preferred as recommended by evidence-based guidelines. [Ann Intern Med. 2015;163(6)(suppl):S1-S40] Second, this study illustrates the importance of collecting context-specific variables when performing head-to-head comparisons of vascular access devices. Covariates, such as detailed indications for use, insertion details, types of infusions delivered, frequency of catheter access,

whether devices were used for phlebotomy, and dressing and flushing practices, are all examples of confounders that may affect outcomes. While larger trials may allow for balance of these unmeasured aspects, the validity of small trials will always be threatened in the absence of these details.

Bottom line: Midline catheters for short durations (<15 days) appears to be a safe alternative to PICCs.

Maternal Vaccine Effectiveness Against Influenza-Associated Hospitalizations and Emergency Department Visits in Infants JAMA Pediatr published online December 18, 2023

doi:10.1001/jamapediatrics.2023.5639

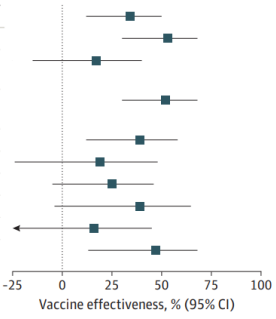
In a test-negative case control study of data from the New Vaccine Surveillance Network (NVSN) throughout three consecutive influenza seasons, investigators assessed the impact of influenza vaccination during pregnancy on infant influenza-related ED visits and hospitalizations.

Among 3764 eligible infants aged <6 months with respiratory illness, 223 had influenza with reported or confirmed maternal influenza immunization status. Key findings are:

- In all, 53% of enrolled infants were born to vaccinated mothers, and 42% tested positive for influenza.
- Infants with influenza were older and more likely to be non-Hispanic Black and publicly insured.
- Overall effectiveness of maternal vaccination against ED visits or hospitalization was 34% and was highest when vaccine was given during the third trimester compared with other trimesters (54% vs. 17%); rates were most pronounced against influenza A/H1N1 (39%).
- Younger infants benefitted most from maternal vaccination (effectiveness was 53% for infants aged <3 months).

Figure 2. Effectiveness of Maternal Influenza Vaccination During Pregnancy Against Influenza Hospitalizations and Emergency Department (ED) Visits in Infants

Infants <6 mo of age	Vaccinated mothers, No./total No. (%)		Effectiveness of maternal vaccination against influenza illness in infants, % (95% CI)
	Infants with influenza illness	Control infants	
Overall effectiveness of maternal vaccination	94/223 (42)	1913/3541 (54)	34 (12 to 50)
Infants <3 mo of age	49/106 (46)	1293/2147 (60)	53 (30 to 68)
Mother vaccinated during first or second trimester of pregnancy	59/188 (31)	1009/2637 (38)	17 (-15 to 40)
Mother vaccinated during third trimester of pregnancy	35/164 (21)	904/2532 (36)	52 (30 to 68)
Hospital admission	55/125 (44)	1416/2541 (56)	39 (12 to 58)
ED visit	39/98 (40)	497/1000 (50)	19 (-24 to 48)
Influenza A	70/157 (45)	1913/3541 (54)	25 (-5 to 46)
H1N1	21/53 (40)	1913/3541 (54)	39 (-4 to 65)
H3N2	42/87 (48)	1913/3541 (54)	16 (-29 to 45)
Influenza B	25/67 (37)	1913/3541 (54)	47 (13 to 68)



Comment: In this study, 46% of the persons vaccinated during pregnancy were identified as having plausible self-report with vaccine receipt at a feasible timing. The dependence on self-report underscores the need to expand vaccine registries from children to persons of all ages. Accurate vaccine record systems are needed to support pregnancy-specific vaccine recommendations, which include the Tdap, influenza, Covid-19, and RSV vaccine. This study also demonstrated disparities with non-Hispanic Black infants and those with public insurance being more likely to be born to unvaccinated mothers and being more likely to have influenza-related hospitalizations or ED visits. The current study strengthens the evidence that infants benefit when persons receive the quadrivalent-inactivated influenza vaccine during pregnancy. With only half of pregnant persons receiving the influenza vaccine in this study and nationally, there is a huge opportunity to improve vaccine coverage and health outcomes for all pregnant persons and newborns.

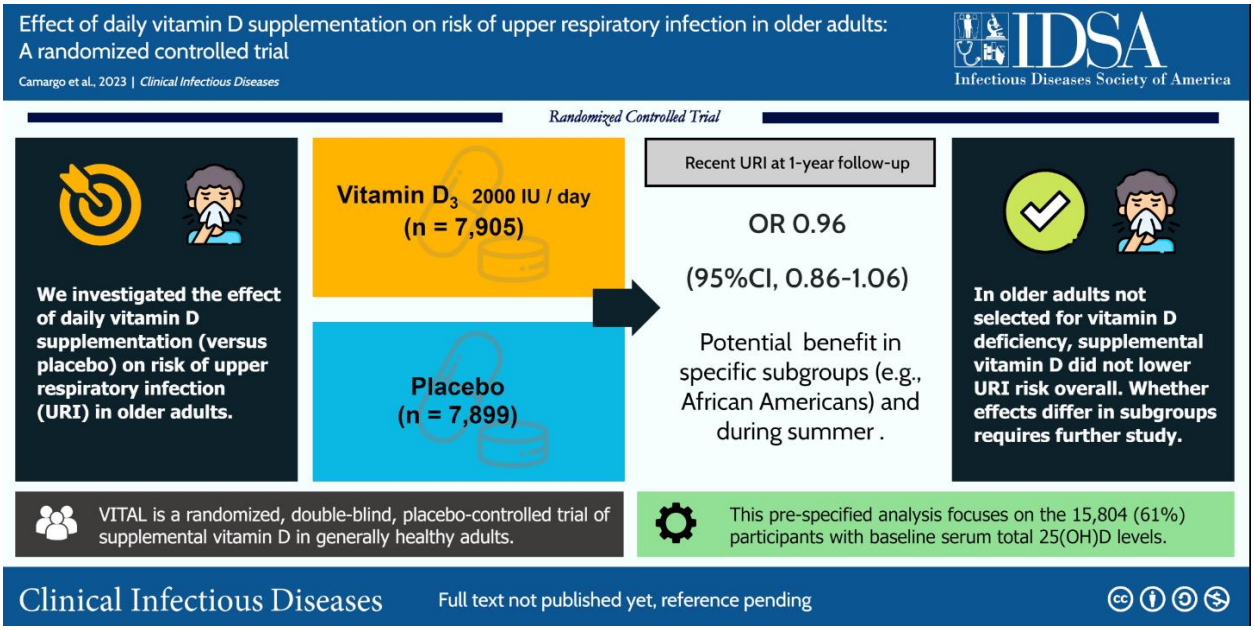
Bottom line: The findings in this study indicate that maternal influenza vaccination during pregnancy provided important protection for the infant in the first few months of life before infants are eligible for vaccination.

Effect of Daily Vitamin D Supplementation on Risk of Upper Respiratory Infection in Older Adults: A Randomized Controlled Trial Clin Infect Dis published online December 18, 2023

doi.org/10.1093/cid/ciad770

VITAL (VITamin D and OmegA-3 TriaL) is a randomized, double-blind, placebo-controlled trial of supplemental vitamin D and/or omega-3 fatty acids in generally healthy men (age ≥50 years) and women (age ≥55 years). This prespecified analysis focuses on vitamin D3 (2000 IU/day) versus placebo in the 15,804 (61%) participants with baseline serum total 25-hydroxyvitamin D level. The primary outcome was self-report of a recent URI at 1-year follow-up.

Participants had a mean age of 68 years and 51% were women; 76% were non-Hispanic White, 16% Black, and 8% other race/ethnicity. The mean 25-hydroxyvitamin D level at baseline was 31 (standard deviation, 10) ng/mL, with < 12 ng/mL in 2.4%. The overall effect of vitamin D supplementation on recent URI was nonsignificant (odds ratio [OR], 0.96 [95% confidence interval {CI}, .86–1.06]). In the prespecified subgroup of primary interest (<12 ng/mL and denied taking concurrent vitamin D), which had only 255 participants, vitamin D supplementation was nonsignificant (OR, 0.60 [95% CI, .28–1.30]). Statistical power to assess the effect modification in other subgroups, however, was limited. Black participants may have derived benefit, this also may have been due to chance. There may have been a benefit during the summer.



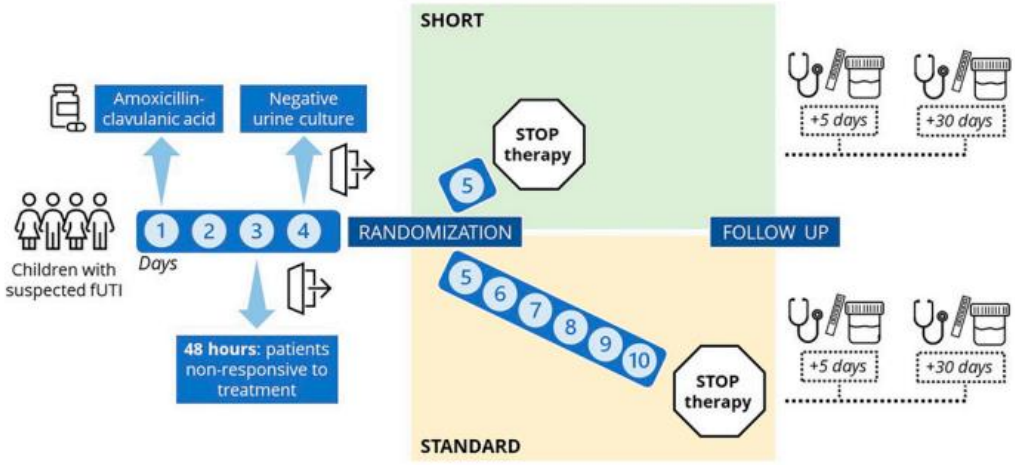
Comment: In this large RCT of generally healthy older US adults, the investigators found that a vitamin D supplement of 2000 IU daily did not lower risk of URI after 1 year of treatment. Analyses in the subgroup of interest (n = 255) required exclusion of >98% of the study population. Although recall bias is minimized when asking about the "past few days," it would have been better to have viral testing to confirm the URI diagnosis. The intervention appeared safe, without evidence of harm over 5 years.

Bottom line: In older adults not selected for vitamin D deficiency, supplemental vitamin D did not lower URI risk overall. Whether effects differ in subgroups requires further study.

Short Oral Antibiotic Therapy for Pediatric Febrile Urinary Tract Infections: A Randomized Trial Pediatrics 2024 153 (1): e2023062598.

https://doi.org/10.1542/peds.2023-062598

In a multicenter trial, Italian investigators assessed recurrent infection within 30 days of completing 5-day versus 10-day treatment courses. Secondary end points were clinical response, adverse events, and antibiotic resistance. (Short-Course Oral Antibiotic Therapy of Acute Pyelonephritis in Children [STOP] trial)



In all, 140 children with febrile UTIs were randomized 1:1 on day 5 of antibiotic treatment (amoxicillin-clavulanate) to either stopping therapy or adding an additional 5 days of antibiotics, with follow-up for microscopic urine examination 5 and 30 days, respectively, after antibiotic completion. Key findings were:

- E. coli was the primary causative organism in both the 5- and 10-day treatment groups (86.1% and 88.6%, respectively).
- UTI recurrence rates within 30 days of treatment completion were 2.8% (5-day treatment) vs. 14.3% (10-day treatment); rates of febrile UTI recurrence were 1.4% vs. 5.7%.
- Both groups had similar resolution of signs and symptoms (97.2% and 92.9%), with additional antibiotic therapy required in 1.4% and 8.6%.
- Adverse events were similarly uncommon in both groups.
- The likelihood of resistant organisms emerging after therapy was very low in both groups.

Comment: The results of STOP contrast with those of the recently published Short Course Therapy for UTI in Children (SCOUT) trial, which also compared 5 versus 10 days of therapy for UTI in children. The authors of this randomized, placebo-controlled trial(SCOUT) evaluated 664 children aged 2 months to 10 years (62% afebrile, 96% female, 23% >6 years old) at 2 US hospitals from May 2012 through February 2023. Treatment failure by day 11 to 14 occurred in 4.2% (14/336) assigned to short-course therapy versus 0.6% (2/328) assigned to longer therapy. The risk difference was 3.6% (P < .01, upper bound of 95% CI, 5.5%). [JAMA Pediatr. 2023; 177:782–789 reviewed in ID Watch last year] The authors of STOP defined febrile UTI as the presence of fever >38C with a positive urine dipstick for nitrite or leukocyte esterase in a urine specimen collected by clean catch or urinary bag. The isolation of a single species in a culture of urine obtained by clean catch (>100 000 colony-forming units [CFU]/mL) or bladder catheterization (>10,000 CFU/mL) was required for confirmation. The STOP exclusion criteria included having complicated febrile UTI (defined as persistence of fever >48 hours after commencing treatment), the need to change the antibiotic regimen, dehydration, vomiting, the presence of a urinary catheter, immunodeficiency, and neurogenic bladder. Randomization (on day 4 after enrollment after culture results were available) was stratified by the isolation of E coli versus non-E. coli microbes. The treatment duration was unblind. Of the total number of study participants, 13 had grade III or higher vesicoureteral reflux (VUR). On the other hand SCOUT

defined UTI as (1) the presence of 1 or more of fever (at least 38C), suprapubic, abdominal, or flank pain, urinary urgency, frequency, or hesitancy, dysuria, and poor feeding or vomiting, (pyuria (>10 white blood cells/mL or 5 white blood cells/high power field) or positive leukocyte esterase of dipstick urinalysis, and urine culture with the growth of a single pathogen (>50,000 CFU/mL, suprapubic or catheterized specimen, or >100,000 CFU/mL, clean voided specimen). SCOUT recruited children from primary care sites, inpatient units, and emergency departments. The primary outcome of the recurrence of UTI between day 6 and days 11 to 14 after the initiation of therapy led to longer post-treatment follow-up for the 5-day group versus the 10-day group, potentially skewing outcome results. Clinically it may be difficult to distinguish between cystitis and pyelonephritis in children. The criterion of febrile UTI in STOP may (or may not) have yielded predominantly subjects with pyelonephritis.

In a commentary “Data from STOP provide some comfort that 5 days of oral therapy in young children with uncomplicated febrile UTI might be sufficient. Given the almost 4-fold greater sample size and slightly more rigorous study design of SCOUT” they conclude direct and indirect (adult) data support treating UTI in children that appears limited to cystitis with courses no longer than 5 days. However for pyelonephritis, they prefer until more data is available, to maintain a modest preference for 10 days. They go on to say choosing a shorter course with close follow-up may be reasonable after a discussion of risks and benefits, especially when the child is not ill enough to require hospitalization and does not have GU tract anomalies or severe reflux for which UTI recurrence due to undertreatment may increase the risk of nephron loss to a degree that could have long-term consequences.

Bottom line: Given benefits of reduced antimicrobial exposure, for select patients (see discussion above) physicians can consider 5 days rather than 10 days; however, given the small ample size in this paper larger studies are needed in children with pyelonephritis.

Editor’s Choice

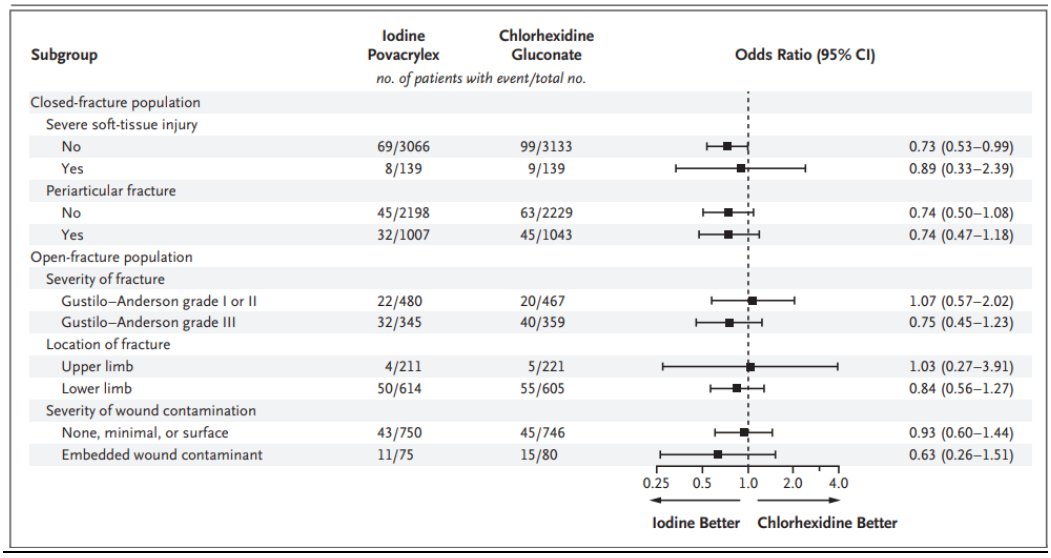
Skin Antisepsis before Surgical Fixation of Extremity Fractures N Engl J Med 2024; 390:409-20.

DOI: 10.1056/NEJMoa2307679

This was a cluster-randomized, crossover trial at 25 hospitals in the US and Canada. They randomly assigned hospitals to use a solution of 0.7% iodine povacrylex in 74% isopropyl alcohol[duraprep] (iodine group) or 2% chlorhexidine gluconate in 70% isopropyl alcohol[chloraprep] (chlorhexidine group) as preoperative antisepsis for surgical procedures to repair extremity fractures. Every 2 months, the hospitals alternated interventions. Separate populations of patients with either open or closed fractures were enrolled and included in the analysis. The primary outcome was surgical-site infection (SSI), which included superficial incisional infection within 30 days or deep incisional or organ-space infection within 90 days. The secondary outcome was unplanned reoperation for fracture-healing complications.

A total of 6785 patients with a closed fracture and 1700 patients with an open fracture were enrolled in the study. In the closed-fracture population, SSI occurred in 77 patients (2.4%) in the iodine group and in 108 patients (3.3%) in the chlorhexidine group (odds ratio, 0.74; 95% confidence interval [CI], 0.55 to 1.00; P=0.049). In the open-fracture population, SSI occurred in

54 patients (6.5%) in the iodine group and in 60 patients (7.3%) in the chlorhexidine group (odd ratio, 0.86; 95% CI, 0.58 to 1.27; P=0.45). The frequencies of unplanned reoperation, 1-year outcomes, and serious adverse events were similar in the two groups.



Subgroup	Iodine Povacrylex	Chlorhexidine Gluconate	Odds Ratio (95% CI)
	no. of patients with event/total no.		
Closed-fracture population			
Severe soft-tissue injury			
No	69/3066	99/3133	0.73 (0.53–0.99)
Yes	8/139	9/139	0.89 (0.33–2.39)
Periarticular fracture			
No	45/2198	63/2229	0.74 (0.50–1.08)
Yes	32/1007	45/1043	0.74 (0.47–1.18)
Open-fracture population			
Severity of fracture			
Gustilo–Anderson grade I or II	22/480	20/467	1.07 (0.57–2.02)
Gustilo–Anderson grade III	32/345	40/359	0.75 (0.45–1.23)
Location of fracture			
Upper limb	4/211	5/221	1.03 (0.27–3.91)
Lower limb	50/614	55/605	0.84 (0.56–1.27)
Severity of wound contamination			
None, minimal, or surface	43/750	45/746	0.93 (0.60–1.44)
Embedded wound contaminant	11/75	15/80	0.63 (0.26–1.51)

Comment: In patients who were undergoing surgical fixation of a closed fracture of a lower limb or the pelvis, they found that the risk of SSIs was lower with skin antisepsis provided by iodine povacrylex in alcohol than with antisepsis provided by chlorhexidine gluconate in alcohol. In contrast, the risk of SSIs did not differ significantly between the two trial groups in the open-fracture population. The authors claim the findings of previous trials of preoperative skin antisepsis have been inconsistent. [Cochrane Database Syst Rev 2015;4:CD003949] Unless contraindicated, clinical practice guidelines support the use of alcohol-based solutions, and some recommend chlorhexidine plus alcohol as the preferred agent. [Infect Control Hosp Epidemiol 2023; 44:695-720] In some prior trials chlorhexidene was compared with PI not iodine povacrylex.

However, two previous studies have directly compared chlorhexidine gluconate in alcohol with iodine povacrylex in alcohol to reduce surgical-site infection. The results of one randomized, controlled trial involving 788 patients who underwent elective colorectal surgery under clean-contaminated conditions (i.e., in which the surgical area is entered under controlled conditions with a low probability of contamination) was inconclusive (between-group difference, 2.8 percentage points; 95% CI, -3.2 to 8.9). [Ann Surg 2017; 266:946-51] Conversely, a prospective study involving 3209 general surgery patients favored iodine povacrylex for the prevention of surgical-site infection (3.9% vs. 7.1%). [Infect Control Hosp Epidemiol 2009; 30:964-71] The authors point out that the iodophor that was used in this trial differs from povidone iodine. Iodine povacrylex is an iodophor that is available in alcohol and unique due to its copolymer, povacrylex. The structure of the iodine povacrylex copolymer may provide important benefits beyond those of traditional povidone iodine for the prevention of SSIs. Iodine is inactivated by organic matter, but povacrylex is resistant to fluids and blood, thereby potentially offering longer protection than povidone iodine or other agents.

Of interest they did not observe the same benefit of iodine povacrylex in the open-fracture population. One explanation is that open fracture wounds are exposed to heterogeneous

environmental contamination and prolonged bacterial exposure before surgery. However, the baseline infection risk in the open-fracture population was lower than anticipated, which reduced the statistical power for the primary comparison.

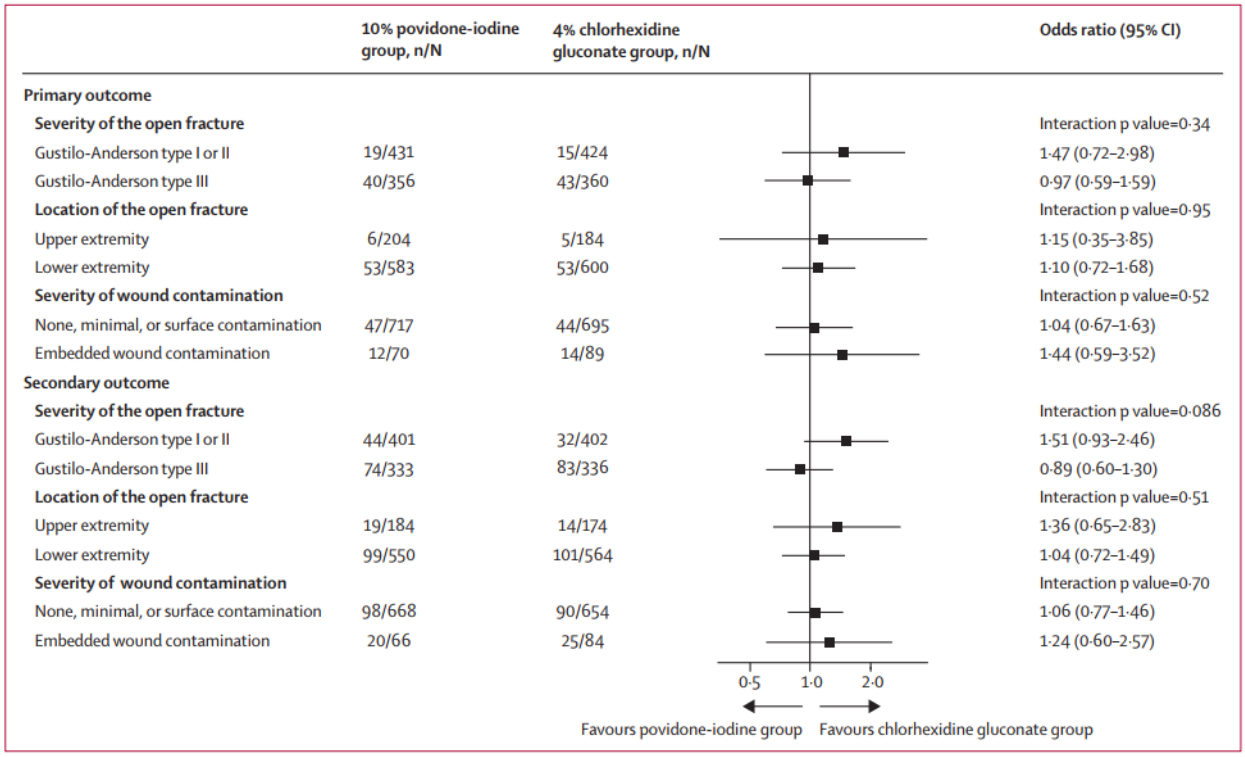
Bottom line: Findings suggest that the use of iodine povacrylex in alcohol as preoperative skin antisepsis could prevent SSIs in patients with closed fractures, but such use is unlikely to improve the outcomes in patients with open fractures likely due to deep wound contamination. The trial was limited to patients who were undergoing surgery for a fracture, so the generalizability of these findings to other surgical procedures is unknown. Lastly, results with iodine povacrylex may not be generalizable to all iodine preparations. See next review

Aqueous skin antisepsis before surgical fixation of open fractures (Aqueous-PREP): a multiple-period, cluster randomised, crossover trial Lancet 2022; 400: 1334–44 article provided by Susan Huang

The investigators set out to compare the effect of aqueous 10% povidone-iodine versus aqueous 4% chlorhexidine gluconate on the risk of surgical site infection in patients who required surgery for an open fracture because many surgeons avoid alcohol-based solutions for antisepsis of open wounds because of the potential for tissue toxicity.

They conducted a multiple-period, cluster-randomized, crossover trial (Aqueous-PREP) at 14 hospitals in Canada, Spain, and the US. Eligible patients were adults aged 18 years or older with an open extremity fracture treated with a surgical fixation implant. For inclusion, the open fracture required formal surgical debridement within 72 hours of the injury. Participating sites were randomly assigned (1:1) to use either aqueous 10% povidone-iodine or aqueous 4% chlorhexidine gluconate immediately before surgical incision; sites then alternated between the study interventions every 2 months. Participants, health-care providers, and study personnel were aware of the treatment assignment due to the color of the solutions. The outcome adjudicators and data analysts were masked to treatment allocation. The primary outcome was surgical site infection (SSI), guided by the 2017 CDC's National Healthcare Safety Network (NHSN) reporting criteria, which included superficial incisional infection within 30 days or deep incisional or organ space infection within 90 days of surgery. The primary analyses followed the intention-to-treat principle and included all participants in the groups to which they were randomly assigned.

Between April 8, 2018, and June 8, 2021, 3619 patients were assessed for eligibility and 1683 were enrolled and randomly assigned to povidone-iodine (n=847) or chlorhexidine gluconate (n=836). The trial's adjudication committee determined that 45 participants were ineligible, leaving 1638 participants in the primary analysis, with 828 in the povidone-iodine group and 810 in the chlorhexidine gluconate group (mean age 44·9 years [SD 18·0]; 629 [38%] were female and 1009 [62%] were male). Among 1571 participants in whom the primary outcome was known, an SSI occurred in 59 (7%) of 787 participants in the povidone-iodine group and 58 (7%) of 784 in the chlorhexidine gluconate group (odds ratio 1·11, 95% CI 0·74 to 1·65; p=0·61; risk difference 0·6%, 95% CI –1·4 to 3·4).



Comment: In this multiple-period, cluster-randomized, crossover trial undergoing surgical fixation of an open extremity fracture the odds of surgical site infection or unplanned fracture-related reoperations did not differ between patients assigned to receive skin antisepsis with aqueous 10% povidone-iodine or aqueous 4% chlorhexidine gluconate. Two-thirds of participants received adjunctive antisepsis, most frequently with alcohol, before final skin preparation, and the primary outcome event rate was lower than anticipated, possibly reducing study power. In this hybrid method, the intact skin remote from the open wound is cleaned with an alcohol antiseptic, and the traumatic wound receives the aqueous solution only. Their results call into question previous literature, which suggests solutions with chlorhexidine (usually with alcohol) are more effective than solutions with povidone-iodine in preventing surgical site infections. A meta-analysis by WHO concluded there is moderate evidence to suggest chlorhexidine gluconate in alcohol reduces the risk of surgical site infection compared with aqueous povidone-iodine [no alcohol] (OR 0·65, 95% CI 0·47–0·90). [WHO Global guidelines for the prevention of surgical site infection. 2018] However, it is unclear if the observed benefits were due to the effectiveness of chlorhexidine, its alcohol solvent, or their combination. Alcohol is a potent antiseptic and could independently or synergistically lower the risk of surgical site infections. This current study has a few limitations, including unmasked treatment allocation. Their primary outcome event rate was lower than anticipated, which was likely to be due to strict adherence application of the CDC criteria for superficial incisional infections, which does not include pin site infections. Lastly the uncontrolled use of adjunctive skin preparations before final antisepsis is another limitation of our study design.

The investigators also searched PubMed for studies published in any language from database inception to June 8, 2022, using the terms “antisepsis” AND “surgery” AND “chlorhexidine” AND “povidone-iodine”. They identified 20 randomized controlled trials comparing povidone-iodine with chlorhexidine. However, none of these trials included patients with open fractures. Only one

of the 20 trials compared the two interventions in aqueous-based solutions; in 534 patients who had clean contaminated abdominal surgery, there was no difference in the risk of surgical site infection between the povidone-iodine and chlorhexidine groups (odds ratio [OR] 1·07, 95% CI 0·52–2·21; p=0·85). They also identified five systematic reviews and meta-analyses, including a Cochrane review. Although none of the meta-analyses included an aqueous-based chlorhexidine group, they all concluded antisepsis with chlorhexidine was superior to povidone-iodine in preventing surgical site infections. The study populations included in the meta-analyses consisted of patients who had clean or clean-contaminated surgery.

Several international guidelines strongly recommend skin preparation with alcohol-based solutions, with chlorhexidine gluconate in alcohol being most frequently cited. [see discussion in prior review above] These recommendations are based on systematic reviews of general surgery, obstetrics, and gynecology trials that have shown superiority of chlorhexidine over iodine. Many surgeons avoid alcohol-based solutions for antisepsis of open wounds because of the potential for tissue toxicity. The updated Compendium states "data from recent trials favor the use of CHG–alcohol over povidone-iodine–alcohol." [Infect Control Hosp Epidemiol 2023; 44: s100-s125] One of the most frequently quoted trials was a randomized trial comparing skin antiseptic agents for C-sections.[N Engl J Med 2016;374:647-55] They compared a chlorhexidine–alcohol combination (2% chlorhexidine gluconate with 70% isopropyl alcohol) or an iodine–alcohol combination (8.3% povidone–iodine with 72.5% isopropyl alcohol) [not 0.7% iodine povacrylex in 74% isopropyl alcohol] They reported the use of chlorhexidine–alcohol for preoperative skin antisepsis resulted in a significantly lower risk of SSI after C-section.

Bottom line: For patients who require surgical fixation of an open fracture, either aqueous 10% povidone-iodine or aqueous 4% chlorhexidine gluconate can be used. These findings might also have implications for antisepsis of other open traumatic wounds.

Topical Antibiotic Prophylaxis for Preventing Surgical Site Infections of Clean Wounds: A Systematic Review and Meta-Analysis Surg Infect published online January 29, 2024

doi.org/10.1089/sur.2023.182

Investigators conducted a systematic review and meta-analysis of randomized controlled trials to compare the efficacy and safety of topical antibiotics with nonantibiotic agents for the prevention of SSIs among patients with clean postoperative incisions. The final meta-analysis included 11 studies, and the primary outcome was the incidence of SSIs. Across all studies, 3687 patients received topical antibiotics and 3820 received nonantibiotic agents. The investigators used fixed- and random-effects models to compare outcomes between the groups. The agents used were mupirocin, bacitracin, PI, and vancomycin powder.

There were 149 SSI events among patients who received topical antibiotics and 159 SSI events among those who received nonantibiotic agents. In the pooled analysis, the use of topical antibiotics was not significantly associated with reduced risk of developing postoperative SSI (risk ratio [RR], 0.83; 95% CI, 0.61-1.16; I^2=0%).

Similar findings were observed after patients were stratified into subgroups by type of surgical procedure. The use of topical antibiotics was not associated with reduced SSI risk for patients who underwent spinal (RR, 0.75; 95% CI, 0.40-1.38; I^2=0%), orthopedic (RR, 0.69; 95% CI, 0.37-1.29 I^2=0%), dermatologic (RR, 0.77; 95% CI, 0.39-1.55 I^2=0%), or cardiothoracic procedures (RR, 1.31; 95% CI, 0.83-2.06 I^2=0%).

In regard to timing of treatment application, there was no significant difference in SSI incidence observed between patients who received topical antibiotics vs nonantibiotic agents (RR, 0.80; 95% CI, 0.56-1.14; I^2=0%). Moreover, data captured from 5 studies indicated no significant between-group difference in the incidence of contact dermatitis (RR, 1.13; 95% CI, 0.36-3.58; I^2=37%).

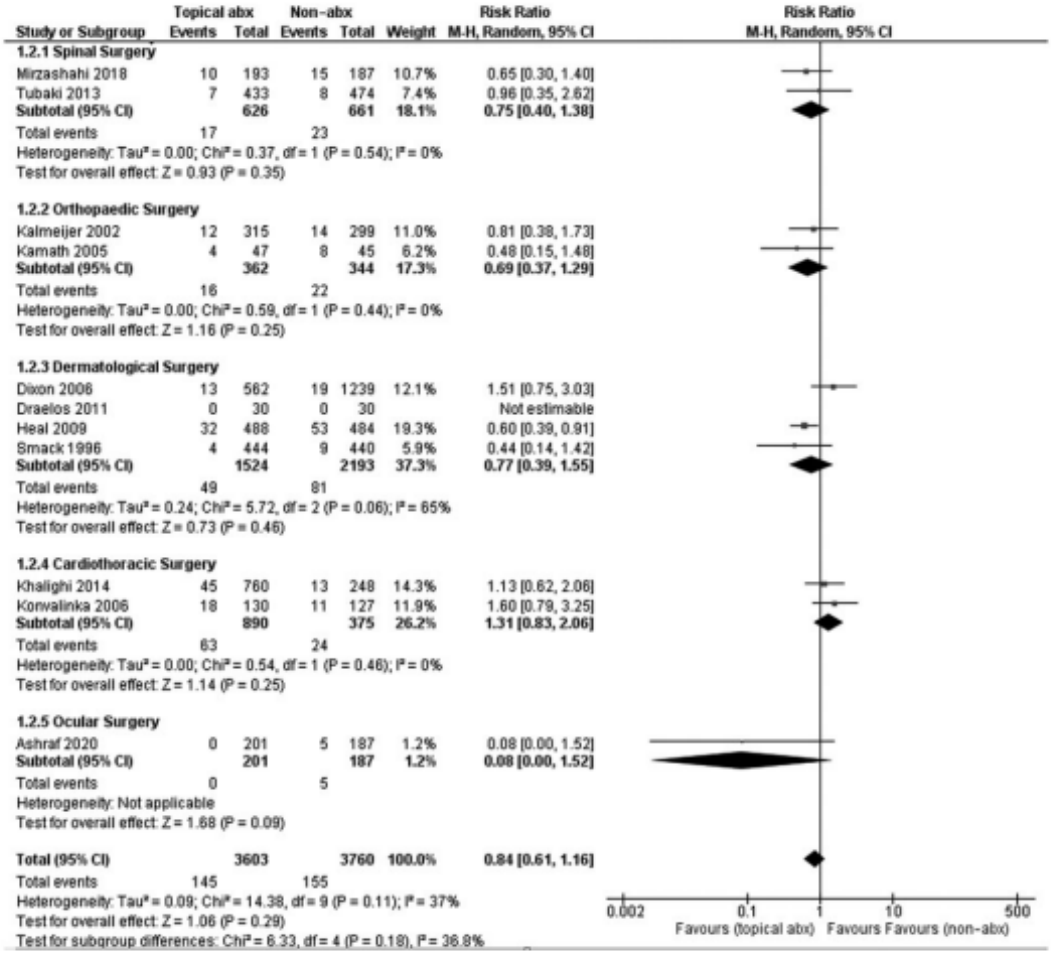


FIG. 2. Meta-analysis of surgical site infections.

Comment: Limitations of this analysis were the inclusion of studies with a potential high risk of bias, and was limited to clean post-operative incisions, and the results might not be applicable to other types of incisions under other conditions.

Bottom line: Based on this review topical antibiotic agents do not need to be applied to surgical sites for the prevention of infection, with no beneficial effects identified for dermatologic, spinal, orthopedic, or cardiothoracic surgery.

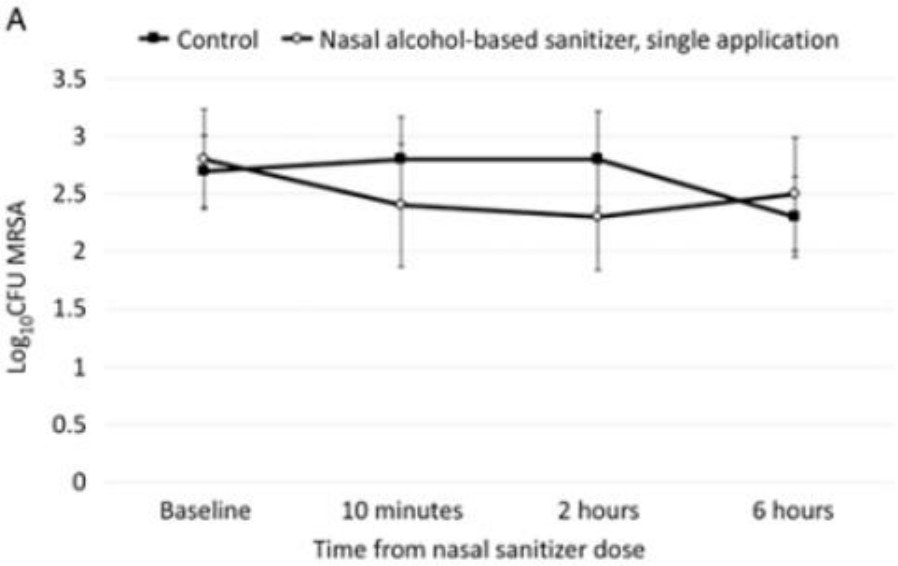
Nasal Sanitizer (Nozin) under FDA Scrutiny February 6, 2024

The FDA sent a warning letter to healthcare company Global Life Technologies Corp in February regarding its over-the-counter product Nozin Nasal Sanitizer. The FDA is calling out nasally administered antiseptic Nozin Nasal Sanitizer for misbranding violations and operating as an unapproved new drug. In its letter, the FDA called the product an unapproved new drug and listed multiple quotes from the company's website as examples of misbranded drug violations. The FDA is giving Global Life Technologies 15 days to respond.

According to the FDA, Nozin Nasal Sanitizer is misbranded under the Federal Food, Drug, and Cosmetic Act (FD&C Act) as it does not follow proper regulatory guidelines for non-prescription drugs. The FDA says that certain category III ingredients like ethyl alcohol used in Nozin must undergo additional safety and effectiveness data before they can be used in consumer antiseptics. The FDA is also calling out the company for over-emphasizing the alleged benefits of its product, which could be misleading and harm public health practices, the agency says.

The FDA states that the rhetoric on Global Life Technologies Corp's website "may lead to a false sense of security for the general public that may result in infrequent hand washing or the substitution of these products for protective gloves and clothing, which are the principal methods for protecting against the spread of diseases caused by pathogenic microorganisms."

Comment: Most of the studies on Nozin are based on quasi experimental studies using a bundled approach. There are very few peer reviewed publications and most studies are abstract presentations. Nosin has a very short half-life with ~1 log reduction. See graph below on nasal effectiveness against MRSA. [Infect Control Hosp Epidemiol 2019; 40, 1436–1437]



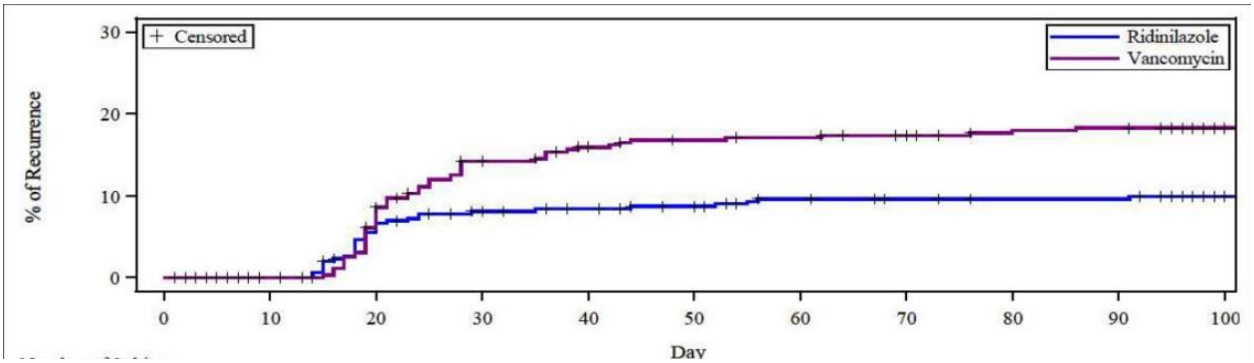
Bottom line: Until better studies are done, if nasal decolonization is indicated I would stick with the evidenced based agents like mupirocin or possibly iodophor.

A Randomized, Double-Blind, Phase 3 Safety and Efficacy Study of Ridinilazole Versus Vancomycin for Treatment of Clostridioides difficile Infection: Clinical Outcomes With Microbiome and Metabolome Correlates of Response Clin Infect Dis published online February 2, 2024

doi.org/10.1093/cid/ciad792

This trial was conducted at 157 sites in 26 countries with adults with CDI. They were randomized 1:1 to receive 10 days of ridinilazole(RDZ)—a narrow-spectrum antibiotic with targeted activity against C difficile—or 10 days of PO vancomycin. RDZ is a bis-benzimidazole bactericidal antibiotic that preferentially binds to AATTT-rich sequences in the C. difficile DNA minor groove impacting downstream cell septum formation. The primary endpoint was SCR, defined as clinical response and no recurrent CDI (rCDI) through 30 days after end of treatment, in the modified intention-to-treat (mITT) population. Secondary endpoints included rCDI and change in relative abundance of microbiome-derived secondary bile acids (SBAs) and clinical response, recurrence, and SCR (days 70 and 100). An additional predefined secondary endpoint included change in the relative abundance of microbiome-derived SBAs in stool samples from baseline to EOT (end of treatment). Exploratory endpoints included changes in relative abundance of primary, conjugated primary BAs, and SBAs and in microbiome composition in stool samples at days 40, 70, and 100. Bile acid and microbiome results up to day 40 are presented here because the primary endpoint is determined at day 40.

RDZ and vancomycin achieved an SCR of 70% and 73%, respectively, for an absolute treatment difference of 2.2% (95% confidence interval [CI], –4.2% to 8.6%), which did not meet the superiority criteria. However, RDZ resulted in a relative 53% reduction in the rCDI rate compared with vancomycin (8.1% in the RDZ group vs 17.3% in the vancomycin group; absolute treatment difference, –9.2%), with subgroup analyses showing a consistent benefit for RDZ in high-risk groups. RDZ also increased microbiome diversity and SBAs and did not increase the resistome, while vancomycin worsened CDI-associated dysbiosis, reduced SBAs, and increased the resistome. Adverse events were similar for both treatment groups (47.1% for RDZ vs 47.2% for vancomycin), with the majority considered mild to moderate in severity, and adverse events leading to discontinuation of the study drug were lower in the RDZ group (0.8%) than in the vancomycin group (2.9%).



Comment: In this study, the investigators show that RDZ is well tolerated, safe, and effective for the treatment of both CDI and the prevention of rCDI. reflecting the activity and selectivity of RDZ against C. difficile. RDZ did not demonstrate superiority to vancomycin in SCR at 30 days post-EOT. However, RDZ decreased the incidence of rCDI by 53% when compared with vancomycin, an effect that is likely due to the RDZ microbiome-sparing specificity seen in previous studies. The investigators proposed potential explanations as to why the SCR in this study was different than expected based on the phase 2 study conducted 6 years earlier that showed a higher SCR for RDZ (66.7%) over vancomycin (42.4%). [Lancet Infect Dis 2017; 17:735–44] First, the current study was carried out during the Covid-19 pandemic when the incidence of CDI decreased due to major changes in infection prevention worldwide. Second, a larger proportion of patients were enrolled in Europe in the global phase 3 study as compared with the phase 2 study, which enrolled a smaller number of patients. Third, the distribution of infecting ribotype and hypervirulent strains known to impact disease severity has shifted and decreased considerably in the past 5 years and was only 11% in the current study compared to 36% in other older studies.

Bottom line: Although RDZ did not meet superiority in SCR, RDZ reduced rCDI and preserved microbiome diversity and SBAs compared with vancomycin.

Editor's Choice

AGA Clinical Practice Guideline on Fecal Microbiota–Based Therapies for Select Gastrointestinal Diseases

Gastroenterology 2024; 166:409–434 Highlights

doi.org/10.1053/j.gastro.2024.01.008

1. In immunocompetent adults with recurrent C difficile infection, the AGA suggests the use of fecal microbiota–based therapies upon completion of standard care antibiotics over no fecal microbiota–based therapies. (Conditional recommendation, low certainty evidence)
    a. Recurrent CDI is typically defined as clinically significant diarrhea with a confirmatory positive test within 8 weeks of completing antibiotics for CDI.
    b. Fecal microbiota–based therapies include conventional FMT, fecal microbiota live-jslm (REBYOTA) and fecal microbiota spores live-brpk (VOWST (SER-109)
    c. Prevention with fecal microbiota–based therapies can be considered in patients after the second recurrence (third episode) of CDI or in select patients at high risk of either recurrent CDI or a morbid CDI recurrence.
    d. Fecal microbiota–based therapies should be given upon completion of a course of standard of care antibiotics for recurrent CDI. The fecal microbiota–based therapies are to prevent recurrence, not for CDI treatment.
    e. Ideally, antibiotics for CDI should be stopped 1–3 days before conventional FMT to allow adequate time for antibiotics to wash out of the system.
    f. Conventional FMT should be performed with appropriately screened donor stool. FMT can be delivered via multiple routes. There is insufficient evidence to recommend a specific route.
    g. Alternatives to fecal microbiota–based therapies:
        i. A vancomycin taper, tapered-pulsed fidaxomicin, or bezlotoxumab are reasonable alternative therapies to prevent recurrent CDI

2. In mildly or moderately immunocompromised adults with recurrent C difficile infection, the AGA suggests the use of conventional fecal microbiota transplant upon completion of standard of care antibiotics over no fecal microbiota transplant. (Conditional recommendation, very low certainty of evidence).
3. In severely immunocompromised adults with recurrent C difficile infection, the AGA suggests against the use of fecal microbiota– based therapies upon completion of standard of care antibiotics over no fecal microbiota–based therapies. (Conditional recommendation, very low certainty of evidence)
    a. Severely immunocompromised includes patients receiving active cytotoxic therapy for solid tumors and hematologic malignancies, patients who have received chimeric antigen receptor T-cell therapy or hematopoietic cell transplant (only when neutropenic), any neutropenia, patients with severe primary immunodeficiency, patients with advanced or untreated HIV infection (CD4 counts.
4. In adults hospitalized with severe or fulminant C difficile infection not responding to antimicrobial therapy, the AGA suggests the use of conventional fecal microbiota transplant over no fecal microbiota transplant. (Conditional recommendation, very low certainty of evidence)
    a. Severe CDI is defined as patients with CDI and a leukocyte count ≥15 x 10^9 cells/L and/or creatinine ≥1.5 mg/dL.
    b. Fulminant CDI presents as severe disease with shock, ileus, or megacolon.
    c. FMT is not advised in patients with bowel perforation or obstruction.
5. In adults with ulcerative colitis, the AGA suggests against the use of conventional fecal microbiota transplant, except in the context of clinical trials. (Conditional recommendation, very low certainty of evidence)
6. In adults with Crohn's disease, the AGA suggests against the use of conventional fecal microbiota transplant, except in the context of a clinical trial. (Conditional recommendation, very low certainty of evidence).
7. In adults with irritable bowel syndrome, the AGA suggests against the use of conventional fecal microbiota transplant, except in the context of clinical trials. (Conditional recommendation, very low certainty of evidence).

Comment: Fecal microbiota–based therapies are effective therapy to prevent recurrent C difficile in select patients. Conventional fecal microbiota transplant is an adjuvant treatment for select adults hospitalized with severe or fulminant C difficile infection not responding to standard care antibiotics. Fecal microbiota transplant cannot yet be recommended in other GI conditions. Future studies are needed to further define the characteristics of intervention in terms of route (upper vs lower gastrointestinal tract), frequency, type of donor (single vs pooled), timing (primary induction vs rescue/concomitant therapy), preparation of stool (aerobic vs anaerobic; frozen vs fresh), and duration of therapy.

Bottom line: This is welcomed guidance and includes conventional FMT, fecal microbiota live-jslm (REBYOTA) and fecal microbiota spores live-brpk (VOWST (SER-109).

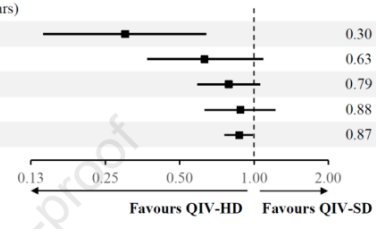
Effectiveness of high-dose vs. standard-dose quadrivalent influenza vaccine 2 against recurrent hospitalisations and mortality in relation to influenza circulation: a post-hoc analysis of the DANFLU-1 randomised clinical trial Clin Microbiol Infect published online January 27, 2024

doi.org/10.1016/j.cmi.2024.01.017

The investigators did a post-hoc analysis of a pragmatic, open-label, registry based, randomized trial of QIV-HD (high dose) vs. QIV-SD (standard dose) conducted during the 2021-2022 influenza season among adults aged 65-79 years. Participants were enrolled in October-November 2021 and followed for outcomes from 14 days post-vaccination until May 31, 2022. The primary outcomes were hospitalizations for pneumonia or influenza, respiratory hospitalizations, cardio-respiratory hospitalizations, cardiovascular hospitalizations, all-cause hospitalizations, and all-cause death. Outcomes were analyzed as recurrent events. Cumulative numbers of events were assessed weekly. Cumulative relative effectiveness estimates were calculated and descriptively compared to influenza circulation.

Among 12,477 randomly assigned participants, receiving QIV-HD was associated with lower incidence rates of hospitalizations for pneumonia or influenza (10 vs. 33 events, IRR 0.30 [95% CI 21 0.14-0.64], p=0.002) and all-cause hospitalizations (647 vs. 742 events, IRR 0.87 [95% CI 0.76- 22 0.99], p=0.032) compared with QIV-SD.

	QIV-HD (n=6,245)	QIV-SD (n=6,232)	Incidence rate ratio (95% CI)	p value
	No. of events (incidence rate/100 person-years)			
Hospitalisations for pneumonia or influenza	10 (0.3)	33 (0.9)	0.30 (0.14 to 0.64)	0.002
Respiratory hospitalisations	30 (0.8)	46 (1.2)	0.63 (0.37 to 1.09)	0.10
Cardio-respiratory hospitalisations	118 (3.1)	147 (3.9)	0.79 (0.59 to 1.06)	0.12
Cardiovascular hospitalisations	90 (2.4)	102 (2.7)	0.88 (0.63 to 1.22)	0.44
All-cause hospitalisations	647 (17.1)	742 (19.7)	0.87 (0.76 to 0.99)	0.032



Comment: In this post-hoc analysis, QIV-HD was associated with lower incidence rates of hospitalizations for pneumonia or influenza and all-cause hospitalizations compared with QIV-SD, with trends evident independent of influenza circulation levels. HD influenza vaccine was developed to provide older adults with better protection against influenza and its complications than SD influenza vaccines. In an individually randomized trial among adults aged ≥65 years, HD trivalent influenza vaccine (TIV-HD) demonstrated superior efficacy against laboratory-confirmed influenza infection and was associated with a lower incidence of serious pneumonia compared with SD trivalent influenza vaccine (TIV-SD).[N Engl J Med 2014;371:635–45] In cluster-randomized trials among nursing home residents, TIV-HD was more effective in reducing the incidence of hospitalization due to influenza-like illness or pneumonia and all-cause hospitalization compared with SD. [The Lancet Resp Med 2017; 5:738–46] Based on the data available in the registries, the investigators were unable to discern with certainty whether recurrent events were new, clinically separate events or whether they represented repeated events during a single disease process. Due to the pragmatic nature of the trial, no systematic influenza testing was performed.

Bottom line: This post hoc review supports ACIP recommendation to administer HD influenza vaccine over standard doses for persons ≥65.

Fatal Alaskapox Infection in a Southcentral Alaska Resident State of Alaska Epidemiology Bulletin February 9, 2024

Alaskapox virus (AKPV) is a recently discovered orthopoxvirus that was first identified in an adult living near Fairbanks in 2015. Seven AKPV infections to date have been reported to the Alaska Section of Epidemiology (SOE). Until December 2023, all reported infections occurred in residents of the Fairbanks area and involved self-limiting illness consisting of a localized rash and lymphadenopathy. Small mammal testing in the Fairbanks area identified evidence of current or prior AKPV infection in four different species (though mostly in red-backed voles). This Bulletin describes a recently reported fatal case of Alaskapox in a resident of the Kenai Peninsula.

The case was an elderly man from the Kenai Peninsula with a history of drug-induced immunosuppression secondary to cancer treatment noted a tender red papule in his right axilla. Over the next 6 weeks, he presented to his primary provider and the local ED several times for clinical evaluation of the lesion and was prescribed multiple antibiotic regimens. A punch biopsy revealed no evidence of malignancy or bacterial infection. Despite antibiotic therapy, the patient experienced fatigue and increasing induration and pain in the right axilla and shoulder. On November 17th , he was hospitalized due to extensive progression of presumed infectious cellulitis that impacted the range of motion of his right arm. The patient was subsequently transferred to a hospital in Anchorage. Computed tomography and magnetic resonance imaging revealed extensive myositis involving his right axilla and shoulder musculature. Four smaller pox-like lesions were also present in diffuse locations across his body. An extensive battery of laboratory tests was performed to discern the cause of the infection, including a plasma microbial cell-free DNA sequencing assay performed by Karius, Inc. The test was initially reported as positive for cowpox virus based on viral sequence comparison on December 8th. A lesion swab was sent to the Alaska State Public Health Laboratory for subsequent testing; it tested positive on a generic orthopoxvirus PCR assay but negative on a non-variola orthopoxvirus PCR assay (which ruled out cowpox, mpox, and vaccinia viruses, but not AKPV). A lesion swab subsequently submitted to the CDC was consistent with AKPV; the genome sequence was phylogenetically distinct from prior Fairbanks AKPV isolates. Treatment with intravenous tecovirimat, intravenous vaccinia immunoglobulin (VIGIV), and oral brincidofovir was initiated. Approximately 1 week into therapy, his condition began to improve with plaque recession, reduced erythema, and subsequent epithelization around the axillary lesion. However, despite intensive medical support in a long-term care setting, he later exhibited delayed wound healing, malnutrition, acute renal failure, and respiratory failure. He died in late January 2024. The route of exposure in this case remains unclear, although scratches from the stray cat represent a possible source of inoculation through fomite transmission.

Comment: This is the first case of severe Alaskapox infection resulting in hospitalization and death. The patient's immunocompromised status likely contributed to illness severity. Moreover, being the first case of Alaskapox identified outside of the Interior region, it indicates that AKPV appears to be more geographically widespread in Alaska's small mammals than previously known and warrants increased statewide awareness among clinicians. Hospitalized Alaskapox patients with immunosuppression should be placed under contact precautions. While human-to-human transmission of AKPV has not yet been observed, some orthopoxviruses can spread by

direct contact with lesions (particularly broken skin contact with secretions). Consider prescribing antiviral and VIGIV therapy for immunocompromised Alaskapox patients or those with progressive disease.

Bottom line: Alaskapox infection appears to be a rare illness and does not pose a widespread risk for now. The use of the Karius test provided the first clue and can be a useful test especially for intravascular infections with organisms that are difficult to culture by routine means. The Karius Test isolates, identifies, and quantifies the microbial cell free DNA signal found in blood.

COVID-19

Early Estimates of Updated 2023–2024 (Monovalent XBB.1.5) COVID-19 Vaccine Effectiveness Against Symptomatic SARS-CoV-2 Infection Attributable to Co-Circulating Omicron Variants Among Immunocompetent Adults — Increasing Community Access to Testing Program, United States, September 2023–January 2024 MMWR 2024 / 73(4);77–83

Data from the Increasing Community Access to Testing SARS-CoV-2 pharmacy testing program were analyzed to estimate updated Covid-19 vaccine effectiveness (VE) (i.e., receipt versus no receipt of updated vaccination) against symptomatic SARS-CoV-2 infection, including by SGTF (*S*-gene target failure) result. Among 9,222 total eligible tests, overall, VE among adults aged ≥18 years was 54% (95% CI = 46%–60%) at a median of 52 days after vaccination. Among 2,199 tests performed at a laboratory with SGTF testing, VE 60–119 days after vaccination was 49% (95% CI = 19%–68%) among tests exhibiting SGTF and 60% (95% CI = 35%–75%) among tests without SGTF. Updated Covid-19 vaccines provide protection against symptomatic infection, including against currently circulating lineages.

Comment: This report provides early estimates of effectiveness of updated monovalent XBB.1.5 Covid-19 vaccines against symptomatic SARS-CoV-2 infection and the first estimates of VE against symptomatic infection with the JN.1 lineage. CDC recommended updated 2023–2024 Covid-19 vaccination with a monovalent XBB.1.5–derived vaccine for all persons aged ≥6 months to prevent Covid-19, especially severe disease. During fall 2023, XBB lineages co-circulated with JN.1, an Omicron BA.2.86 lineage that emerged in September 2023. These variants have amino acid substitutions that increase escape from neutralizing antibodies. XBB lineages predominated through December 2023, when JN.1 became predominant in the US. Reduction or failure of spike gene (*S*-gene) amplification (i.e., *S*-gene target failure [SGTF]) in real-time reverse transcription–polymerase chain reaction testing is a time-dependent, proxy indicator of JN.1 infection. Detection of *S*-gene target presence (SGTP) by a widely used commercial test was noted in most lineages that circulated in 2023, including XBB lineages, whereas *S*-gene target failure (SGTF), resulting from a mutation in the *S*-gene, is detected in JN.1 and other BA.2.86 lineages. Vaccination status, previous infection history, and underlying medical conditions were self-reported and might be subject to recall bias. Previous infections are likely underreported. Studies have demonstrated that previous infection provides some protection against repeat infection and US adults now have a high prevalence of infection-

induced SARS-CoV-2 immunity. Registration questionnaires also did not ask registrants about the number of updated vaccine doses received. CDC will continue monitoring VE, including for expected waning and against severe disease. CDC recommends all persons aged ≥6 months should receive an updated Covid-19 vaccine dose. Uptake of the monovalent XBB.1.5–derived vaccine has only been ~22%.

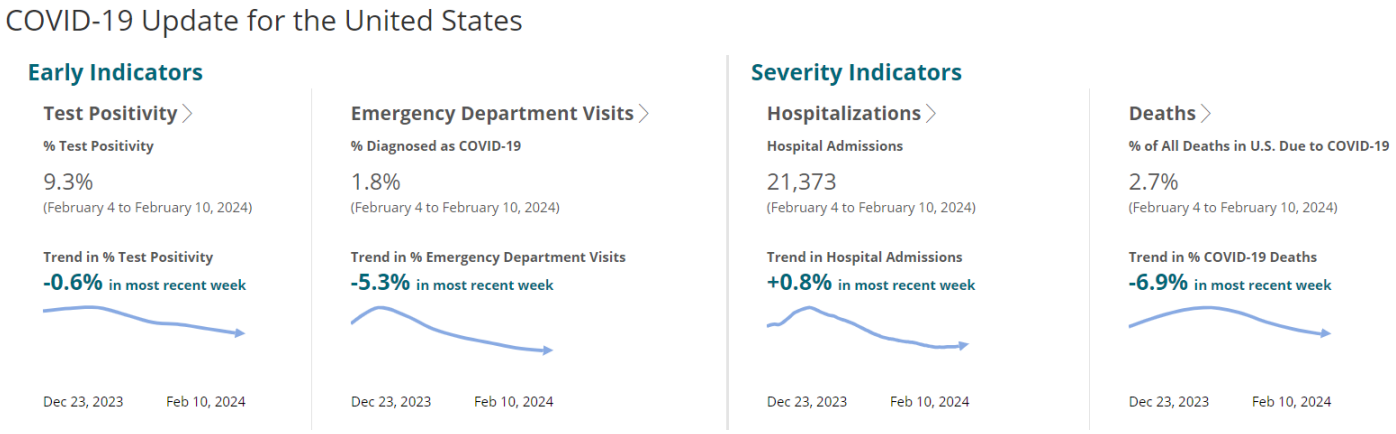
Bottom line: Receipt of updated Covid-19 vaccine provided approximately 54% increased protection against symptomatic SARS-CoV-2 infection compared with no receipt of updated vaccine. Vaccination provides some protection against JN.1 and other circulating lineages.

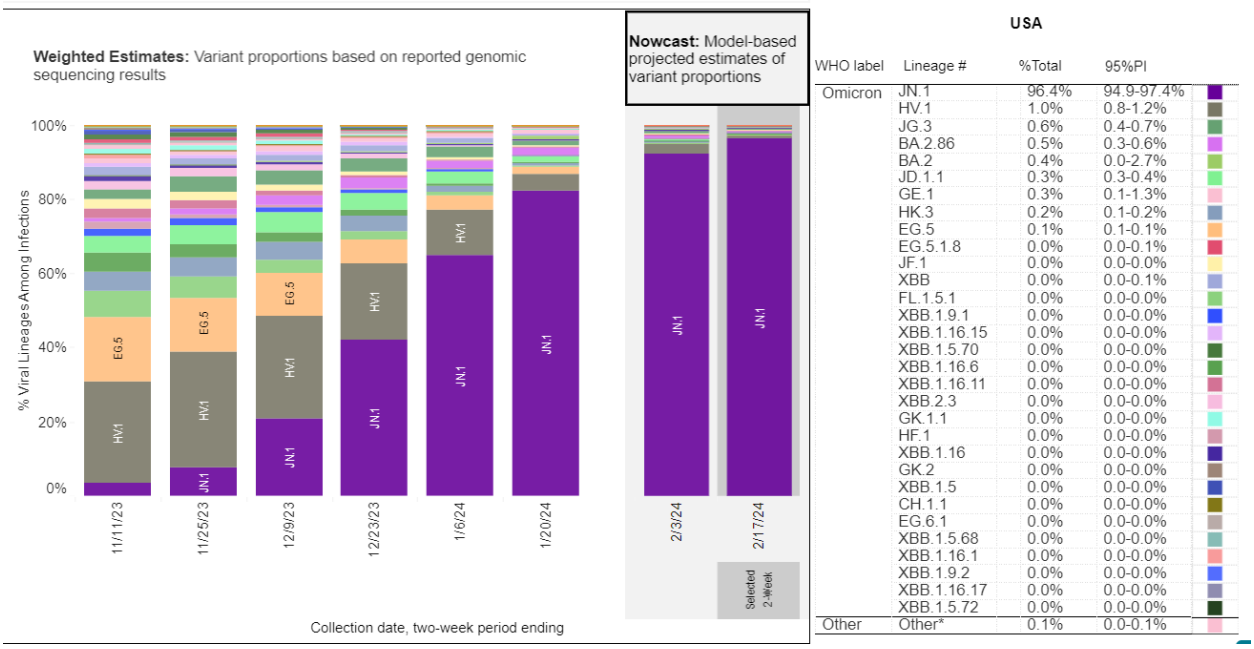
CDC May Recommend COVID-19 Boosters for Some This Spring

An advisory panel to the CDC is expected to vote on whether to recommend a spring booster during a February 28 meeting. The panel is expected to focus on the safety of high-risk Americans, including people 65 and older, people with multiple comorbidities, and anyone with a weakened immune system. A spring booster would be the same shot approved last fall, which targets the XBB.1.5 subvariant. Fortunately, the current booster formulation also works well against the JN.1 subvariant, the leading cause of most Covid-19 infections in the US now. See below.

Bottom line: The logic is based on evidence that either vaccine or previous infection probably gives four to six months of relative protection against serious illness, hospitalizations, and deaths, but wanes after that so waiting until the fall may be a mistake for high-risk individuals.

COVID-19 by the Numbers





USA

WHO label	Lineage #	%Total	95%PI
Omicron	JN.1	96.4%	94.9-97.4%
	HV.1	1.0%	0.8-1.2%
	JG.3	0.6%	0.4-0.7%
	BA.2.86	0.5%	0.3-0.6%
	BA.2	0.4%	0.0-2.7%
	JD.1.1	0.3%	0.3-0.4%
	GE.1	0.3%	0.1-1.3%
	HK.3	0.2%	0.1-0.2%
	EG.5	0.1%	0.1-0.1%
	EG.5.1.8	0.0%	0.0-0.1%
	JF.1	0.0%	0.0-0.0%
	XBB	0.0%	0.0-0.1%
	FL.1.5.1	0.0%	0.0-0.0%
	XBB.1.9.1	0.0%	0.0-0.0%
	XBB.1.16.15	0.0%	0.0-0.0%
	XBB.1.5.70	0.0%	0.0-0.0%
	XBB.1.16.6	0.0%	0.0-0.0%
	XBB.1.16.11	0.0%	0.0-0.0%
	XBB.2.3	0.0%	0.0-0.0%
	GK.1.1	0.0%	0.0-0.0%
	HF.1	0.0%	0.0-0.0%
	XBB.1.16	0.0%	0.0-0.0%
	GK.2	0.0%	0.0-0.0%
	XBB.1.5	0.0%	0.0-0.0%
	CH.1.1	0.0%	0.0-0.0%
	EG.6.1	0.0%	0.0-0.0%
	XBB.1.5.68	0.0%	0.0-0.0%
	XBB.1.16.1	0.0%	0.0-0.0%
	XBB.1.9.2	0.0%	0.0-0.0%
	XBB.1.16.17	0.0%	0.0-0.0%
	XBB.1.5.72	0.0%	0.0-0.0%
Other	Other*	0.1%	0.0-0.1%

Comment: All indicators show a downward trend for both early and severity indicators. JN.1 now accounts for >95% of circulating variants. Looking at the last 3 years we have seen a marked decrease in admissions and deaths. Covid-19 can still be life threatening to the elderly, people with multiple comorbidities, and the immunocompromised.

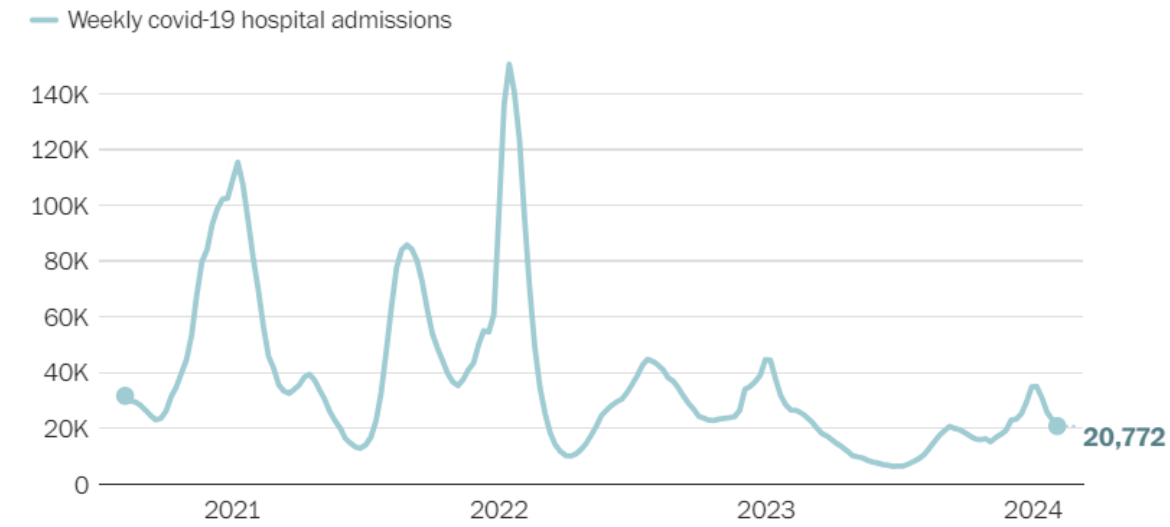
Bottom line: The worst of the pandemic is now behind us. We still have an obligation to protect the most vulnerable. Stay home if ill, get vaccinated, and if in high-risk group consider early antivirals [i.e. Paxlovid] administration. See next review.

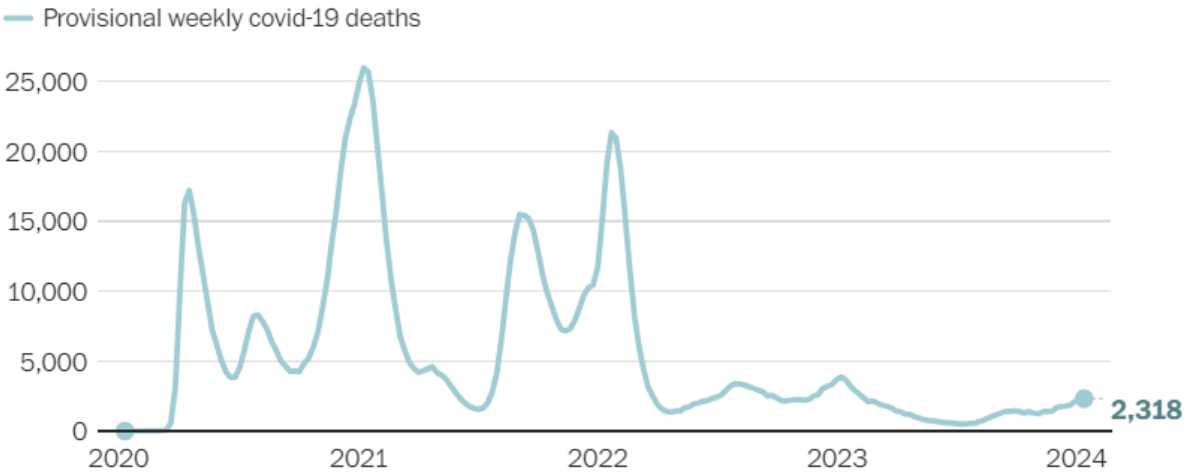
CDC plans to drop five-day Covid-19 Isolation Guidelines February 13, 2024

Americans who test positive for SARS-CoV-2 may no longer need to routinely stay home from work and school for five days under new guidance under discussion at CDC. The agency is relaxing its Covid-19 isolation recommendations for the first time since 2021 to align with guidance on influenza and RSV. The CDC plans to recommend that people who test positive for the SARS-CoV-2 use clinical symptoms to determine when to end isolation. Under the new approach, people would no longer need to stay home if they have been fever-free for at least 24 hours without the aid of medication and their symptoms are mild and improving. The new isolation recommendations would not apply to hospitals and other health-care settings with more vulnerable populations. The proposed federal recommendations follow similar moves by Oregon and California. California still recommends people wear masks indoors when they are around others for 10 days after testing positive — even if they have no symptoms — or becoming sick. Individuals, however, may remove their mask sooner than 10 days if you have two sequential negative tests at least one day apart. It's not clear whether the updated CDC guidance will continue to recommend masking for 10 days. Many other countries, including the UK, Denmark, Finland, Norway and Australia, made changes to isolation recommendations in 2022.

Currently, most people have developed a some level of immunity to the virus because of prior infection and/or vaccination which may merit a shift to a more practical approach. In addition, if

a vulnerable person contracts Covid-19 we now have effective treatments such as Paxlovid. The reality, however, is the latest versions of Covid-19 vaccine was only 54 percent effective at preventing symptomatic infection in adults. (see above) However, there remains strong protection against severe disease and death. (see graphs below)





Sadly CDC data shows only 22 percent of adults and 12 percent of children had received the updated vaccine as of February 9th, despite data showing the vaccines provide robust protection against serious illness including against JN.1.

Comment: Not everyone is happy with this proposal. Some public health officials feel we should treat Covid-19 differently from other respiratory viruses because it's deadlier than the flu and increases the risk of developing long-term complications. At least 7 percent of Americans report having suffered from a number of lingering Covid-19 symptoms, including fatigue, difficulty breathing, brain fog, joint pain and ongoing loss of taste and smell, according to the CDC. The proposed change is likely to prompt strong negative reaction from vulnerable groups, including people older than 65, people with multiple comorbidities, and those who are immunocompromised. Micheal Osterholm has said "Public health has to be realistic in making recommendations to the public today, we have to try to get the most out of what people are

willing to do. … You can be absolutely right in the science and yet accomplish nothing because no one will listen to you." Instead, I believe we should now focus on recommending measures for vulnerable Americans who are at highest risk of severe illness and death from Covid-19. This should include improving vaccination rates and making Paxlovid more available. Given the level of community immunity we should now focus on reducing severe morbidity and mortality. Stay home when you are ill until your fever has resolved, and your symptoms have improved. If you are going to be around vulnerable populations follow California's recommendations that people should wear masks indoors when they are around others for 10 days after testing positive — even if they have no symptoms. Individuals, however, may remove their mask sooner than 10 days if you have two sequential negative tests at least one day apart. Lastly if you are in a high-risk group and influenza, RSV, and Covid-19 are circulating consider wearing a mask when indoors around other people.

Bottom line: Use common sense. Stay home if ill until fever is gone, and symptoms have improved. Wear a mask up to day 10 if you are indoors and/or around vulnerable populations. If you are in a high-risk group consider wearing a mask indoors (outside your home) when there is increased respiratory viral activity [Covid-19, influenza, RSV] in your community.