Infectious Diseases Watch

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Ed Septimus, MD

General Infectious Diseases

Rifampin Based Therapy for Patients with Staphylococcus aureus Native Vertebral Osteomyelitis: A Systematic Review and Meta-Analysis

Clin Infect Dis published online September 18, 2023

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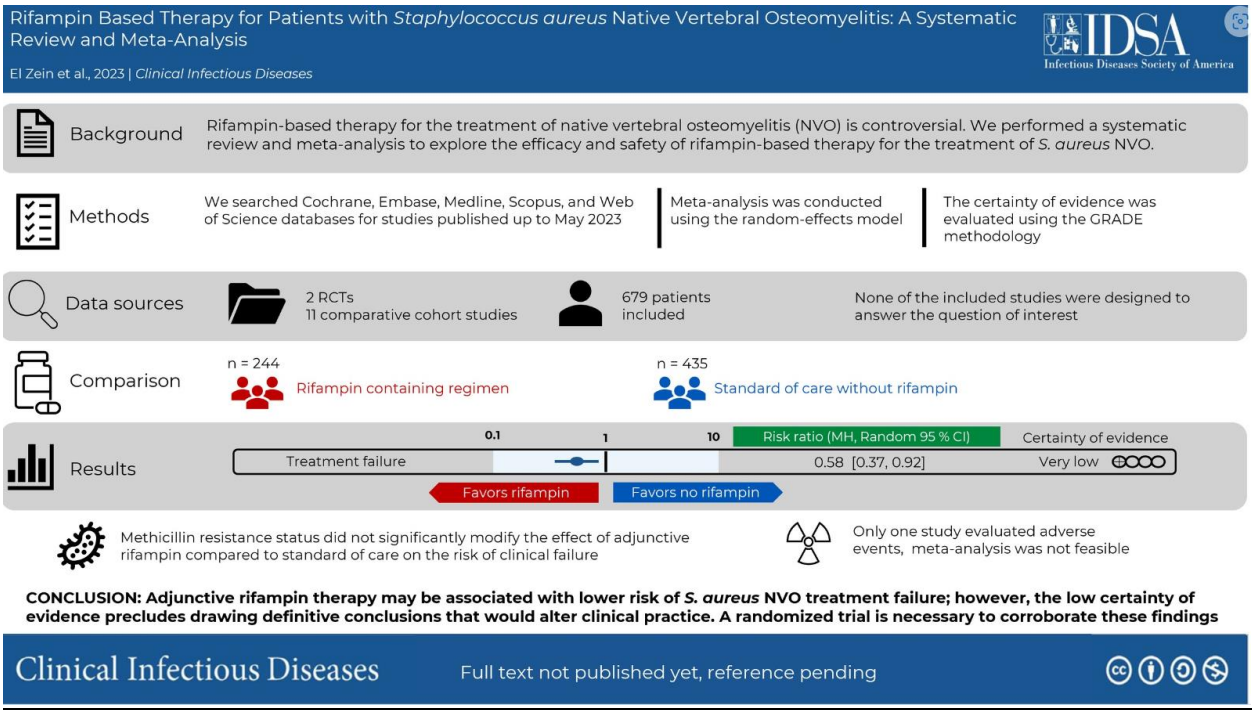
There is some evidence suggests that S. aureus biofilm formation of necrotic bone and intracellular bacterial persistence play an important role in the pathogenesis of chronic osteomyelitis and development of antibiotic tolerance. (Frontiers in immunology. 2021; 12:638085) Rifampin exhibits activity against S. aureus in biofilms while retaining bactericidal properties against intracellular organisms. In Europe, the combination of oral fluoroquinolones and rifampin is frequently used for the treatment of staphylococcal bone infection (OFID. 2022;9(8): ofac366). The rationale for this dual treatment includes data on high bone penetration and resistance development prevention in comparison to fluoroquinolone or rifampin monotherapy. Dual therapy with rifampin is well-established in the treatment of select patients with orthopedic device related infections including spine implant (Infection. 2020;48(4): e59-68) and prosthetic joint infections (PJI) (Clin Infect Dis. 2013;56(1):e1-e25) Cohort studies and RCTs have not been designed to answer the question on the use of adjunctive rifampin for the treatment of S. aureus native vertebral osteomyelitis (NVO). Therefore, the authors performed a systematic review to evaluate the efficacy and safety of adjunctive rifampin for the treatment of NVO caused by S. aureus.

They included studies that reported on adults with NVO treated with rifampin vs other treatments. The primary outcome was treatment failure. The secondary outcome was adverse events associated with antibiotic therapy. The literature was searched by a medical librarian (DJG) for the concepts of vertebral osteomyelitis, S. aureus, rifampin, rifapentine, rifabutin, rifamycins or other antibiotic treatments. Search strategies were created using a combination of keywords and standardized index terms. Searches were run on January 13, 2023, and updated on May 23, 2023, in Ovid Cochrane Central Register of Controlled Trials (1991+), Ovid Embase (1974+), Ovid Medline (1946+ including E-pub ahead of print, in-process, and other non-indexed citations), Scopus (1788+), and Web of Science Core Collection (Science Citation Index Expanded 1975+ and Emerging Sources Citation Index 2015+). After removing case reports, animal and pediatric studies based on the exclusion criteria, a total of 3,964 citations were retrieved. The risk of bias for comparative cohort studies was assessed using the Newcastle-Ottawa Scale. Each item on the Newcastle- Ottawa scale was judged as having "low

risk", "high risk" or "unclear risk" of bias. The certainty of evidence was evaluated using the GRADE methodology and synthesized using GRADEpro.

In total, 13 studies were included in this systematic review, comprising two RCTs and 11 comparative cohort studies. Authors of seven studies supplied additional patient-level data specifically related to vertebral osteomyelitis without spine instrumentation caused by S. aureus. Overall, 244 patients with S. aureus NVO (35.9%) received a rifampin-containing regimen and 435 (64.1%) did not. In the 13 included studies, clinical failure occurred in 38 patients (15.6%) in the rifampin group and 95 patients (21.8%) in the standard-of-care group without rifampin. Meta-analysis including all 679 patients with S. aureus NVO showed a 14% absolute risk reduction in clinical failure in patients treated with a rifampin-based regimen compared to standard-of-care without rifampin (RD -14%; 95% CI: -19%, -8%; *P* <0.001; *I2* = 0%,). RR of clinical failure in patients who received adjunctive rifampin was 0.58 (95% CI: 0.37, 0.92, *P* = 0.02, *I2* = 21%). Among the 331 evaluable patients with MSSA and 52 with MRSA NVO, rifampin was administered to 139 (42.0%) and 20 patients (38.5%), respectively. Studies predominantly using rifampin-fluoroquinolone combinations demonstrated a lower risk of treatment failure compared to those employing other combinations. Others included glycopeptides, β-lactams, tetracyclines, clindamycin and less commonly daptomycin, trimethoprim-sulfamethoxazole (TMP-SMX), and aminoglycosides. Only one study evaluated adverse events, therefore, a meta-analysis was not feasible.



Comment: In this systematic review and meta-analysis, the authors identified an association between the use of adjunctive rifampin and a decreased risk of clinical failure in patients with S. aureus NVO, but low certainty. Subgroup analysis did not allow for conclusions to be drawn about the effect of rifampin containing regimens on clinical failure in patients with MRSA or those at high-risk for recurrence. (Older and sicker patients may be inherently at an increased

risk for treatment failure while being less likely to receive rifampin therapy due to intolerance or drug-drug interactions. Other potential confounders included source control, the dosage, timing, and overall duration of antibiotics and/or adjunctive rifampin therapy, as well as the potential effects of companion drugs. Additionally, S. aureus isolates resistant to rifampin may also be multidrug-resistant and associated with worse outcomes) However, even though adjunctive rifampin therapy might be associated with lower risk of S. aureus NVO treatment failure the low certainty of evidence precludes drawing definitive conclusions that would alter clinical practice at this time. A randomized trial will be necessary to validate these findings.

Guidelines for the Use of Doxycycline Post-Exposure Prophylaxis for Bacterial Sexually Transmitted Infection (STI) Prevention Request for Comment October 2, 2023

Dubbed Doxy-PEP, short for doxycycline postexposure, the approach calls for taking doxycycline after a potential STI exposure rather than waiting until after a disease is diagnosed. If the draft recommendation is adopted, Doxy-PEP would be recommended for gay and bisexual men; other men who have sex with men; and transgender women who have been diagnosed with at least one STI caused by bacteria in the past year. Those infections include gonorrhea, chlamydia, or syphilis.

The CDC is expected to advise doctors that prescribing a 200mg dose of doxycycline “should be considered” for these patients within 72 hours after oral, vaginal, or anal sex. The agency needs more data before recommending it for other groups.

Comment: Studies have shown the so-called ‘doxy PEP’ regimen – a single, 200mg dose taken no later than 72 hours after unprotected sex – can reduce acquisition of chlamydia and syphilis by nearly 80%, and gonorrhea by about 50%. We are seeing a surge in new cases of syphilis and other STDs. Prevention including using condoms remains our best intervention in reversing this trend.

Wastewater-based surveillance identifies start to the pediatric respiratory syncytial virus season in two cities in Ontario, Canada Front Public Health published online September 26, 2023

DOI 10.3389/fpubh.2023.1261165

The investigators compared citywide wastewater samples and pediatric RSV in Ottawa and Hamilton between August 1, 2022, and March 5, 2023. 24 hour composite wastewater samples were collected daily and 5 days a week at the wastewater treatment facilities in Ottawa and Hamilton, Ontario, Canada, respectively. RSV WBS samples were analyzed in real-time for RSV by PCR.

RSV wastewater-based surveillance (WBS) measurements in both Ottawa and Hamilton showed a lead time of 12 days when comparing the WBS data set to pediatric RSV data set (Spearman’s $\rho = 0.90$). WBS identify early RSV community transmission and declared the start of the RSV season 36 and 12 days in advance of the provincial RSV season start (October 31)

for the city of Ottawa and Hamilton, respectively. The differing RSV start dates in the two cities is likely associated with geographical and regional variation in the incidence of RSV between the cities. Wastewater surveillance can provide a lead time of 1-2 weeks for most monitored respiratory viruses. Alexandria Boehm from Stanford shared “Wastewater Insights into Viral Disease” at ID Week this past October supporting the use of wastewater surveillance for respiratory viruses.

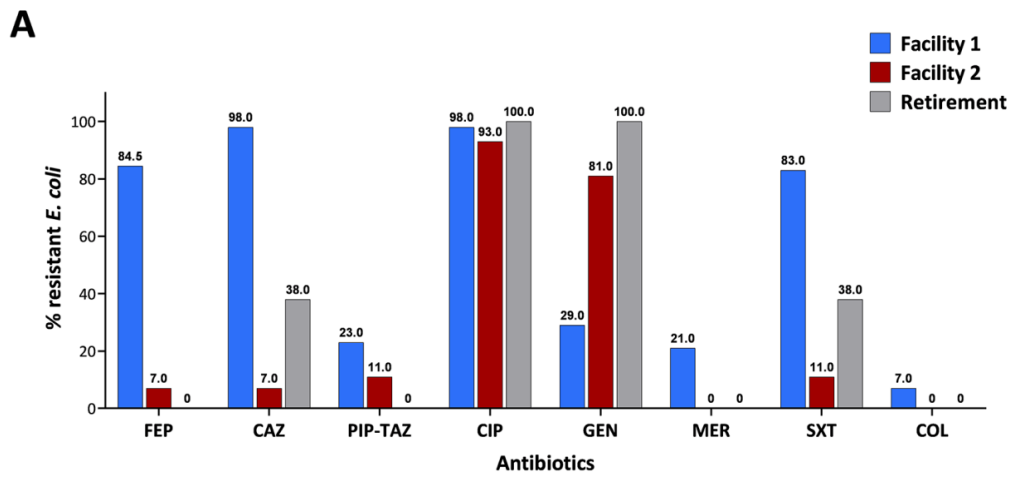
The scope of antimicrobial resistance in residential aged care facilities determined through analysis of *Escherichia coli* and the total wastewater resistome. Microbiol Spectrum published online October 3, 2023

doi.org/10.1128/spectrum.00731-23

In the study, investigators collected wastewater samples from two residential aged care facilities (RACFs) and one retirement village in Adelaide Australia. One of the RACFs had implemented an antimicrobial stewardship program 3 years prior to the study (RACF-2). The samples were collected at five different time points over 18 months (October 2019 to February 2021), and E coli were isolated and assessed for phenotypic and genotypic resistance. Whole-genome sequencing was conducted to identify resistance genes.

Of the 93 antibiotic-resistant E coli isolates analyzed (58 from RACF 1, 27 from RACF 2, and 8 from the retirement village), 66.7% and 97.6% were resistant to ceftazidime and ciprofloxacin, respectively. In addition, high levels of resistance to trimethoprim-sulfamethoxazole (54.8%) and gentamicin (50.5%) were observed. A much higher incidence of resistance to cefepime (84.5%) and ceftazidime (98.3%) was found in RACF 1, while RACF 2 had higher levels of gentamicin resistance (66.7%).

Although all isolates analyzed in the study were resistant to at least one antibiotic, RACF-1—which did not have an antimicrobial stewardship program—also harbored a greater number of multidrug-resistant (MDR) *E coli* isolates, with 93.1% of isolates recovered from the facility shown to be resistant to at least three antibiotics, compared with 18.5% in RACF 2. Further analysis revealed the presence of the international high-risk E coli clone, ST131, and a higher prevalence of mobile resistance genes in RACF-1, as well. Analysis of the entire resistome also revealed a greater number of mobile resistance genes. Metagenomic analysis of the prevalence of these and other mobile resistance genes within the sampled wastewater revealed that RACF-1(Facility 1 below) harbored a greater number of mobile resistance determinants.



Comment: RACFs have been identified as sites harboring elevated levels of AMR bacteria and presenting an environment which is highly selective to their development and emergence. In this study, the prevalence of AMR E. coli (most ESBLs) was used as an indicator of the incidence and persistence of bacterial resistance in two RACFs, one of which has implemented an AMS program (Facility 2), while the other has not (Facility 1). Assessment of the prevalence of E. coli in these two RACFs and in one retirement village was carried out with an in-depth analysis of 93 AMR E. coli isolates recovered from wastewater samples. Results revealed a high proportion of MDR E. coli isolates (66.7%) which were more frequently recovered from Facility 1. While Facility 2 isolates displayed high-level gentamicin resistance trend not observed in Facility 1 E. coli isolates. These results highlight several concerns, including the high prevalence of ESBL-producing E. coli in Facility 1 and the number of ciprofloxacin-resistant E. coli isolates prevalent in both facilities.

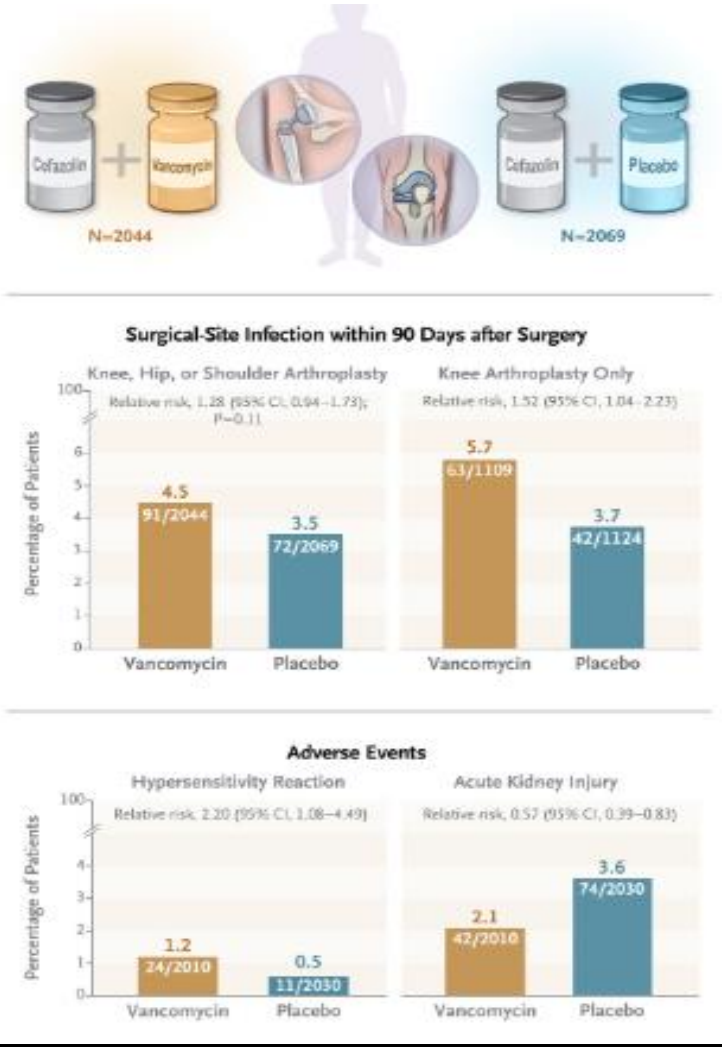
Implementation of AMS programs in RACFs can be challenging and is dependent on numerous factors including access to resources, staff education and a high prevalence of bacterial colonization and challenges in diagnosing and treating infections. Nonetheless, the benefits of such programs can help mitigate the spread and continual development of AMR. While the study was limited to three sites and 300 residents, the findings suggest a wider problem, as inappropriate antibiotic use is known to be common in nursing homes. Given our ageing population, there is a crucial need to regularly monitor these facilities and mitigate the threat of AMR. I would add monitoring around hospitals as well. The CDC's NWSS (National Wastewater Surveillance System) core antimicrobial resistance genes target now include carbapenemases, ESBLs, colistin resistance, and colistin.

Trial of Vancomycin and Cefazolin as Surgical Prophylaxis in Arthroplasty N Engl J Med 2023; 389:1488-98.

DOI: 10.1056/NEJMoa2301401

This was a multicenter, double-blind, superiority, placebo-controlled trial, randomly assigned adult patients without MRSA colonization who were undergoing arthroplasty to receive 1.5 g of vancomycin or normal saline placebo, in addition to cefazolin prophylaxis [2 g of cefazolin, administered intravenously within 60 minutes before skin incision]. There was no postop dosing of vancomycin. The primary outcome was surgical-site infection within 90 days after surgery. In addition to the presurgical screening and decolonization processes, they assessed perioperative carriage of staphylococcus species in a separate sub study. Anterior nares and groin swabs were collected preoperatively before the administration of prophylaxis.

A total of 4239 patients underwent randomization. Among 4113 patients in the modified intention-to-treat population (2233 undergoing knee arthroplasty, 1850 undergoing hip arthroplasty, and 30 undergoing shoulder arthroplasty), surgical site infections occurred in 91 of 2044 patients (4.5%) in the vancomycin group and in 72 of 2069 patients (3.5%) in the placebo group (relative risk, 1.28; 95% confidence interval [CI], 0.94 to 1.73; P = 0.11). Among patients undergoing knee arthroplasty, surgical-site infections occurred in 63 of 1109 patients (5.7%) in the vancomycin group and in 42 of 1124 patients (3.7%) in the placebo group (relative risk, 1.52; 95% CI, 1.04 to 2.23). Among patients undergoing hip arthroplasty, surgical-site infections occurred in 28 of 920 patients (3.0%) in the vancomycin group and in 29 of 930 patients (3.1%) in the placebo group (relative risk, 0.98; 95% CI, 0.59 to 1.63). Adverse events occurred in 35 of 2010 patients (1.7%) in the vancomycin group and in 35 of 2030 patients (1.7%) in the placebo group, including hypersensitivity reactions in 24 of 2010 patients (1.2%) and 11 of 2030 patients (0.5%), respectively (relative risk, 2.20; 95% CI, 1.08 to 4.49), and acute kidney injury(AKI) in 42 of 2010 patients (2.1%) and 74 of 2030 patients (3.6%), respectively (relative risk, 0.57; 95% CI, 0.39 to 0.83).



Comment: This was a pragmatic trial involving patients undergoing arthroplasty. The investigators found the addition of vancomycin was not superior to surgical antimicrobial prophylaxis with cefazolin alone. The results of subgroup analyses suggested a possible increased risk of surgical-site infection in knee arthroplasty with the addition of vancomycin on secondary analysis. Vancomycin prophylaxis was associated with an increased risk of hypersensitivity reactions and a decreased risk of AKI. This may seem difficult to explain except in those studies showing an increased incidence of AKI, vancomycin was frequently continued for up to 24 hours postoperatively. [Clin Orthop Relat Res 2015; 473:2197-203] In this trial vancomycin was not given postoperatively. I cannot explain the increased incidence of AKI observed in the placebo group. The SSIs rates are higher than expected partly based since they included superficial SSIs.

In this trial MSSA was the most common pathogen in this trial. The overall prevalence of MRSA carriage preoperatively in our cohort was low partly due to the exclusion of patients with known infection or colonization with MRSA, although such patients represented only a small percentage of the population (85 of 7075 screened patients [1.2%]. Cohort studies have suggested that infections caused by MRSA may be due in part to hospital acquisition rather than preoperative or community colonization. [JAMA 2008;299: 1149-57] Most surgical-site infections

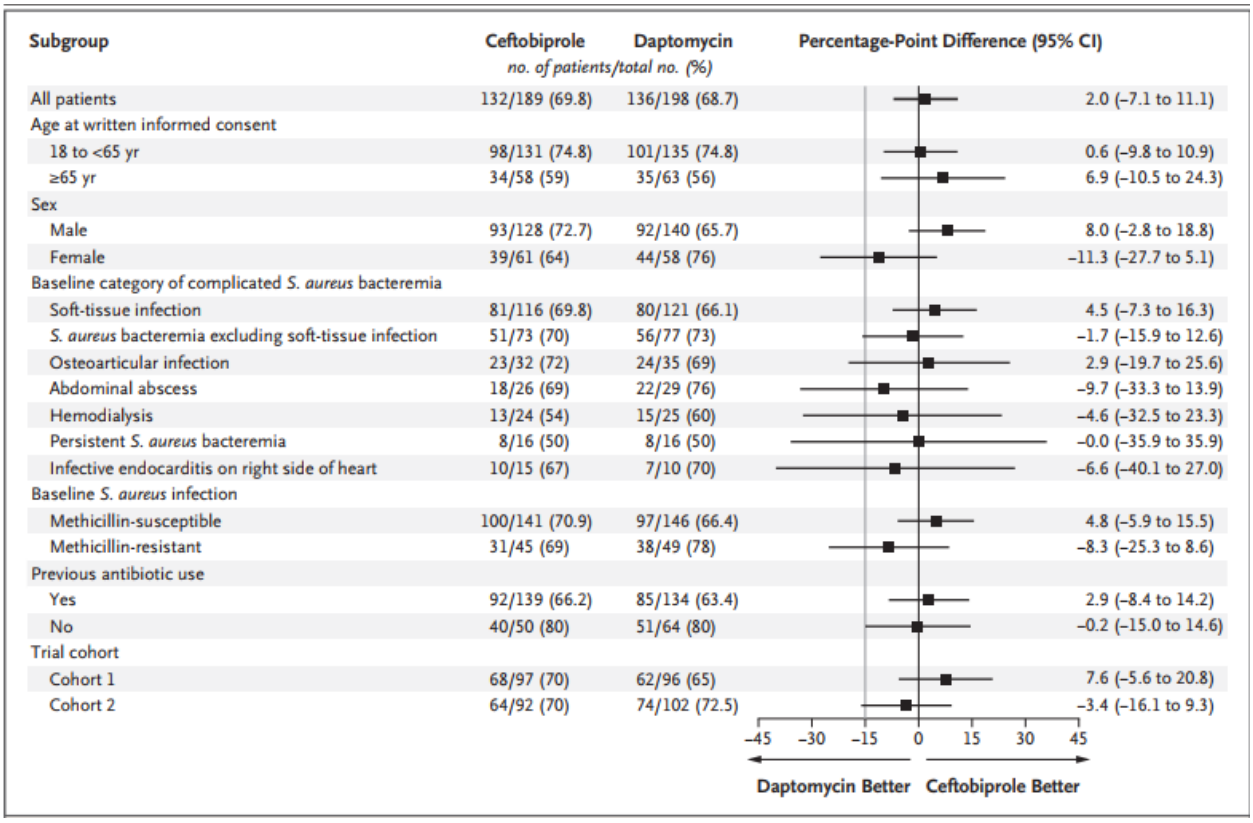
observed in this trial were superficial. Current Australian guidelines recommend the addition of vancomycin in arthroplasty patients with known MRSA infection or colonization. Since patients with history of MRSA infection or colonization were excluded from this study the authors caution these findings do not apply to this patient population.

Ceftobiprole for Treatment of Complicated Staphylococcus aureus Bacteremia N Eng J Med published online September 27, 2023

DOI: 10.1056/NEJMoa2300220

Ceftobiprole — a cephalosporin with activity against MRSA — is available in several European countries and Canada. In a phase 3 noninferiority trial to evaluate ceftobiprole in the management of complicated S. aureus bacteremia, Holland et al. randomized 399 patients (median age, 58; median BMI, 28; 96% white) 1:1 to receive intravenous ceftobiprole (500 mg every 6 hours, then every 8 hours after 8 days) or daptomycin (6–10 mg/kg every 24 hours). Complicated S. aureus bacteremia was defined as persistent S. aureus bacteremia (positive blood cultures despite receipt of appropriate antibiotics for ≥3 days before randomization); S. aureus bacteremia associated with long-term hemodialysis; or S. aureus bacteremia arising from soft-tissue infection, abdominal abscess, osteoarticular infection, septic thrombophlebitis, septic pulmonary embolus, epidural or cerebral abscess, or native-valve infective endocarditis on the right side of the heart. Exclusion criteria included unremovable endovascular prosthetic material, pneumonia, and receipt of potentially effective antibiotics for more than 48 hours within 7 days before randomization in the absence of persistent S. aureus bacteremia. Two sets of peripheral-blood cultures were obtained at baseline, daily for the first 3 days after randomization, and every 48 to 72 hours thereafter until they were negative for S. aureus at two time points that were at least 24 hours apart. At least one post-treatment blood culture was obtained in the period between 7 days after the end-of-treatment visit and the post-treatment evaluation visit 70 days after randomization. Although >97% of participants were enrolled outside the US, the trial was funded and reviewed by the FDA under a special protocol assessment.

The most common risk factors for S. aureus bacteremia were recent surgery (40%) and diabetes mellitus (35%). Soft-tissue infection was the primary source in 61% of participants and median duration of therapy was 21 days. Treatment success was 70% with ceftobiprole and 69% with daptomycin, demonstrating noninferiority of ceftobiprole. In both groups, reasons for treatment failure were similar (including death [9%]) and median time to bacteremia clearance was 4 days. Adverse events also were similar between groups, although gastrointestinal disturbance (mostly nausea) was more common with ceftobiprole.



Subgroup	Ceftobiprole	Daptomycin	Percentage-Point Difference (95% CI)
	no. of patients/total no. (%)		
All patients	132/189 (69.8)	136/198 (68.7)	2.0 (–7.1 to 11.1)
Age at written informed consent			
18 to <65 yr	98/131 (74.8)	101/135 (74.8)	0.6 (–9.8 to 10.9)
≥65 yr	34/58 (59)	35/63 (56)	6.9 (–10.5 to 24.3)
Sex			
Male	93/128 (72.7)	92/140 (65.7)	8.0 (–2.8 to 18.8)
Female	39/61 (64)	44/58 (76)	–11.3 (–27.7 to 5.1)
Baseline category of complicated *S. aureus* bacteremia			
Soft-tissue infection	81/116 (69.8)	80/121 (66.1)	4.5 (–7.3 to 16.3)
S. aureus bacteremia excluding soft-tissue infection	51/73 (70)	56/77 (73)	–1.7 (–15.9 to 12.6)
Osteoarticular infection	23/32 (72)	24/35 (69)	2.9 (–19.7 to 25.6)
Abdominal abscess	18/26 (69)	22/29 (76)	–9.7 (–33.3 to 13.9)
Hemodialysis	13/24 (54)	15/25 (60)	–4.6 (–32.5 to 23.3)
Persistent *S. aureus* bacteremia	8/16 (50)	8/16 (50)	–0.0 (–35.9 to 35.9)
Infective endocarditis on right side of heart	10/15 (67)	7/10 (70)	–6.6 (–40.1 to 27.0)
Baseline *S. aureus* infection			
Methicillin-susceptible	100/141 (70.9)	97/146 (66.4)	4.8 (–5.9 to 15.5)
Methicillin-resistant	31/45 (69)	38/49 (78)	–8.3 (–25.3 to 8.6)
Previous antibiotic use			
Yes	92/139 (66.2)	85/134 (63.4)	2.9 (–8.4 to 14.2)
No	40/50 (80)	51/64 (80)	–0.2 (–15.0 to 14.6)
Trial cohort			
Cohort 1	68/97 (70)	62/96 (65)	7.6 (–5.6 to 20.8)
Cohort 2	64/92 (70)	74/102 (72.5)	–3.4 (–16.1 to 9.3)

Comment: Although ceftobiprole was noninferior to daptomycin against S aureus bacteremia almost two thirds of study participants had soft tissue infection as the source of their bacteremia. Only 8% had persistent bacteremia and only 6% had endocarditis. I would argue this was a study of not so complicated S aureus bacteremia. Additional studies are needed to see how ceftobiprole performs in complicated endovascular infections. Approximately one quarter of the patients had MRSA infection, so definitive conclusions about efficacy in this subgroup could not be assessed. It would be interesting to compare ceftaroline with ceftobiprole since ceftaroline has performed well against MRSA bacteremia. Pharmacy tells me it is easier to dose ceftaroline versus ceftobiprole (5-minute vs 120-minute infusion time). Lastly, ceftobiprole also has activity against pseudomonas which may have greater impact on the host microbiota and increased risk for antimicrobial resistance. I am not sure why this was published in the N Engl J Med.

Editor's Choice

Cefepime vs Piperacillin-Tazobactam in Adults Hospitalized With Acute Infection

JAMA published online October 14, 2023

doi:10.1001/jama.2023.20583

The Antibiotic Choice on Renal Outcomes (ACORN) was a randomized clinical trial compared cefepime vs piperacillin-tazobactam in adults for whom a clinician ordered an antipseudomonal antibiotic within 12 hours of presentation to the hospital in the emergency department or medical ICU. Patients were randomized in a1:1ratio to cefepime or piperacillin-tazobactam. The

primary outcome was the highest stage of acute kidney injury or death by day 14, measured on a 5-level ordinal scale ranging from no acute kidney injury to death. The two secondary outcomes were the incidence of major adverse kidney events on day 14 and the number of days alive and free of delirium and coma within 14 days. 80% of the population received at least 1 dose of vancomycin.

Among the 2,511 patients (median age, 58 years; 42.7% female) included in the primary analysis, the highest stage of AKI or death was not significantly different between the cefepime group and the piperacillin-tazobactam group. There were 85 patients (7%) with stage 3 AKI and 92 (7.6%) who died in the cefepime group, compared with 97 patients (7.5%) with stage 3 AKI and 78 (6%) who died in the piperacillin-tazobactam group (odds ratio [OR], 0.95; 95% confidence interval [CI], 0.80 to 1.13).

The incidence of major adverse kidney events at day 14 did not differ between the cefepime group (10.2%) and the piperacillin-tazobactam group (8.8%; absolute difference, 1.4%; 95% CI, −1.0% to 3.8%). However, patients in the cefepime group experienced fewer days alive and free of delirium and coma within 14 days than those in the piperacillin-tazobactam group (mean, 11.9 days vs 12.2 days; OR, 0.79; 95% CI, 0.65 to 0.95).

Comment: Two commonly prescribed antibiotics for empirical treatment of sepsis are the β-lactams piperacillin-tazobactam and cefepime. Both provide broad in vitro activity against gram-positive and gram-negative organisms, including P aeruginosa. They are often used in combination with vancomycin to include activity against MRSA. The reported increased risk of AKI from the combination of piperacillin-tazobactam plus vancomycin compared with other β-lactam agents has resulted in a shift away from the empirical use of piperacillin-tazobactam among many prescribers. Meta-analyses of observational studies found vancomycin plus piperacillin-tazobactam is associated with greater incidence of AKI with odds ratios (ORs) of up to 3.6 [Pharmacotherapy. 2016;36(12):1217-1228] The FDA has warned that coadministration of piperacillin-tazobactam with vancomycin may increase the incidence of AKI. However, whether this association reflects actual kidney damage has been questioned, and there are key weaknesses in the retrospective observational studies including the reliance on serum creatinine level as the measure of AKI, unmeasured confounding, and some inconsistencies across studies.[Clin Infect Dis. 2020;71:426-432] A recent prospective clinical study suggest that increases in serum creatinine level may reflect inhibition of tubular secretion of creatinine without underlying kidney injury. Levels of kidney injury biomarkers such as kidney injury molecule 1 and cystatin C are not increased when administration of vancomycin plus piperacillin-tazobactam is compared with either drug alone or the combination of vancomycin plus cefepime. [Intensive Care Med. 2022; 48:1144-1155] see next review

Cefepime on the other hand has been associated with neurotoxicity including altered mental status, myoclonus, and nonconvulsive seizure epilepticus. [J Antimicrob Chemother. 2022;77(11):2908-2921] The risk for cefepime neurotoxicity appears to be increased with kidney dysfunction and higher cefepime exposures, usually described as elevated trough serum concentrations. Because kidney dysfunction is common in patients with sepsis, some fear the use of cefepime may precipitate delirium in an already compromised population. Patients in the cefepime group had fewer days alive and free of delirium and coma within 14 days with a mean difference of 0.3 days (OR, 0.79 [95% CI, 0.65-0.95]). The significant difference was only observed in patients with confirmed sepsis, whereas there was no difference in delirium in patients without confirmed sepsis.

There were a few limitations to this trial. Participants received a short duration of antibiotic treatment (median, 3 days [IQR, 1-4 days]) and nearly 50% did not actually have sepsis. Since this was an unblind open-label study, there is potential for bias in the ascertainment of the outcomes. Are participants known to be receiving piperacillin-tazobactam or cefepime more likely to have investigations for AKI and neurotoxicity, respectively? The dosing regimens for both piperacillin-tazobactam and cefepime may not reflect updated clinical use. Piperacillin-tazobactam was intravenously administered with a dose of 3.375 g every 8 hours in the trial as a 4-hour infusion. However, dosing should be at a higher dose of 3.375 to 4.5 g every 6 hours over 30- to 240-minute infusions based on the 2023 CLSI clinical breakpoints. Cefepime was administered via rapid IV push, which is associated with enhanced toxic effects compared with intermittent or extended infusions. [Antibiotics (Basel). 2023;12(6):996] Thus, the dosing regimens may have reduced the risk of AKI with piperacillin-tazobactam due to the lower dose used and exaggerated the risk of neurotoxicity with cefepime due to the rapid IV push.

Nonetheless, this trial provides the best evidence to date to show there is no difference in the incidence of AKI between use of piperacillin-tazobactam and vancomycin vs cefepime and vancomycin. I think another important question is whether antibiotics with antipseudomonal activity are even indicated at least for community-onset and low-acuity sepsis where pseudomonas is infrequent.

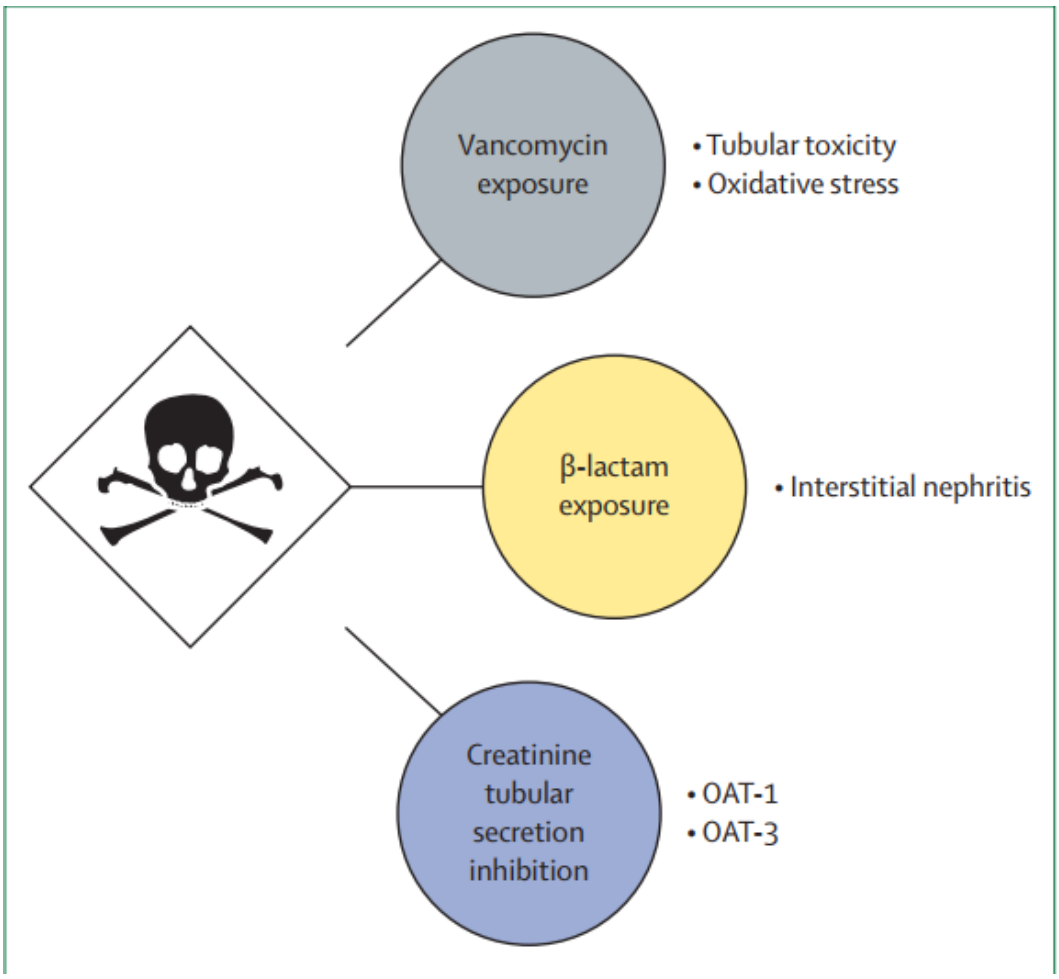
Understanding vancomycin nephrotoxicity augmented by β-lactams: a synthesis of endosymbiosis, proximal renal tubule mitochondrial metabolism, and β-lactam chemistry

Lancet Infect Dis published online October 23, 2023

doi.org/10.1016/ S1473-3099(23)00432-2

Vancomycin associated nephrotoxicity had been well established, nevertheless β-lactams, such as piperacillin–tazobactam, have also been independently associated with acute kidney injury (AKI). Vancomycin AKI increases with the addition of piperacillin–tazobactam based on increases in serum creatinine. Numerous studies have characterized AKI rates in vancomycin in combination with piperacillin–tazobactam or cefepime, reporting an increased risk for AKI in patients given vancomycin with piperacillin–tazobactam compared with vancomycin alone or vancomycin with cefepime. Additionally, several studies have compared meropenem in combination with vancomycin to vancomycin with piperacillin–tazobactam, with most reporting increased AKI with only piperacillin– tazobactam. [Antimicrob Agents Chemother 2019; 63: e02658-18]

The nephrotoxicity of some β-lactams when combined with vancomycin can be explained by the augmentation of the oxidative stress on the proximal tubule already mediated by vancomycin. [Drug Metab Dispos 2013; 41**:** 791–800]



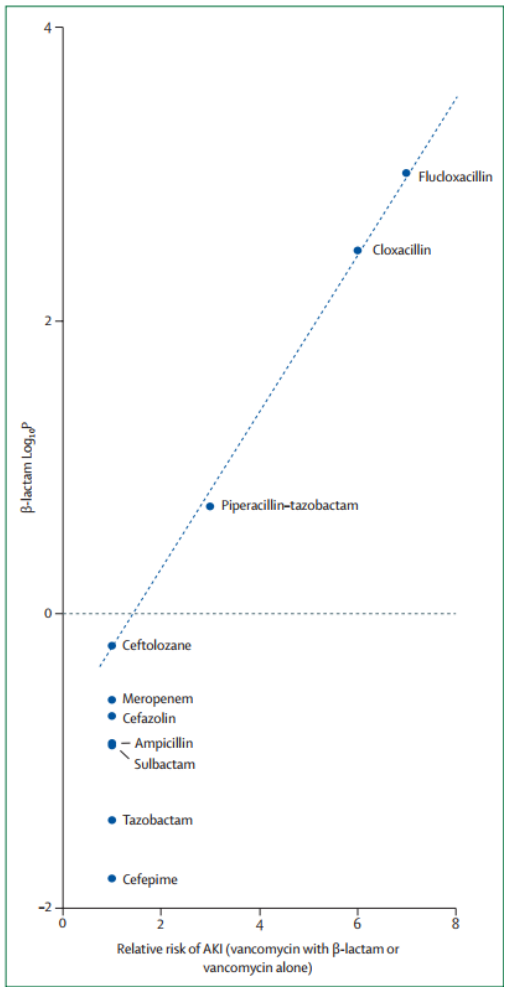
β-lactam proximal tubule cell accumulation depends on its affinity to transporters in the basolateral membrane as the first step in secretion, followed by proximal tubular cell uptake, and then apical membrane efflux into urine for elimination. A key component of the first step of basolateral membrane uptake into proximal tubular cells is the organic anion transporter-3 (OAT-3). Some β-lactams are better OAT-3 substrates than others as seen by OAT-3 affinity, which would be a crucial first step to set up proximal tubular injury.

Vancomycin alone carries an approximate 2·5-fold relative risk of AKI compared with other gram-positive antibiotics, such as linezolid or ceftaroline, and is most often reversible with vancomycin discontinuation but can occasionally be permanent. The pathogenesis of vancomycin-mediated nephrotoxicity appears to be multifactorial, including mitochondrial dysfunction resulting in oxidative stress by reactive oxygen species, induction of renal tubular apoptosis, and the formation of casts. Added nephrotoxicity of some β-lactams when combined with vancomycin is augmentation of the oxidative stress on the proximal tubule already placed by vancomycin via intracellular β-lactam accumulation, which varies among β-lactams.

A key component to the first step of basolateral membrane uptake into proximal tubular cells is OAT-3. Some β-lactams are more efficient substrates of OAT-3 as shown by OAT-3 affinity, the first step that sets up proximal tubular injury. For most β-lactams, there is sufficient efflux out from the proximal tubular cell via the tubular apical lumen into the urine that β-lactams are rarely

nephrotoxic by themselves. Investigators assessed the affinity of various β-lactams as substrates for OAT-3, their uptake by OAT-3 expressing cells, and their inhibition of OAT-3 based on β-lactam hydrophobicity. They found that β-lactam hydrophobicity was strongly related to OAT-3 affinity and uptake. [Drug Metab Dispos 2013; 41: 791–800]

Uncertainty exists as to whether increases in creatinine observed in patients taking vancomycin with β-lactam represent a true reflection of decreased glomerular filtration rate versus inhibition of transporters in the renal tubule that are responsible for creatinine secretion. OAT-3 is one such transporter involved in creatinine secretion. [Am J Physiol Renal Physiol 2012; 302: F1293–99] Therefore, β-lactam with OAT-3 affinity might compete and potentially interfere with creatinine secretion. Recently there has been interest in alternative biomarkers such as cystatin C, as a more reliable measure of renal function than creatinine. A recent study by Miano and colleagues measured creatinine and cystatin C before therapy and at day 2 after initiation of vancomycin with piperacillin–tazobactam, or vancomycin with cefepime in critically ill patients. [Intensive Care Med 2022; 48: 1144–55] They found increases in creatinine in vancomycin with piperacillin–tazobactam and not in vancomycin with cefepime at day 2, but no differences in cystatin C between the two regimens. They concluded that the increases in creatinine seen with vancomycin with piperacillin–tazobactam were the results of pseudo-toxicity. However, most cases of clinical AKI occur after 4–8 days of vancomycin with piperacillin– tazobactam, not at 48 hours.



Comment: This comprehensive review of the literature described the interactions of vancomycin with β-lactam treatment with proximal renal tubular cells which helps explain the enhanced nephrotoxicity observed with some vancomycin and β-lactam combinations. Hydrophobic β-lactams (e.g., piperacillin and anti-staphylococcal β-lactams) with high OAT-3 affinity have been shown to enhance vancomycin nephrotoxicity as measured by increases in serum creatinine, whereas hydrophilic β-lactams(e.g., most cephalosporins and carbapenems) do not. Vancomycin alone provides oxidative stress on the highly metabolic proximal tubular cells. Hydrophobic β-lactams could have greater OAT-3 mediated uptake into proximal tubular cells than hydrophilic β-lactams, thereby causing greater mitochondrial stress on these susceptible cells. Furthermore, the serum creatinine rise seen with vancomycin and hydrophobic β-lactams might represent competition for creatinine-secreting transporters (of which OAT-3 is one), thus, indicating creatinine retention rather than true renal injury. Although it is possible that the severity of AKI with vancomycin plus OAT-3 binding hydrophobic β-lactam might be overestimated, reflecting the issues of creatinine secretion, the scientific basis for renal injury at the level of the proximal tubular mitochondria is still substantial. See review above

Is short-course antibiotic therapy suitable for Pseudomonas aeruginosa bloodstream infections in onco-hematology patients with febrile neutropenia? Results of a multi-institutional analysis Cin Infect Dis published online November 5, 2023

DOI: 10.1093/cid/ciad605

RCTs investigating antibiotic durations either exclude or underrepresent immunocompromised patients. As a result, many clinicians are reluctant to prescribe short course therapy for this population. In the case of P aeruginosa (PA) bloodstream infections (BSI), it is thought that more aggressive management is necessary compared to other gram-negative organisms, especially in the patients with hematological malignancies. Several studies have suggested that short-course antibiotic therapy does not increase the risk of infection recurrence or infection-related mortality [eClinicalMedicine. 2023; 55:101750 ; Intensive Care Med. 2022;48:841-849] but these studies are limited due to limitations such as a small proportion of immunocompromised patients, small sample sizes, and low utilization rates of short-course therapy. [Clinical Microbiology and Infection. 2023; 29:143-149]

All patients with hematological malignancies with a positive blood culture for PA admitted to two hospitals between Jan 2014 to Jan 2023 were evaluated. After review of the durations of targeted antibiotic therapy prescribed, short course was defined as 7–11 days of antibiotics, while prolonged course was defined as 12-21 days. Patients who met any of the following conditions were excluded: 1) receipt of less than 7 days of antibiotic therapy; 2) receipt of more than 21 days of antibiotic therapy; 3) inability to complete the planned course of therapy due to death or withdrawal of care; 4) receipt of aminoglycoside monotherapy during any portion of the treatment course; 5) had early onset of septic shock. 6) lost to follow-up within 90 days after stopping antibiotic therapy. All patients received peripherally inserted central catheter (PICC) for the administration of chemotherapy drugs. In our center, routine antibiotic prophylaxis is not included in the protocol, even for neutropenic patients upon discharge. Definite treatment for PA infections was formulated based on the susceptibility testing of the initial blood culture. The indications for discontinuation of antibiotic therapy included: clinical improvement with resolution

of infection-related signs and symptoms; negative blood cultures; successful control or removal of the identified source of infection (e.g., central venous catheterization); resolution of infection-related manifestations, normalization of inflammatory markers, and neutropenia recovery.

The primary outcome was a composite outcome that included recurrent PA infection or death, both within 30 days of discontinuing antibiotic therapy. The second outcome included recurrent PA infection within 90 days and recurrent fever within 7 days of discontinuing antibiotic therapy. Other endpoints observed included length of hospital stay (LOS). The recurrence of PA-BSI was defined as the subsequent isolation of PA from blood culture and presentation of infection related symptoms and signs within 90 days after stopping antibiotic therapy. To balance differences with respect to baseline characteristics between the 2 groups, inverse probability of treatment weighting (IPTW) was performed. Covariates used for generating propensity scores included age, sex, primary hematological disease, chemotherapy in this hospitalization, allo-HSCT, immunosuppressive therapy, tumor stage, comorbidities (chronic liver disease, chronic renal disease, and diabetes mellitus), sources of infection, infection source control, shock, oral mucositis, perianal mucositis, ANC < 0.1×10^9/L on day 1 of BSI, duration of neutropenia before BSI, MDR-PA, and CRPA.

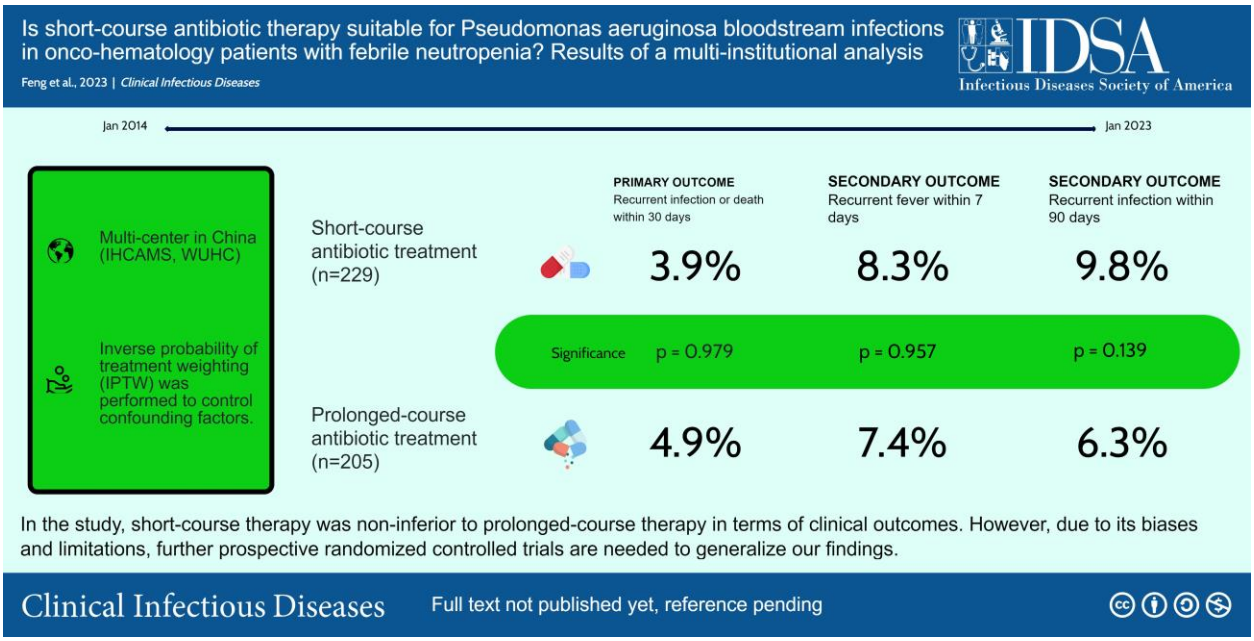
This study, by including patients with hematological malignancies and balancing confounding factors through IPTW, yielded results indicating that there was no difference in fever relapse within 7 days, death or recurrent infection within 30 days and recurrent infection within 90 days of completing antibiotic therapy regardless of whether patients were treated with a short course (median, 8 days) or prolonged course (median, 15 days) of antibiotics. Furthermore, patients treated with shorter courses were discharged from the hospital approximately 3.3 days sooner than those who received prolonged course of treatment.

Comment: Some guidelines recommend antibiotic treatment for PA BSI to be at least 14 days while some studies in immunocompetent populations have already indicated that short-course therapy is non-inferior to prolonged treatment in terms of clinical and microbiological cure rates. Siddharth Swamy et al compared the effectiveness of short-course and prolonged-course treatments in a retrospective analysis of 178 patients with Gram-negative BSI and found that short-course therapy for Gram-negative bacteremia yielded comparable rates of clinical response (78.6% vs. 80.6%, p = 0.202) and microbiological cure (83.3% vs. 91.7%, p = 0.690). [OFID. 2014;1(suppl_1): S201-S202] Rodrigues RD et al indicated that short-term therapy was not associated with 30-day mortality(HR= 1.01, 95% CI 0.47-2.20, p = 0.98) in patients with BSI due to either Acinetobacter or Pseudomonas. [Antibiotics (Basel). 2023;12(3)] Bae M et al included 290 uncomplicated PA BSI and found that no significant difference in the risk of recurrence or 30-day mortality between the prolonged course and short-course groups (HR = 0.68, 95% CI = 0.34 - 1.36, p = 0.28) and the recurrence of PA infection within 180 days (HR = 0.57, 95% CI = 0.29 - 1.10, p = 0.09).[J Antimicrob Chemother. 2021; 77:223-228] In a recent study the investigators included 249 patients with PA BSI for matched analysis. The investigators reported that 65% of the patients were immunocompromised, but only 23% had recent chemotherapy and 8% had allo-HSCT within a year, and only 72 cases in the short-course group, making it difficult to draw firm conclusions. [Clin Infect Dis. 2019; 69:2011-2014]

In the current paper, their study population had a relatively low prevalence of comorbidities due to the populations being predominantly young, similar to the features of BSI in hematological patients. While regarding the sources of BSI, they observed that over 50% of cases were primary BSI. Among patients in whom the source could be determined, pulmonary and the

damaged mucosal including oral and perianal were the main sites, while the CRBSI and urinary tract were quite rare in our study. These findings differed from the previous study reporting that gram-negative BSIs primarily originated from venous catheters and urinary sources. [Clin Infect Dis. 2019; 69:2011-2014] Although a very small number of patients did not completely recover from neutropenia when they stopped antibiotics, they had an upward trend in the ANC and were evenly distributed in both short-course and long-course groups. The neutropenia non recovery populations had worse clinical outcomes, which warrant physicians to take measures other than prolonged the antibiotic duration.

This was a retrospective study, with the limitations associated with the study design. There was variability in the timing of repeating blood cultures after initiating targeted antibiotic therapy. There is no mention of ADEs. Nonetheless the investigators in this study found that short course of antibiotic therapy was not inferior to the prolonged course of therapy in onco-hematological patients with PA BSI, with the potential added benefit of earlier hospital discharge if treated with a shorter course and fewer adverse events.

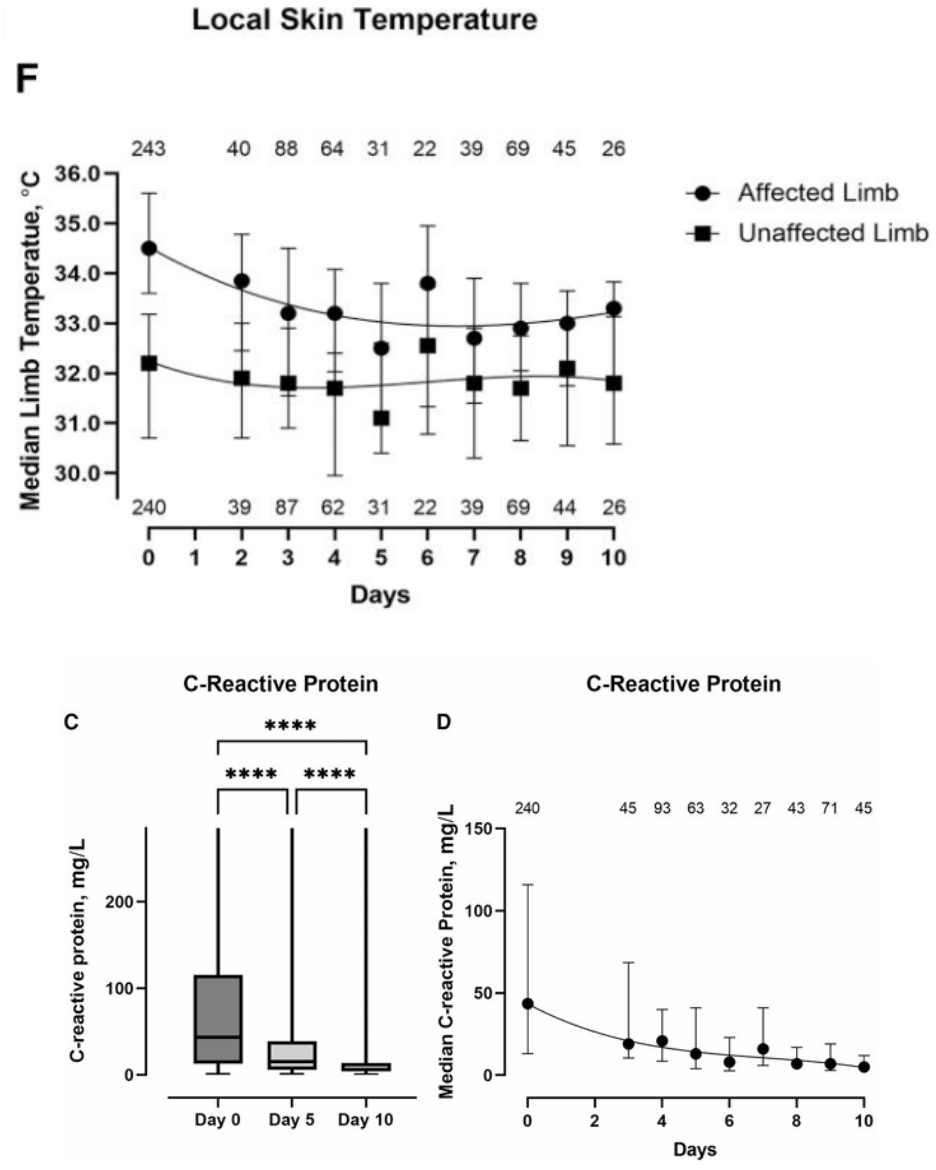


The Natural History of Antibiotic-Treated Lower Limb Cellulitis: Analysis of Data Extracted From a Multicenter Clinical Trial OFID published online September 29, 2023

doi.org/10.1093/ofid/ofad488

Individuals with a diagnosis of lower limb cellulitis who attended at least 1 follow-up appointment were included in this analysis. Data were extracted from a RCT (NCT01876628-Adjunctive clindamycin for cellulitis: a clinical trial comparing flucloxacillin with or without clindamycin for the treatment of limb cellulitis [BMJ Open 2017 Mar 17;7(3):e013260]) of antibiotic therapy for cellulitis from 20 hospitals in the UK. Those with cellulitis of the upper limb were excluded.

Investigators recorded responses to treatment among 247 adults (mean age, 52; 67% men) with confirmed lower-extremity cellulitis who were enrolled in a treatment trial of 7 to 10 days of a β-lactam drug, with or without clindamycin. Between baseline and day 5, surface area of affected skin shrank by 34%; by day 10, the affected area had shrunk by ≈55%. Swelling lessened by almost 50% by day 10, but many patients still had substantial swelling, and the affected leg remained warmer than the unaffected one for most patients. More than half of patients continued to report discomfort in the affected leg at day 10, with pain scores >5 of 10 reported by 14%. On the other hand, C-reactive protein levels fell dramatically during treatment, reaching near-normal levels in all patients by day 10. In fact, most biomarkers demonstrated a return to normal by day 3.



Comment: Cellulitis is both very common and very commonly misdiagnosed: Recent studies have shown that 30% to 60% of patients with presumed cellulitis have something else. [J Hosp Med 2023; 18:254]. Indeed, individuals initially diagnosed and/or treated for cellulitis have an

alternative final diagnosis, such as venous stasis dermatitis, contact dermatitis, eczema, lymph edema, or erythema migrans. [J Am Acad Dermatol 2015; 73:70–5] That confusion has muddied clinical expectations for patients who really do have cellulitis. Approximately 20% of individuals with cellulitis "fail" initial antimicrobial therapy [Am J Emerg Med 2016; 34:1645–52] and are prescribed repeat courses of antimicrobials. It is likely that a proportion of these individuals simply have slowly resolving symptoms and that these "failures" represent the natural history of disease.

This was a post hoc secondary data analysis of the original randomized trial; it is likely that loss to follow-up was not random and patients with greater symptoms may have been more likely to have follow-up. Additionally, trial populations are known to be "healthier" on average than the reference population in which the trial is run. Therefore, I would have liked to see more data on patients with diabetes and patients with other comorbidities.

Nonetheless, this study demonstrates an important message: The improvement in LE cellulitis takes time and residual erythema and warmth is common after an appropriate course of antibiotics not the exception. We should not presume treatment failure and treat again, but rather reassure the patient and continue to monitor the leg over time.

Editor's Choice

Decolonization in Nursing Homes to Prevent Infection and Hospitalization N Engl J Med published online October 10, 2023

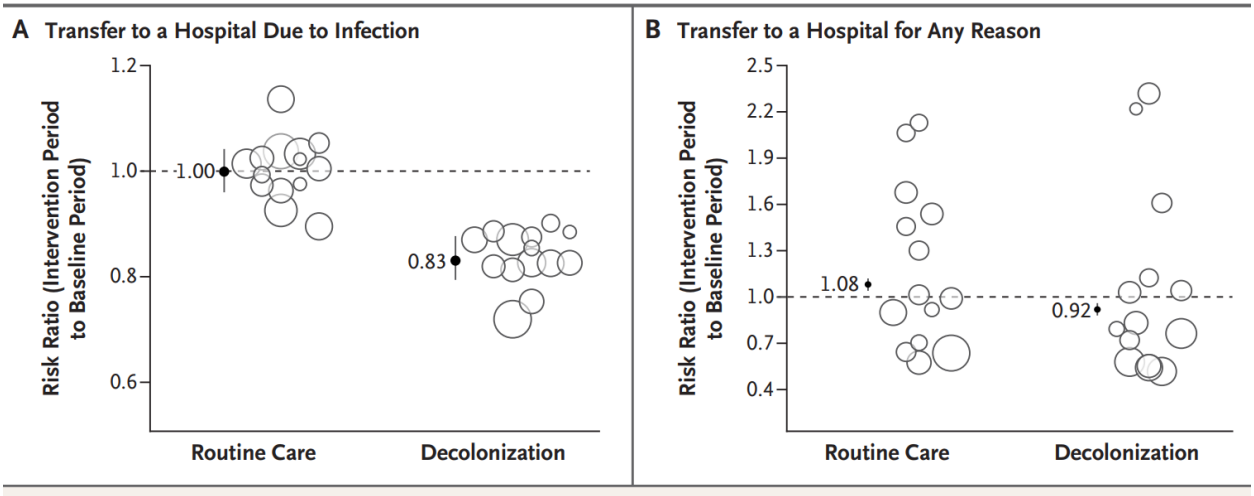
DOI: 10.1056/NEJMoa2215254

The investigators performed a cluster-randomized trial of universal decolonization as compared with routine-care bathing in nursing homes. The trial included an 18-month baseline period and an 18-month intervention period. Decolonization entailed the use of chlorhexidine for all routine bathing and showering (4% chlorhexidine [CHG] rinse-off antiseptic wash for showering and 2% CHG no-rinse cloths for bed bathing) and administration of nasal povidone–iodine twice daily for the first 5 days after admission and then twice daily for 5 days every other week. The primary outcome was transfer to a hospital due to infection. The secondary outcome was transfer to a hospital for any reason. They also looked at the prevalence of MDRO carriage among residents during the two periods.

The mean compliance with the CHG bathing routine and nasal iodophor application was 87% and 67%, respectively, during the intervention period. A microbiologic analysis of swab samples collected from residents of 24 nursing homes in the trial found that MDRO colonization prevalence fell from 48.9% in the decolonization group to 32% by the end of the intervention, while MDRO prevalence in control nursing homes fell only slightly (48.3% to 47.2%). The prevalence of any MDRO significantly declined in decolonization versus control nursing homes (RR, 0.70; 95% CI, 0.58 to 0.84), with reductions in MRSA (RR, 0.73; 95% CI, 0.59 to 0.92), vancomycin-resistant Enterococci (RR, 0.29; 95% CI 0.14 to 0.62), and ESBL–producing bacteria (RR, 0.50; 95% CI, 0.34 to 0.75).

During the baseline period, the proportion of hospital transfers due to infection was 62.2% in the control nursing homes and 62.9% in the decolonization nursing homes. During the intervention

period, the percentage of hospital transfers due to infection fell to 52.2% in the decolonization nursing homes (risk ratio [RR], 0.83; 95% confidence interval [CI], 0.79 to 0.88), while remaining roughly the same (62.6%) in the control nursing homes [RR, 1.00; 95% CI, 0.96 to 1.04] The relative risk reduction in the decolonization nursing homes versus controls was 16.6%.



Comment: In this cluster-randomized trial, a universal decolonization strategy of using over-the-counter topical chlorhexidine for bathing and nasal iodophor in nursing homes was associated with a lower risk of transfer to the hospital due to infection. The intervention products that were used (CHG and nasal iodophor) are relatively inexpensive. They dedicated 4 months to staff training and coaching. Despite these efforts, 3 of 14 intervention sites did not implement decolonization, mostly because of the loss of support due to leadership turnover. Several sites had low adherence to iodophor, especially at admission, because of the requirement that nurses, rather than nursing assistants, administer iodophor to residents. Performing studies in NHs are incredibly difficult and the investigators should be commended. The question can this result be duplicated in a non-study real world setting.

Editor's Choice

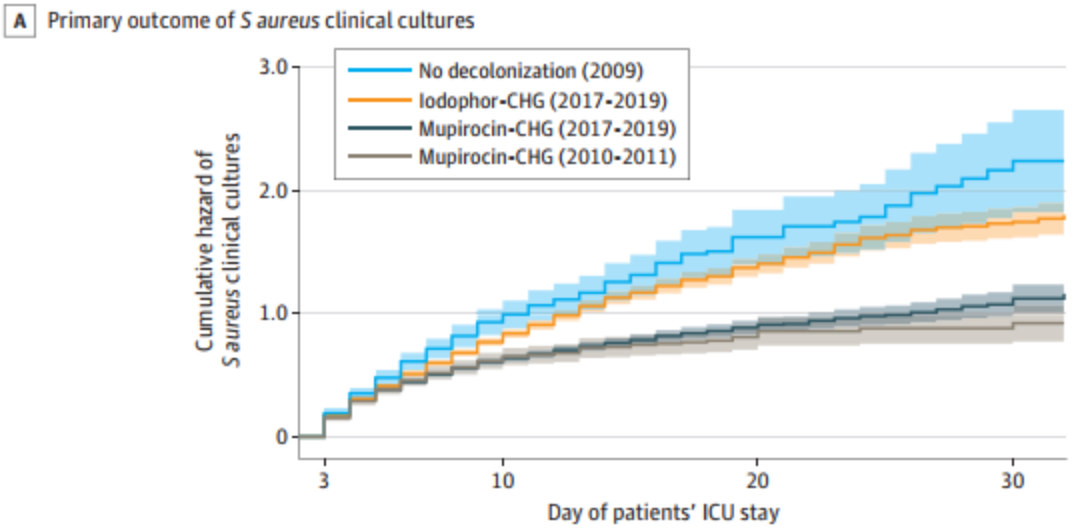
Nasal Iodophor Antiseptic vs Nasal Mupirocin Antibiotic in the Setting of Chlorhexidine Bathing to Prevent Infections in Adult ICUs A Randomized Clinical Trial JAMA. 2023;330(14):1337-1347.

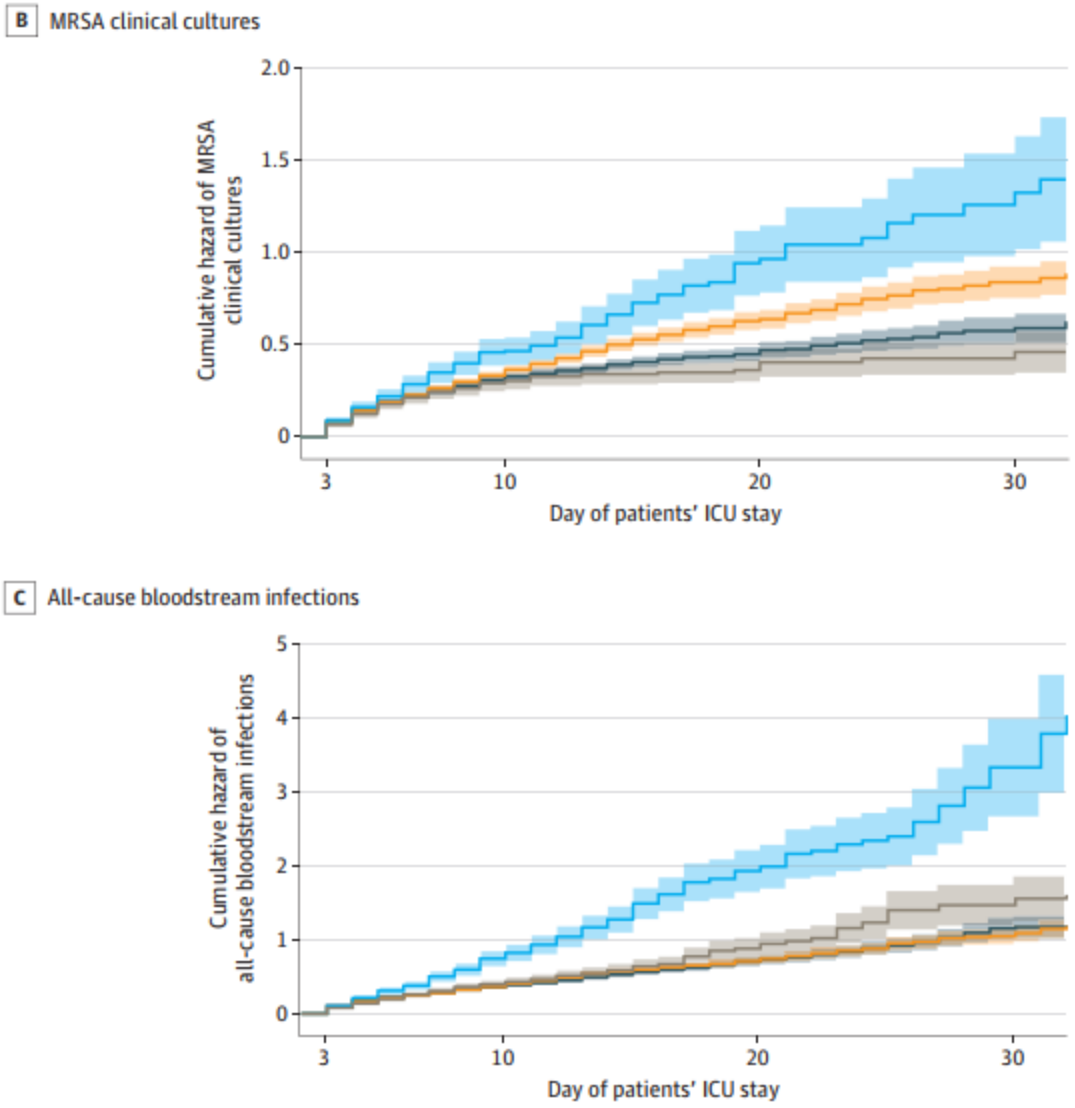
doi:10.1001/jama.2023.17219

This trial was a two-group noninferiority, pragmatic, cluster-randomized trial conducted in US community hospitals, all of which used mupirocin-CHG for universal decolonization in ICUs at baseline. Investigators randomized 137 hospitals (233 ICUs in a single network). Universal decolonization involved switching to iodophor-CHG (intervention) or continuing mupirocin-CHG (baseline). The main outcome was ICU-attributable S aureus clinical cultures (primary outcome), MRSA clinical cultures, and all-cause bloodstream infections (BSIs). Results were also compared with a 2009-2011 trial of mupirocin-CHG vs no decolonization in the same

hospital network. [N Engl J Med. 2013;368:2255-2265.] The prespecified noninferiority margin for the primary outcome was 10%.

Among the 801,668 admissions in 233 ICUs, the participants' mean (SD) age was 63.4 (17.2) years, 46.3% were female, and the mean (SD) ICU length of stay was 4.8 (4.7) days. Hazard ratios (HRs) for S aureus clinical isolates in the intervention vs baseline periods were 1.17 for iodophor-CHG (raw rate: 5.0 vs 4.3/1000 ICU-attributable days) and 0.99 for mupirocin-CHG (raw rate: 4.1 vs 4.0/1000 ICU-attributable days) (HR difference in differences significantly lower by 18.4% [95% CI, 10.7%-26.6%] for mupirocin-CHG, $P < .001$). For MRSA clinical cultures, HRs were 1.13 for iodophor-CHG (raw rate: 2.3 vs 2.1/1000 ICU-attributable days) and 0.99 for mupirocin-CHG (raw rate: 2.0 vs 2.0/1000 ICU-attributable days) (HR difference in differences significantly lower by 14.1% [95% CI, 3.7%-25.5%] for mupirocin-CHG, $P = .007$). For all-pathogen bloodstream infections, HRs were 1.00 (2.7 vs 2.7/1000) for iodophor-CHG and 1.01 (2.6 vs 2.6/1000) for mupirocin-CHG (nonsignificant HR difference in differences, -0.9% [95% CI, -9.0% to 8.0%]; $P = .84$). When compared with baseline controls (from 2009–2011, when no nasal decontamination was used), both interventions resulted in fewer positive clinical cultures and significantly fewer bloodstream infections.





Comment: Nasal iodophor did not meet criteria to be considered noninferior to nasal mupirocin antibiotic for the outcome of S aureus clinical cultures in adult ICU patients in the context of universal daily CHG bathing. In fact, the results were consistent with nasal iodophor being inferior to nasal mupirocin. Looking at it another way, mupirocin was superior to iodophor in reducing S aureus clinical cultures but both agents lowered the risk of BSIs. No data on mupirocin or iodophor resistance among S aureus strains from participating hospitals were provided. The results of this trial may differ depending on local mupirocin resistance. Lastly the role of CHG alone could not be determined in this trial. However, what this trial does show is either nasal agent was better than no nasal agent. When compared with baseline controls (from 2009–2011, when no nasal decontamination was used), both interventions resulted in fewer positive clinical cultures and significantly fewer bloodstream infections.

Last year different investigators published an article entitled "Does nasal povidone-iodine interfere with methicillin-resistant Staphylococcus aureus MRSA) screening?" [Infect Control Hosp Epidemiol, 43: 945–947] This was a small prospective cohort proof-of-concept study of

patients admitted to a medical ICU or stepdown unit and had undergone baseline MRSA nasal screening by PCR that was positive for MRSA. All positive PCR results underwent confirmatory testing via nonquantitative culture using MRSA-specific media. Intranasal P-I was applied twice daily for 5 days or until ICU discharge. At follow-up, 16 (80%) of 20 remained MRSA positive via both PCR and culture. This may provide some insight why P-I was inferior to mupirocin in the current study.

In an editorial accompanying the current article the author concluded "While a study of CHG alone compared with a dual decolonization regimen is still needed, it is becoming harder to argue that the use of a combination decolonization regimen should not be the standard of care for ICU patients." In fact, the CDC recommended in their publication on "Strategies to Prevent HO S aureus BSIs in Acute Care Facilities" CHG + Intranasal antistaphylococcal antibiotic/antiseptic as a core strategy in for patients in the ICU with a CVP or midline. See below. [https://www. cdc.gov/hai/prevent/staph-prevention-strategies. Html]

Table 1: Summary of Decolonization and Pathogen Reduction Strategies by Central Venous Catheter (CVC) or Midline Catheter Presence and Unit Type

Patient Type	Intensive Care Unit	non-Intensive Care Unit
CVC or Midline Catheter Present	Topical chlorhexidine gluconate (at least 2%) + Intranasal antistaphylococcal antibiotic/antiseptic (e.g. mupirocin or iodophor) (**core strategy**)	Topical chlorhexidine gluconate (at least 2%) + Intranasal antistaphylococcal antibiotic/antiseptic (e.g. mupirocin or iodophor) (**supplemental strategy**)
No CVC or Midline Catheter present	Topical chlorhexidine gluconate (at least 2%) + Intranasal antistaphylococcal antibiotic/antiseptic (i.e. mupirocin or iodophor) (**core strategy**)	None (note that decolonization or pathogen reduction strategies may apply to pre-operative surgical patients outside the intensive care unit- see section 2)

Prevalence of Acinetobacter baumannii and Candida auris in Patients Receiving Mechanical Ventilation JAMA published online October 12, 2023

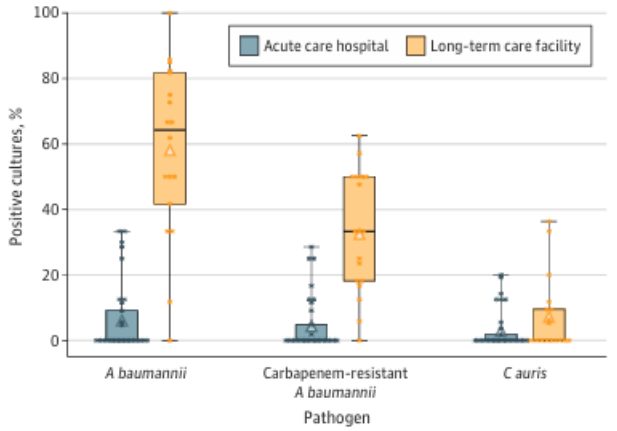
doi:10.1001/jama.2023.21083

The Maryland Multi-Drug Resistant Organism Prevention Collaborative performed a statewide cross-sectional point prevalence of patients receiving mechanical ventilation admitted to acute care hospitals (n = 33) and long-term care facilities (n = 18) between March 7, 2023, and June 8, 2023. Surveillance cultures (sputum, perianal, arm/leg, and axilla/groin) were obtained from all patients receiving mechanical ventilation. Sputum, perianal, and arm/leg cultures were tested for A baumannii, and antibiotic susceptibility testing was performed. Axilla/groin cultures were tested by polymerase chain reaction for C auris. The main outcome was prevalence of A baumannii, carbapenem-resistant A baumannii (CRAB), and C auris. Prevalence was stratified by the type of facility.

A total of 482 patients receiving mechanical ventilation were screened for A baumannii and 470 were screened for C auris. Among the 482 patients who had samples collected, 30.7%

(148/482) grew A baumannii, 88 of the 148 (59.5%) of these A baumannii were CRAB, and C auris was identified in 31 of 470 (6.6%). Patients in long-term care facilities were more likely to be colonized with A baumannii (relative risk [RR], 7.66 [95% CI, 5.11-11.50], *P* < .001), CRAB (RR, 5.48 [95% CI, 3.38-8.91], *P* < .001), and C auris (RR, 1.97 [95% CI, 0.99-3.92], *P* = .05) compared with patients in acute care hospitals. Nine patients (29.0%) with cultures positive for C auris were previously unreported to the Maryland Department of Health.

Figure. Prevalence of *Acinetobacter baumannii*, Carbapenem-Resistant *A baumannii*, and *Candida auris* Colonization Stratified by Type of Facility



Comment: The results demonstrate that patients receiving mechanical ventilation in Maryland were colonized with A baumannii nearly a third of the time; CRAB, 18%, and *C auris,* nearly 7%. Colonization rates for all 3 were higher in the long-term care setting. Patients with A baumannii colonization in an intensive care unit setting often develop infection during the same admission. For patients infected with CRAB, there are limited treatment options. Cefiderocol may demonstrate heteroresistance and IDSA recent update has recommended cefiderocol for only salvage therapy along with a second active agent. [Clin Infect Dis. 2022; 74:2089-2114] High-dose ampicillin-sulbactam, sulbactam-durlobactam, and tetracycline derivatives can be used in combination to treat moderate to severe infection. Sulbactam-durlobactam looks promising based on the ATTACK trial. [Lancet Infect Dis 2023; published online May 11] In addition most C auris are intrinsically resistant to multiple antifungals including azoles. Some isolates of C auris have now developed resistance to all commercially available antifungal agents.

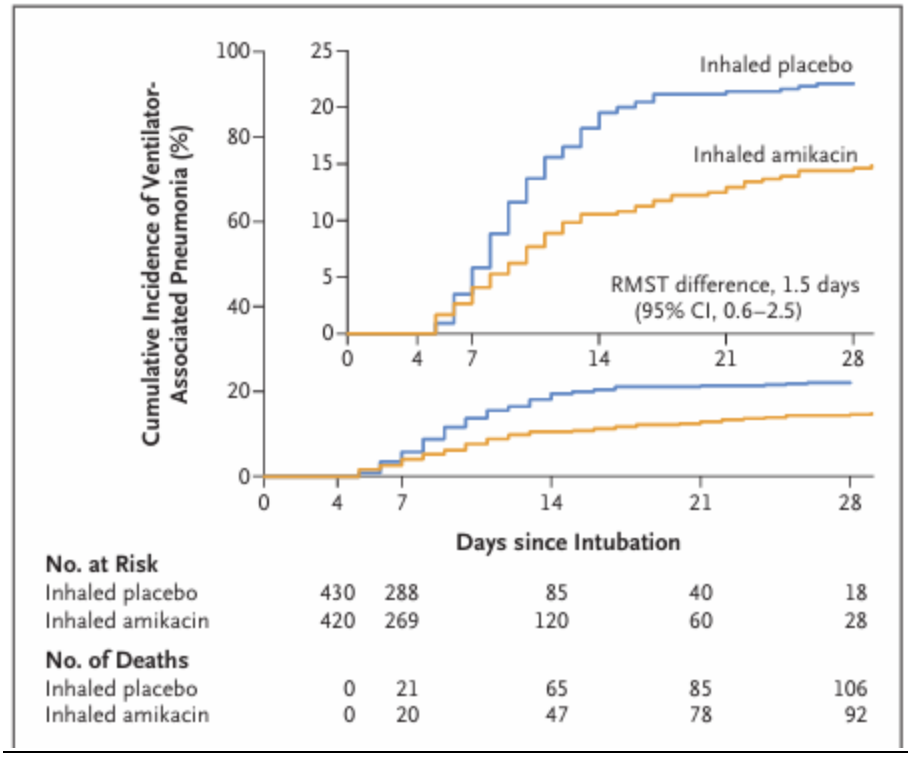
A baumannii surveillance cultures were obtained only from the sputum, arm/leg, and perianal area and only a single axilla/groin culture was obtained for C auris. By not including other sites known to potentially harbor A baumannii and C auris, the colonization rates may have been underestimated.

Inhaled Amikacin to Prevent Ventilator-Associated Pneumonia N Engl J Med published online October 25, 2023

DOI: 10.1056/NEJMoa2310307

This was a multicenter, double-blind, randomized, controlled, superiority trial. Critically ill adults who received invasive mechanical ventilation for at least 72 hours were randomized to receive inhaled amikacin at a dose of 20 mg per kilogram of ideal body weight once daily or to receive placebo for 3 days. Patients were not eligible for enrollment after 96 hours of invasive mechanical ventilation or if they had suspected or confirmed ventilator-associated pneumonia, severe acute kidney injury without renal-replacement therapy, chronic kidney disease (GFR <30 ml per minute), or a tracheostomy tube; if extubation was scheduled within the next 24 hours; or if they were receiving systemic aminoglycoside therapy., The primary outcome was a first episode of ventilator-associated pneumonia(VAP) during 28 days of follow-up. The primary outcome was adjudicated by a blinded centralized committee on the basis of definitions from international guidelines (requiring a positive quantitative bacterial culture in a pulmonary sample and at least two of the following findings: leukocytosis, leukopenia, fever, or purulent secretions with a new infiltrate on a chest radiograph). The diagnostic workup for VAP was standardized among the centers according to international guidelines. Key secondary outcomes included ventilator associated events (VAE) comprising ventilator-associated conditions (i.e., worsening oxygenation over 2 days after a stable or improvement period), infection related ventilator-associated complications (i.e., worsening oxygenation associated with signs of infection and initiation of antibiotic therapy). Safety was assessed.

A total of 850 patients underwent randomization, and 847 were included in the analyses (417 assigned to the amikacin group and 430 to the placebo group). All three daily nebulizations were received by 337 patients (81%) in the amikacin group and 355 patients (82%) in the placebo group. At 28 days, VAP had developed in 62 patients (15%) in the amikacin group and in 95 patients (22%) in the placebo group (difference in restricted mean survival time to VAP, 1.5 days; 95% confidence interval [CI] 0.6 to 2.5; P = 0.004). A ventilator-associated condition occurred in 137 patients (33%) in the amikacin group and in 170 patients (40%) in the placebo group (hazard ratio, 0.79; 95% CI, 0.64 to 0.99). An infection-related ventilator-associated complication occurred in 74 patients (18%) in the amikacin group and in 111 patients (26%) in the placebo group (hazard ratio, 0.66; 95% CI, 0.50 to 0.89). Trial-related serious adverse effects were seen in 7 patients (1.7%) in the amikacin group and in 4 patients (0.9%) in the placebo group. A serious adverse effect that was considered by central review to be related to the trial occurred in 7 patients (1.7%) in the amikacin group (4 with increased resistance of the expiratory limb filter, 1 with obstruction of the tracheal tube, and 2 with bronchospasms) and in 4 patients (0.9%) in the placebo group (1 with increased resistance of the expiratory limb filter, 1 with obstruction of the tracheal tube, 1 with bronchospasm, and 1 with a decrease in pulse oximetry measurements). A total of 99 patients (24%) in the amikacin group and 112 patients (26%) in the placebo group died in the ICU.



Comment: In this large multicenter trial, a 3-day course of amikacin reduced the burden of VAP by day 28 as compared with placebo. Results were consistent with regard to VAEs as well. The enrollment of patients after at least 3 days of invasive mechanical ventilation may have enabled amikacin to act early to control the tracheobronchial spread of bacteria before pneumonia occurred, with a majority of patients being extubated a few days after the end of the intervention and thus no longer at risk for VAP. Of note, among all the patients in the trial in whom VAP developed, the lengths of mechanical ventilation and ICU stay, and the administration of systemic antibiotics were twice as high as those observed in patients in whom VAP did not develop. This trial was not powered to investigate other patient-centered outcomes such as death or length of stay in the ICU and hospital. The widespread use of inhaled amikacin could lead to resistance. Certain gram-negative organisms may already be resistant to amikacin such as acinetobacter, pseudomonas, and stenotrophomonas to name a few.

Respiratory syncytial virus burden and risk factors for severe disease in patients presenting to the emergency department with flu-like symptoms or acute respiratory failure Resp Medicine published online September 6, 2023

doi.org/10.1016/j.rmed.2023.107404

This was a retrospective, single center, cohort study included all consecutive patients referred to the ED with flu-like symptoms or acute respiratory failure (aRF) tested per protocol for SARS-CoV-2, RSV, Influenza A (InvA) during the 2022–2023 autumn/winter season. Clinical characteristics and patients' outcomes were captured. Respiratory failure, need for respiratory support, shock, sepsis, or in-hospital death defined severe disease.

The analysis included 717 patients (65.1% negative swab, 14.1% InvA, 8.5% RSV, 8.6% SARS-CoV- 2, 3.6% other viruses 12% [Enterovirus/Rhinovirus, Influenza B virus, Human Metapneumovirus.]) Compared with the study cohort, RSV patients had the highest occurrence of aRF (62.7%) and severe disease (70.5%); mortality was similar to InvA (6.6% vs 5.9%, p = 0.874). Compared with InvA patients, RSV patients were older (p = 0.009), had higher Charlson index (p = 0.001), higher prevalence of chronic heart failure (p = 0.001) and were more frequently on ICS[inhaled corticosteroids] (p = 0.026) and immunosuppressants (p = 0.018). Heart failure [OR (95%CI):3.286 (1.031–10.835); p = 0.041], chronic exposure to ICS [OR (95% CI):2.377 (1.254–4.505); p = 0.008] and immunosuppressants [OR (95%CI):3.661 (1.246–10.754); p = 0.018] predicted RSV infection. Glucose ≥120 mg/dL [OR (95%CI):5.839 (1.155–29.519); p = 0.033], leucocytes ≥8000 cells/μL [OR (95%CI):5.929 (1.090–32.268); p = 0.039], and past/active smoking [OR (95%CI):7.347 (1.301–41.500); p = 0.024] predicted severe RSV disease.

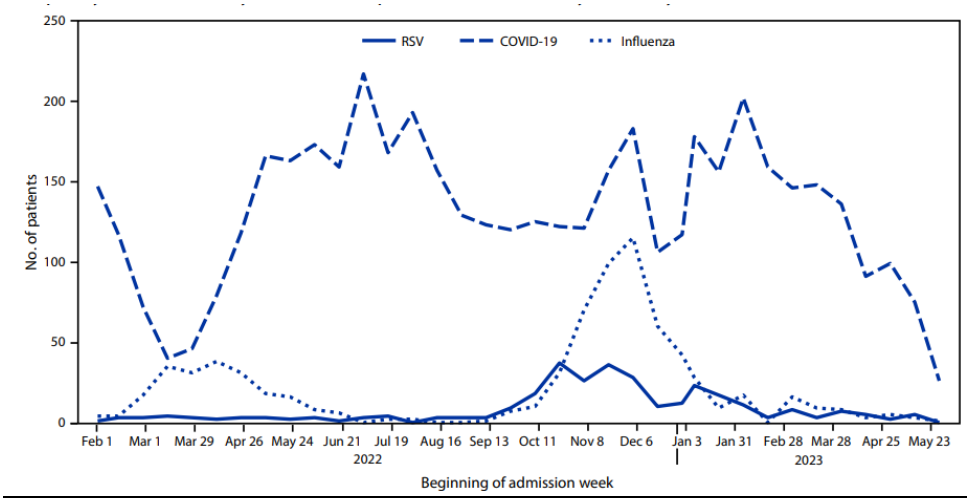
Comment: RSV infection is associated with significant mortality and morbidity. Preventive strategies for RSV infection such as vaccination is strongly recommended, especially in older patients with cardiovascular and chronic respiratory conditions. The sample size and the lack of ethnic heterogeneity might have influenced patients' outcomes. The study was also conducted during the winter season representing the tail of the SARS-Cov-2 pandemic might have led to a possible mis-estimation of RSV incidence. See next review.

Disease Severity of Respiratory Syncytial Virus Compared with COVID-19 and Influenza Among Hospitalized Adults Aged ≥60 Years — IVY Network, 20 U.S. States, February 2022–May 2023 MMWR 2023; 72(40);1083–1088.

During February 1, 2022–May 31, 2023, adults aged ≥60 years with acute respiratory illness and laboratory-confirmed RSV, SARS-CoV-2, or influenza infection who were admitted to any of 25 hospitals in 20 U.S. states participating in the Investigating Respiratory Viruses in the Acutely Ill (IVY) Network were eligible for inclusion in this analysis. Demographic and clinical data were obtained from patient or proxy interview and medical records, including in-hospital outcomes observed by day 28 of hospitalization. Upper respiratory specimens were collected from enrolled patients near the time of admission and tested at a central laboratory (Vanderbilt University Medical Center, Nashville, Tennessee) by PCR for RSV, SARS-CoV-2, and influenza. Patients who received a positive RSV, SARS-CoV-2 or influenza result based on either hospital or central laboratory testing within 10 days of illness onset or within 3 days of hospital admission were included.

Severity of RSV disease was compared with Covid-19 and influenza severity using the following in-hospital outcomes: 1) standard flow oxygen therapy, defined as receipt of supplemental oxygen at < 30 L/minute; 2) receipt of high-flow nasal cannula (HFNC) or noninvasive ventilation (NIV); 3) intensive care unit (ICU) admission; and 4) receipt of invasive mechanical ventilation (IMV) or death. For this analysis, enrolled patients were excluded if they had confirmed or inconclusive laboratory test results indicating coinfection with RSV, SARS-CoV-2, or influenza or if data for in-hospital outcomes were missing. In-hospital outcomes were compared among patients hospitalized with RSV disease, Covid-19, and influenza using multivariable logistic regression.

During February 1, 2022–May 31, 2023, a total of 6,061 adults aged ≥60 years were enrolled in IVY Network with acute respiratory illness and laboratory-confirmed infection with RSV, SARS-CoV-2, or influenza. After exclusion of 277 patients, 5,784 were included in this analysis, among whom 304 (5.3%) were hospitalized with RSV, 4,734 (81.8%) with Covid-19, and 746 (12.9%) with influenza. Substantial seasonal variation in hospital admissions was observed for RSV and influenza, but SARS-CoV-2 admissions exhibited less seasonal variation. See below



The median age of adults hospitalized with RSV (72 years) was similar to the age of those hospitalized with Covid-19 (74 years) and influenza (71 years). In adjusted analyses comparing RSV severity with Covid-19, patients hospitalized with RSV were more likely than hospitalized Covid-19 patients or hospitalized influenza patients were to receive standard flow oxygen (adjusted odds ratio [aOR] = 2.97 [COVID-19] and 2.07 [influenza]), HFNC or NIV (aOR = 2.25 [COVID-19] and 1.99 [influenza]), or to be admitted to an ICU (aOR = 1.49 [COVID-19] and 1.55 [influenza]). The odds of the composite outcome of IMV or death between patients hospitalized with RSV and patients hospitalized with Covid-19 was similar (aOR 1.39; 95% CI = 0.98–1.96); however, among hospitalized adults aged ≥60 years with RSV, the odds of IMV or death were significantly higher compared with hospitalized influenza patients (aOR 2.08; 95% CI = 1.33–3.26).

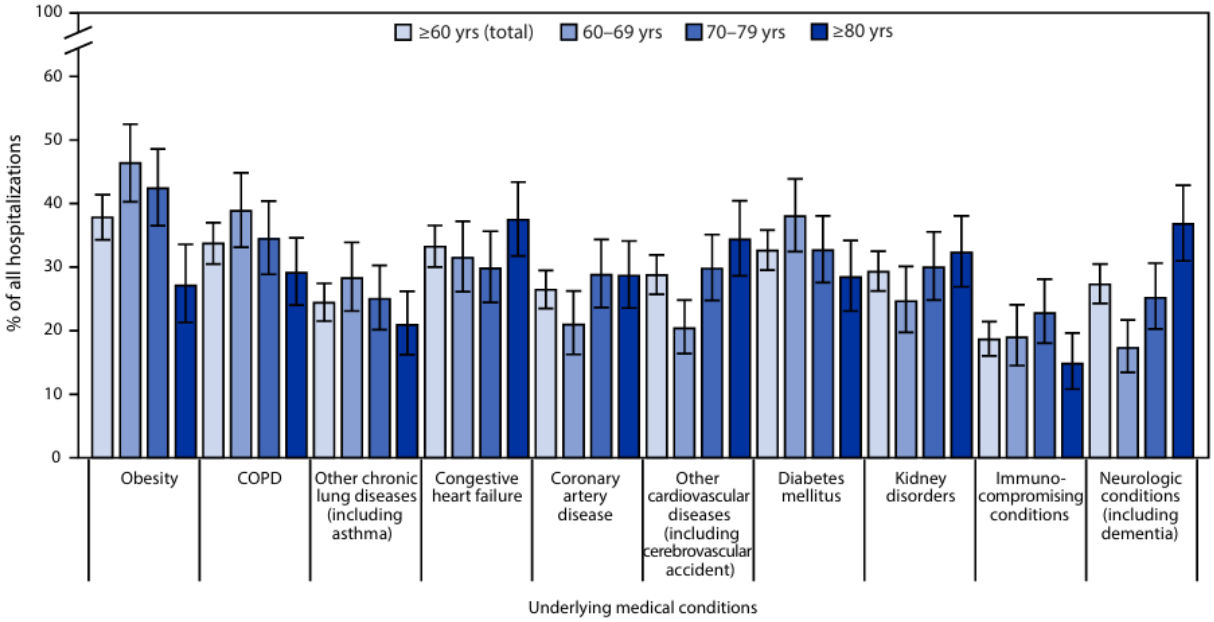
	No./Total no. (%)						
In-hospital outcomes	RSV patients n = 304	COVID-19 patients n = 4734	Influenza patients n = 746	RSV vs. COVID-19 aOR† (95% CI)	p-value	RSV vs. influenza aOR† (95% CI)	p-value
Standard flow oxygen therapy§	157/197 (79.7)	2,169/3,726 (58.2)	390/593 (65.8)	2.97 (2.07–4.27)	<0.001	2.07 (1.37–3.11)	<0.001
HFNC or NIV¶	59/256 (23.0)	495/4,223 (11.7)	94/687 (13.7)	2.25 (1.65–3.07)	<0.001	1.99 (1.36–2.90)	<0.001
ICU admission	74/304 (24.3)	819/4,734 (17.3)	125/746 (16.8)	1.49 (1.13–1.97)	0.005	1.55 (1.11–2.19)	0.01
IMV or death	41/304 (13.5)	481/4,734 (10.2)	52/746 (7.0)	1.39 (0.98–1.96)	0.07	2.08 (1.33–3.26)	0.001

Comment: An important finding in this analysis is that older adults hospitalized with RSV were also more likely to receive standard flow oxygen therapy, HFNC or NIV, or be admitted to an ICU, compared with patients hospitalized with Covid-19. Although Covid-19 and influenza vaccination, as well as antiviral or immunomodulatory treatments, have been shown to reduce severity of in-hospital outcomes, results were presented as unstratified respiratory virus groups to represent the overall population hospitalized with RSV, Covid-19, or influenza during the analysis period. The high RSV disease severity observed among older adults in this analysis is important to guide decision-making for RSV vaccination in this population. ACIP/CDC

recommended health care providers and older adults should consider RSV disease severity when making a shared clinical decision about RSV vaccination. See next review.

Characteristics and Outcomes Among Adults Aged ≥60 Years Hospitalized with Laboratory-Confirmed Respiratory Syncytial Virus — RSV-NET, 12 States, July 2022–June 2023 MMWR 2023; 72:1075-1082

The investigators examined factors contributing to mortality and morbidity among 3218 hospitalized patients aged ≥60 and identified through RSV surveillance (RSV-NET; 300 U.S. hospitals in 12 states) from July 2022 through June 2023. Of these patients, 54.1% were 75 or older and 17.2% were admitted from a long-term care facility. Most were tested for Covid-19 and influenza. Likelihood of severe outcomes was not greater with multiple infections than with RSV alone. The most common comorbidities were obesity, COPD, CHF, and diabetes; 18% of patients were considered immunocompromised. About 20% of patients (especially those older than 75 and those with multiple comorbidities — particularly COPD and CHF) proceeded to severe outcomes including ICU admission and death.



Comment: Based on the three publications reviewed, physicians and patients should consider age (particularly age ≥75 years), LTCF residence, and underlying medical conditions, including COPD and CHF, in shared decision-making regarding RSV vaccination to prevent severe RSV-associated outcomes. We now have two effective vaccines Arexvy and Abrsysvo recommended for adults aged ≥60. The article points out that severely ill patients might have been more likely to undergo RSV testing, potentially overestimating the proportion of severe outcomes among hospitalized patients. In addition, because RSV-NET covers 9% of the US population, these findings might not be nationally generalizable.

Mpox Vaccine October 25, 2023

Gay and bisexual men at high risk for mpox infection should get vaccinated for the virus even after the current outbreak ends according to the ACIP (Advisory Committee on Immunization Practices). The committee's recommendation now goes to the director of the CDC for final approval.

More than 30,000 US mpox cases were reported last year. The number dropped dramatically this year, to about 800. The daily average of new US cases is one to four per day, though some people likely aren't being diagnosed, according to the CDC. Two deaths were reported in September, bringing the total to 54 in the US since mpox hit last year.

A two-dose vaccine, Jynneos, is recommended primarily for men who have sex with men who have more than one sex partner, who have recently had a sexually transmitted disease, or who are at higher risk for infections through sexual contact for other reasons. About 500,000 people in the US have gotten the recommended two doses of the vaccine, which represents about a quarter of the 2 million who are eligible.

Comment: The new recommendation should serve to remind people the virus is still out there, and that people can still be infected. Mpox is another example of a vaccine preventable disease.

New pentavalent meningococcal vaccine

The FDA has approved a new meningococcal vaccine that covers five serogroups, folding protection against the B group in with coverage against groups A,C, W, and Y. This week ACIP (Advisory Committee on Immunization Practices) recommended that the new vaccine can be used when both the four-group (MenACWY) and the monovalent B group (MenB) vaccines are indicated at the same visit for healthy patients ages 16 to 23 and patients ages 10 and older who have certain underlying health conditions. The vaccine is given as two doses 6 months apart.

Comment: The FDA approved the vaccine last week for ages 10 through 25, but the CDC's advisory panel voted to add the new vaccine option only for people 16 through 23. The approval passed by a 10-to-4 vote. Some members of ACIP were hesitant about the wording of the proposal, due to a desire for a broader recommendation, with some suggesting that the shared decision-making wording isn't clear. They also worried about the complexity of managing meningococcal disease vaccination, with doctors juggling another new type of vaccine alongside two four-group vaccines, which are interchangeable, and two group-B vaccines, which aren't interchangeable. The CDC director will make the final recommendation.

COVID-19

FDA Authorizes Novavax's Updated Covid Vaccine October 2, 2023

A few weeks ago the FDA authorized the use of Novavax's Covid-19 vaccine in people ages 12 and older. The vaccine has been updated to target a strain of the coronavirus that was circulating earlier this year (XBB). The CDC followed to recommend the Novavax shot. This recommendation clears the way for the vaccine to become available in pharmacies and other vaccination sites.

Comment: In September, the FDA cleared the use of the first two updated Covid-19 booster shots: one from Pfizer and one from Moderna. The CDC recommends vaccination for everyone aged six months and older, and at least two months after their last Covid-19 vaccine dose if they have been previously vaccinated.

The rollout of the new boosters has been bumpy. Some people seeking out the shots have had appointments canceled or faced confusion with insurance coverage. For the first time, Covid-19 shots are being distributed through the commercial market, rather than being purchased in bulk and distributed by the federal government.

The Novavax Covid-19 vaccine is different from those offered by Pfizer-BioNTech and Moderna. Those vaccines use messenger RNA, or mRNA, to trigger immune responses. The Novavax vaccine contains a protein resembling one found on the surface of the coronavirus to trigger an immune response. The protein targeted by the updated vaccine is from the XBB.1.5 variant of the coronavirus, which was one of the more prevalent strains circulating in the US in June.

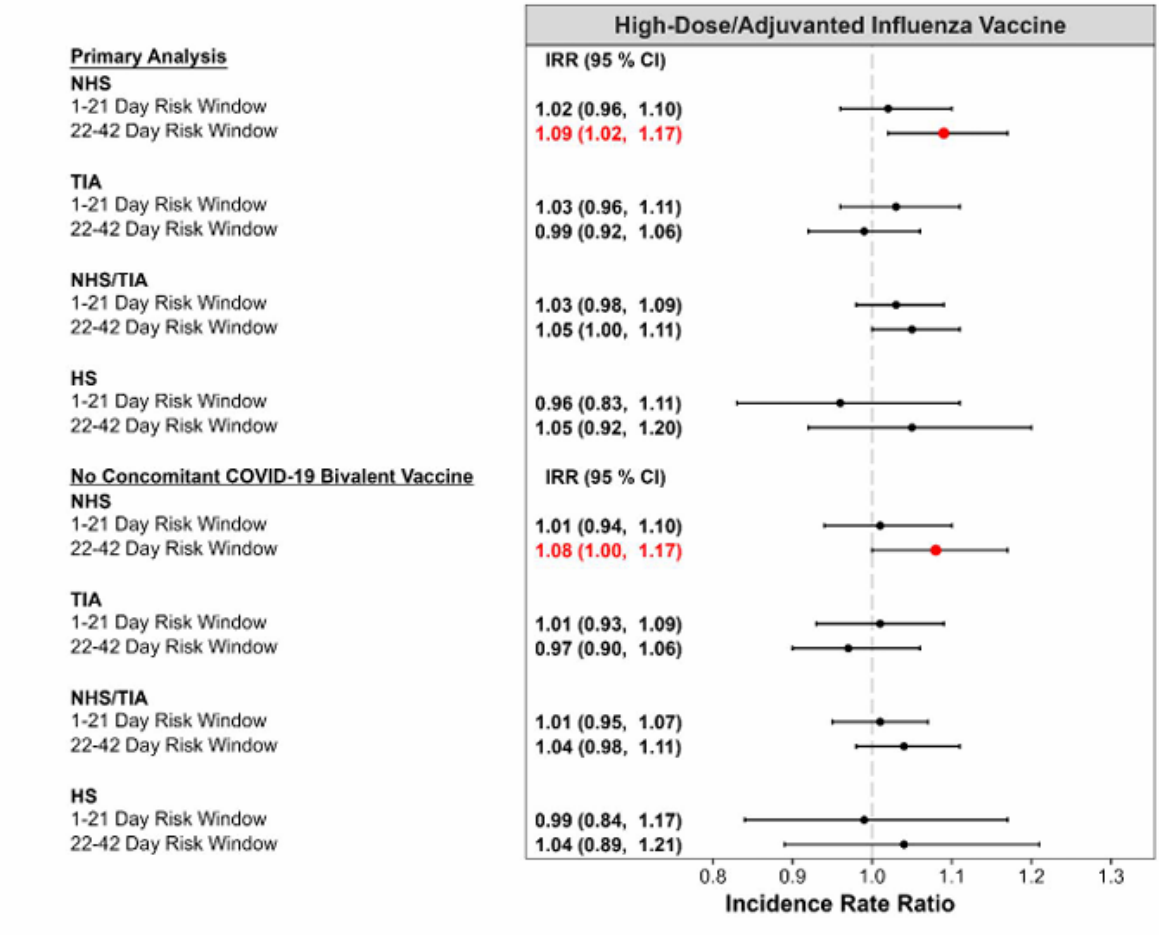
Since June, the XBB.1.5 variant has decreased while newer variants have become more prevalent. However, like XBB.1.5, the newer strains are descendants of Omicron, so the updated vaccine should still work.

Evaluation of Stroke Risk Following COVID-19 mRNA Bivalent Vaccines Among U.S. Adults Aged ≥ 65 Years medRxiv posted October 15, 2023

doi.org/10.1101/2023.10.10.23296624

In January 2023, the FDA and CDC noted a safety concern for ischemic stroke in adults ≥ 65 years receiving the Pfizer Covid-19 bivalent vaccine. Therefore, a self-controlled case series analysis was performed to evaluate stroke risk among Medicare fee-for-service beneficiaries aged ≥ 65 years receiving: 1) a Pfizer or Moderna Covid-19 bivalent vaccine, 2) high dose/adjuvanted influenza vaccines, and 3) concomitant Covid-19 bivalent vaccines and influenza vaccines, from August 31 to November 6, 2022.

The primary analysis did not find elevated stroke risk following Covid-19 bivalent vaccines. In the age subgroup analyses, only the ≥ 85 year age group had a risk of non-hemorrhagic stroke(NHS)e (Incident Rate Ratio (IRR)=1.36, 95% CI 1.09 – 1.69 [1-21 days]) and NHS/TIA (IRR=1.28, 95% CI 1.08 – 1.52 [1-21 days]) with Pfizer bivalent vaccine. Among beneficiaries receiving a concomitant Covid-19 bivalent vaccine and a high-dose/adjuvanted influenza vaccine, an increased risk was observed for NHS (IRR=1.20, 95% CI 1.01 – 1.42 [22-42 days]) with Pfizer bivalent vaccine and for TIA (IRR=1.35, 95% CI 1.06 – 1.74 [1-21 days]) with Moderna vaccine.



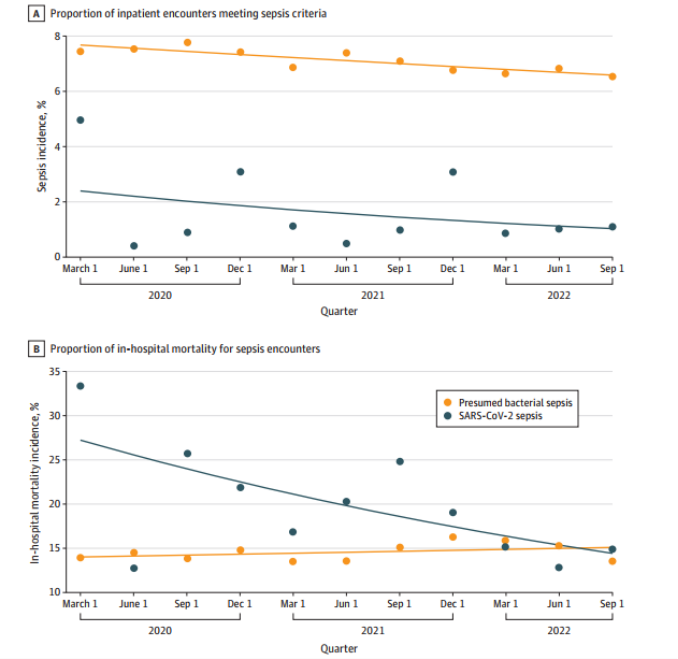
Comment: The Covid vaccines made by Pfizer and Moderna may be linked to a slight increase in the risk of stroke when administered along with a high-dose flu vaccine, according to this analysis by the FDA. The high-dose flu vaccine is usually given to older people, and the risk association is clearest in adults aged 85 and older. But that increase, if real, seems very small, and it is possible that the risk may stem from the influenza vaccine alone. This study was based on observational data, which cannot identify cause and effect. I do not think the findings warrant a change to vaccine recommendations, but findings are suggestive enough to merit further study. This paper has not gone through peer review.

Use of Electronic Clinical Data to Track Incidence and Mortality for SARS-CoV-2–Associated Sepsis JAMA Netw Open 2023;6(9): e2335728.

doi:10.1001/jamanetworkopen.2023.35728

The purpose of this study is to examine the incidence and outcomes of SARS-CoV-2–associated sepsis vs presumed bacterial sepsis using objective electronic clinical criteria. This was a retrospective cohort study included adults hospitalized at 5 Massachusetts hospitals between March 2020 and November 2022. SARS-CoV-2–associated sepsis was defined as a positive SARS-CoV-2 PCR and concurrent organ dysfunction (i.e., oxygen support above simple nasal cannula, vasopressors, elevated lactate level, rise in creatine or bilirubin level, and/or decline in platelets). Presumed bacterial sepsis was defined by modified CDC adult sepsis event criteria (i.e., blood culture order, sustained treatment with antibiotics, and organ dysfunction using identical thresholds as for SARS-CoV-2–associated sepsis). Trends in the quarterly incidence (i.e., proportion of hospitalizations) and in-hospital mortality for SARS-CoV-2–associated and presumed bacterial sepsis were assessed using negative binomial and logistic regression models.

This study included 431,017 hospital encounters from 261,595 individuals (mean [SD] age 57.9 [19.8] years, 241 131 (55.9%) females, 286,397 [66.5%] from academic hospital site). Of these encounters, 23,276 (5.4%) were from SARS-CoV-2, 6558 (1.5%) had SARS-CoV-2–associated sepsis, and 30,604 patients (7.1%) had presumed bacterial sepsis without SARS-CoV-2 infection. Crude in-hospital mortality for SARS-CoV-2–associated sepsis declined from 490 of 1469 (33.4%) in the first quarter to 67 of 450 (14.9%) in the last (adjusted odds ratio [aOR], 0.88 [95% CI, 0.85-0.90] per quarter). Crude mortality for presumed bacterial sepsis was 4451 of 30, 604 patients (14.5%) and stable across quarters (aOR, 1.00 [95% CI, 0.99-1.01]). Medical record reviews of 200 SARS-CoV-2– positive hospitalizations confirmed electronic health record (EHR)–based SARS-CoV-2–associated sepsis criteria performed well relative to sepsis-3 criteria (90.6% [95% CI, 80.7%-96.5%] sensitivity; 91.2% [95% CI, 85.1%-95.4%] specificity).



Comment: These findings suggest that SARS-CoV-2–associated sepsis was common and had higher mortality than presumed bacterial sepsis early in the Covid-19 pandemic. SARS-CoV-2 accounted for approximately 1 in 6 cases of sepsis during the first 33 months of the Covid-19 pandemic. In-hospital mortality rates for SARS-CoV-2–associated sepsis was high but declined over time and ultimately were similar to presumed bacterial sepsis. The observed decrease in SARS-CoV-2–associated sepsis mortality overall mirrors other reports demonstrating improving outcomes for patients with Covid-19 and likely reflects a combination of increased immunity from vaccines and/or prior natural infections, advances in patient management (antivirals, immunomodulators, increased use of non-invasive respiratory support), and less severe strains. Only a minority of patients with SARS-CoV-2–associated sepsis had positive blood or sputum cultures identified, supporting SARS-CoV-2 itself as the primary driver of sepsis in most cases. Numerous prior studies have demonstrated that bacterial coinfections are the exception rather than the norm for patients hospitalized with Covid-19.[Clin Infect Dis. 2021;72:e533-e54; BMC Infect Dis. 2023;23:14] However, these patients are at high risk for HAI bacterial infections, consistent with their observation that many more patients with SARS-CoV-2–associated sepsis had positive cultures across their entire hospitalizations.[Crit Care. 2023; 27:34] There were fluctuations in quarterly incidence and in-hospital mortality for SARS-CoV-2–associated sepsis, and therefore the linear models and reported IRRs are imperfect representations of pandemic trends.

Antibiotic use among hospitalized patients with COVID-19 in the United States, March 2020–June 2022 OFID published online October 7, 2023

doi.org/10.1093/ofid/ofad503

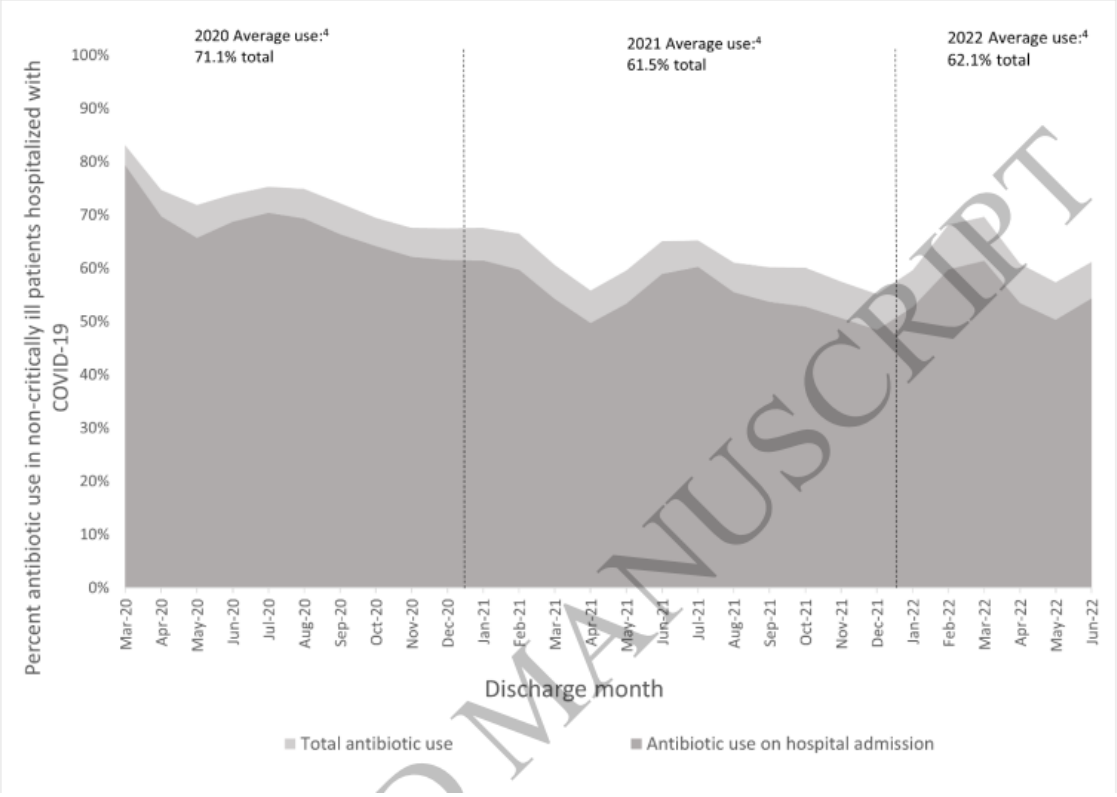
Using data from a hospital-based, all-payer database representing roughly 20% of all US hospitals, researchers with the CDC calculated the monthly proportion of hospital discharges in which patients received at least one antibiotic during their hospital stay, stratified by critical care

status, from March 2020 to June 2022. Critically ill patients were defined as those admitted to an intensive care unit and/or who received invasive mechanical ventilation.

Over the study period, 1,142,752 US adults were hospitalized and discharged with a Covid-19 diagnosis at 711 hospitals, and 69.9% received an antibiotic during their hospital stay, with 88.1% receiving an antibiotic on admission. Patients who received antibiotics were more likely to be older, critically ill, have longer hospital stays, and higher in-hospital mortality. Antibiotic use was significantly higher in critically ill patients than non-critically ill patients (903 days of therapy [DOT] per 1,000 patient days [PD] vs 763 DOT/1,000 PD).

Among non-critically ill Covid-19 patients, 71.1% received an antibiotic in 2020, 92.3% of which were started on admission. Antibiotic use in non-critically ill patients fell to 61.5% in 2021 and 62.1% in 2022, and median days of therapy also significantly declined, falling by 263 DOT/1,000 PD from 2020 to 2022. But the proportion of Covid-19 patients who received antibiotics on admission did not substantially decline. Among non-critically ill COVID patients who received antibiotics in the hospital in 2021 and 2022, 89.7% and 88.2%, respectively, received them on admission.

Ceftriaxone was the most used antibiotic, frequently in combination with azithromycin, which was thought in the early months of the pandemic to potentially impact Covid-19 severity. Use of both antibiotics declined significantly over the study period, particularly azithromycin, after several studies found it had no effect. They reported increases in other antibiotics not recommended as first-line therapy for bacterial pneumonia. Vancomycin, cefepime, and piperacillin-tazobactam were among the antibiotics which increased.



Comment: Recent review and meta-analysis have reported a low prevalence of bacterial infection in patients hospitalized with Covid-19 (8.8% overall and 4.4% with bacterial co-infection in non-ICU patients). [Clinical Microbiology and Infection. 2022; 28:491-501] An earlier study found that bacterial respiratory co-infections were very uncommon (1.2%) at the time of hospital admission. [OFID Jan 2021;8(1): ofaa578] The findings of continued high antibiotic use on hospital admission, particularly among non-critically ill Covid-19 patients, are like other studies conducted earlier during the pandemic, which suggests opportunities to minimize adverse events associated with inappropriate antibiotic prescribing, particularly for non-critically ill inpatients. This highlights opportunities for antibiotic stewardship programs to further drive down inappropriate antibiotic use in non-critically ill patients remain, particularly on admission. The analysis does not account for changes in access to vaccination, therapeutics, and treatments or natural history of infection and immunity throughout the pandemic.

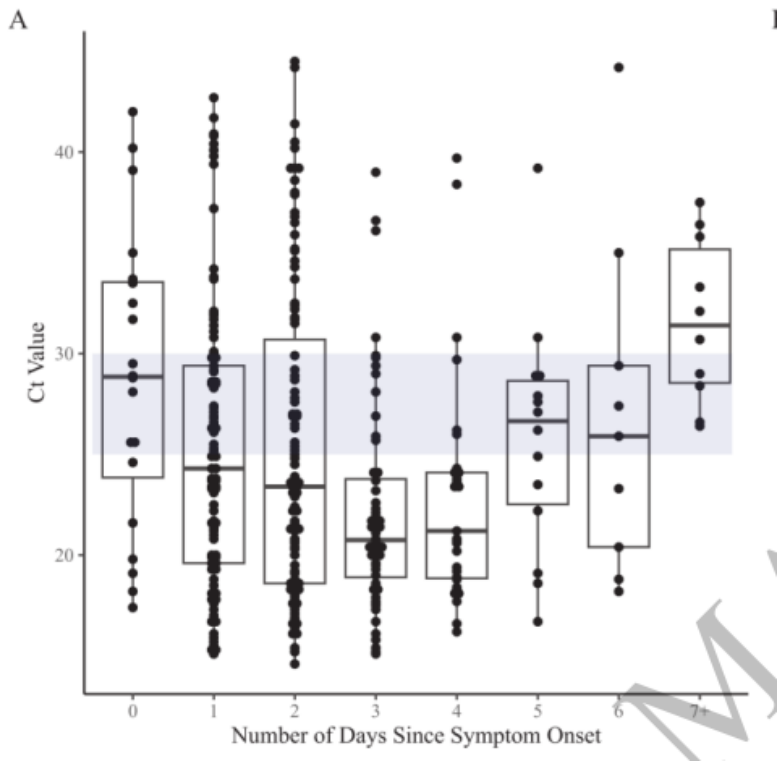
The New Normal: Delayed Peak SARS-CoV-2 Viral Loads Relative to Symptom Onset and Implications for COVID-19 Testing Programs Clin Infect Dis published online September 28, 2023

DOI: 10.1093/cid/ciad582

The investigators assessed SARS-CoV-2 and influenza A viral loads relative to symptom duration in symptomatic adults (>16y) presenting for testing in Georgia (4/2022-4/2023; Omicron variant predominant). Participants provided symptom duration and recent testing history. Nasal swabs were tested by Xpert Xpress SARS-CoV-2/Flu/RSV assay and Ct values recorded. Nucleoprotein concentrations in SARS-CoV-2 PCR-positive samples were measured by Single Molecule Array. To estimate hypothetical antigen rapid diagnostic test (Ag RDT) sensitivity on each day after symptom onset, percentages of individuals with Ct value.

Of 348 newly diagnosed SARS-CoV-2 PCR-positive individuals (65.5% women, median 39.2y), 317/348 (91.1%) had a history of vaccination, natural infection, or both. By both Ct value and antigen concentration measurements, median viral loads rose from the day of symptom onset and peaked on the fourth/fifth day. Ag RDT sensitivity estimates were 30.0 60.0% on the first day, 59.2-74.8% on the third day, and 80.0-93.3% on the fourth day of symptoms. In 74 influenza A PCR-positive individuals (55.4% women; median 35.0y), median influenza viral loads peaked on the second day of symptoms.

SARS-CoV-2



Comment: While there has been discussion that symptom onset might now be occurring earlier in the course of infection due to acquired immunity and/or Omicron, the current relationship between symptom duration and peak viral load in a highly immune population needs to be studied in detail to guide Ag RDT testing practice and duration of transmission. The investigators utilized PCR Ct values as a proxy for viral loads. They did not have enough participants to clearly evaluate the impact of varying forms of immunity (vaccine, prior infection, or both) on Ct value trends, but given that almost everyone presenting for testing in the study window had some known form of immunity, I think that their results are likely generalizable to the larger US population at this point in the pandemic.

Early in the pandemic, multiple studies showed that viral loads were highest at the time of symptom onset and then declined steadily thereafter. Now, in this highly immune population presenting after the early 2022 Omicron surge, their data suggest that viral loads appear to peak around four days after the onset of symptoms. In contrast, influenza A viral loads peaked soon after symptom onset. These findings have implications for ongoing use of Ag RDTs for Covid-19 and influenza.

Preinfection Neutralizing Antibodies, Omicron BA.5 Breakthrough Infection, and Long COVID: A Propensity Score-Matched Analysis J Infect Dis published online September 26, 2023

doi.org/10.1093/infdis/jiad317

The investigators conducted nested case-control analysis among tertiary hospital staff in Tokyo who donated blood samples in June 2022 (1 month before Omicron BA.5 wave), approximately 6 months after receiving a third dose of Covid-19 mRNA vaccine. They measured live virus-neutralizing antibody titers against wild type and Omicron BA.5, and anti–receptor-binding domain (RBD) antibody titers at preinfection, and compared them between cases (staff infected with Omicron) and propensity-matched controls. Among the breakthrough cases, they examined the association between preinfection antibody titers and incidence of long Covid.

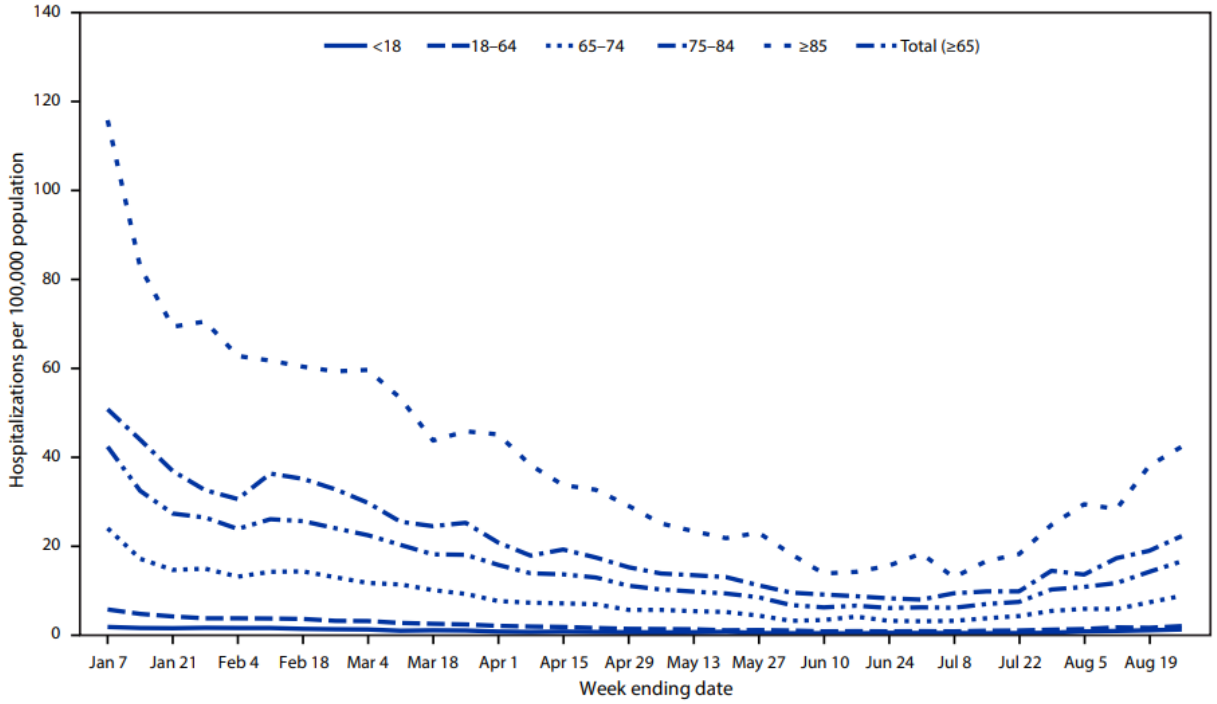
Preinfection anti-RBD and neutralizing antibody titers were lower in cases than controls. Neutralizing titers against wild type and Omicron BA.5 were 64% (95% confidence interval [CI], 42%–77%) and 72% (95% CI, 53%–83%) lower, respectively, in cases than controls. Individuals with previous Omicron BA.1/BA.2 infections were more frequent among controls than cases (10.3% vs 0.8%), and their Omicron BA.5 neutralizing titers were 12.8-fold higher than infection-naive individuals. Among cases, preinfection antibody titers were not associated with incidence of long Covid.

Comment: The preinfection neutralizing antibodies against Omicron BA.5 were lower in infected cases during the Omicron BA.5 wave than in the matched controls in this nested case-control study of a cohort of health care workers approximately 6 months after the third vaccination. The preinfection neutralizing capacity did not show material differences between the breakthrough cases who reported long Covid and those who did not suggesting that vaccine-induced immunity had no apparent protective role against post–Covid-19 symptoms. They did not conduct active surveillance to detect SARS-CoV-2 infection during the follow-up period. Data on virus strain were available for only 39% of the cases; however, the remaining cases of breakthrough infections were most likely due to the Omicron BA.5 variant, which accounted for more than 90% of sequenced Covid-19 samples in Japan during the follow-up (July to September 2022). Their results regarding long Covid symptoms cannot be applied to patients with severe symptoms, because all the included patients with Covid-19 had mild symptoms.

COVID-19–Associated Hospitalizations Among U.S. Adults Aged ≥65 Years — COVID-NET, 13 States, January–August 2023 MMWR 2023;72(40);1089–1094

Data from the COVID-19–Associated Hospitalization Surveillance Network (COVID-NET) were analyzed to estimate Covid-19–associated hospitalization rates during January– August 2023 and identify demographic and clinical characteristics of hospitalized patients aged ≥65 years during January–June 2023. COVID-NET conducts population-based surveillance for laboratory-confirmed Covid-19–associated hospitalizations among catchment area residents in 98 counties and across 13 US states. Covid-19–associated hospitalizations are defined as those among persons who have received a positive SARS-CoV-2 by PCR or rapid antigen detection test result during or within the 14 days preceding hospitalization.

Among adults aged ≥65 years, hospitalization rates more than doubled, from 6.8 per 100,000 during the week ending July 15 to 16.4 per 100,000 during the week ending August 26, 2023. Across all age groups, adults aged ≥65 years accounted for 62.9% (95% CI = 60.1%–65.7%) of Covid-19–associated hospitalizations, 61.3% (95% CI = 54.7%–67.6%) of ICU admissions, and 87.9% (95% CI = 80.5%–93.2%) of in-hospital deaths associated with Covid-19 hospitalizations. Most hospitalized adults aged ≥65 years (90.3%; 95% CI = 87.2%–92.8%) had multiple underlying conditions, and fewer than one quarter (23.5%; 95% CI = 19.5%–27.7%) had received the recommended Covid-19 bivalent vaccine.



Comment: Because adults aged ≥65 years remain at increased risk for Covid-19–associated hospitalization and severe outcomes, we need to advocate this age group should continue to focus on measures to prevent SARS-CoV-2 infection, including vaccination and promoting early treatment for persons who receive a positive SARS-CoV-2 test result to reduce their risk for severe Covid-19–associated outcomes. The COVID-NET catchment areas include approximately 10% of the US population; thus, these findings might not be nationally generalizable.

Editor's Choice

Serotonin reduction in post-acute sequelae of viral infection Cell 2023, 186, 1–17

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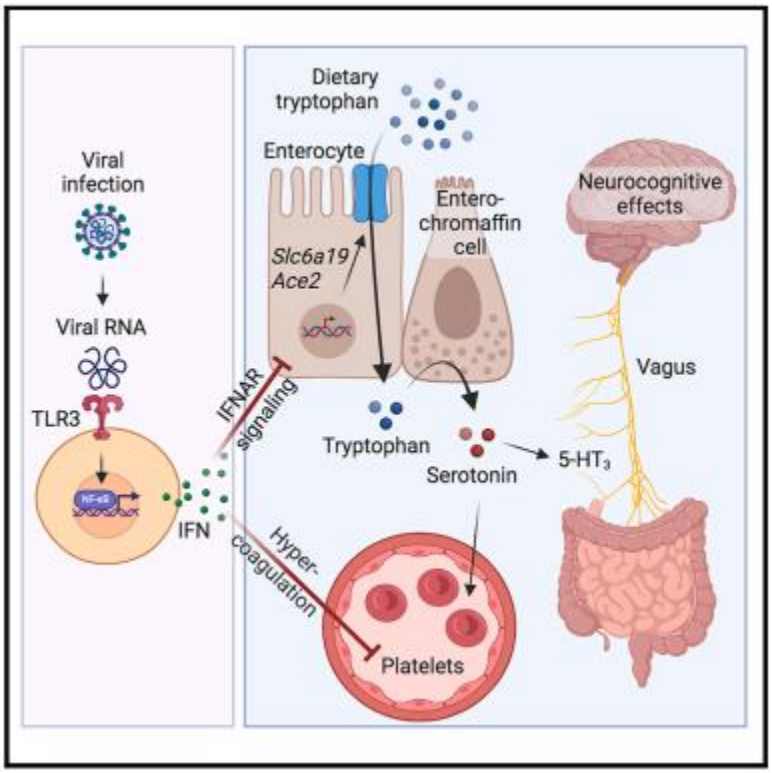
The investigators conducted a large-scale study using blood and stool samples from clinical studies and mouse models. The investigators propose a mechanism that links all four hypotheses in a single pathway and provides actionable insights for therapeutic interventions. They found that PASC (long Covid) are associated with serotonin reduction. Viral infection and type I interferon-driven inflammation reduce serotonin through three mechanisms: diminished

intestinal absorption of the serotonin precursor tryptophan; platelet hyperactivation and thrombocytopenia, which impacts serotonin storage; and enhanced MAO-mediated serotonin turnover. Peripheral serotonin reduction, in turn, impedes the activity of the vagus nerve and thereby impairs hippocampal responses and memory. Replenishing tryptophan or serotonin (through treatment with serotonin precursors or selective serotonin reuptake inhibitor [SSRI] antidepressants) in patients with neurocognitive long-Covid symptoms reversed memory loss in mice.



Comment: This is an elegant study that suggests that long Covid may be associated with reduced circulating serotonin levels. They demonstrated that serotonin depletion is driven by viral RNA-induced type I interferons (IFNs). IFNs can reduce serotonin through diminished tryptophan uptake and hypercoagulability. Peripheral serotonin deficiency can impair cognition via reduced vagal signaling. Tryptophan is a building block of neurotransmitters such as serotonin, a chemical messenger between nerve cells in the brain and body mainly generated in the gastrointestinal tract. (see above) Serotonin helps regulate memory, sleep, digestion, wound healing, and the vagus nerve, a neuronal system that helps the body and the brain communicate.

The investigators cautioned that this study was based on only a small number of patients. They did not demonstrate a direct connection between intestinal viral persistence and chronically elevated levels of type I interferons in humans, which would require collecting a large number of intestinal biopsies from Long Covid patients, however, their results call for the large-scale investigation of the causal connection between the presence of a viral reservoir in the gastrointestinal tract, sustained inflammatory responses, and manifestations of Long Covid.

Association Between Guillain-Barré Syndrome and COVID-19 Infection and Vaccination: A Population-Based Nested Case-Control Study Neurology published online October 18, 2023

DOI: 10.1212/WNL.0000000000207900

The investigators aimed to assess the association between GBS and both SARS-CoV-2 infection and Covid-19 vaccine. They conducted a nested-case control study in a cohort of 3,193,951 patients aged≥16 years, without a diagnosis of prior GBS, from the largest healthcare provider in Israel. Subjects were followed from January 1st, 2021, until June 30th, 2022, for the occurrence of GBS. Ten randomly selected controls were matched to each case of GBS on age and sex. They assessed both SARS-CoV-2 infection and Covid-19 vaccine administration in the prior 6 weeks in cases and controls.

Overall, 76 patients were diagnosed with GBS during follow-up and were matched to 760 controls. A positive test for SARS-CoV-2 was detected in 9 (11.8%) cases, and 18 (2.4%) controls. An administration of Covid-19 vaccine was detected in 8 (10.5%) cases (all Pfizer vaccine), and 136 (17.9%) controls (134 Pfizer vaccine). Multivariable conditional logistic regression models showed that the OR for GBS associated with SARS-CoV-2 infection and Covid-19 vaccine administration was 6.30 (95% CI 2.55-15.56) and 0.41 (95% CI 0.17-0.96), respectively. The results were similar when exposure to SARS-CoV-2 infection or Covid-19 vaccine administration were ascertained in the prior 4 and 8 weeks, although did not reach statistical significance for Covid-19 vaccine at 4 weeks.

Comment: This study suggests that SARS-CoV-2 infection is associated with increased risk of GBS, while Pfizer Covid-19 vaccine is associated with decreased risk of GBS. The study results may be reassuring to patients hesitant to receive Covid-19 vaccines. GBS is still extremely rare, but people should be aware that having a Covid-19 infection can increase their risk of developing the disorder, and receiving an mRNA vaccine can decrease this risk. Research on the risk of GBS and whether there is a vaccine association with an increase in the background risk of GBS needs to be conducted.

Long-term symptom profiles after COVID-19 vs other acute respiratory infections: an analysis of data from the COVIDENCE UK study eClinMed published October 6, 2023

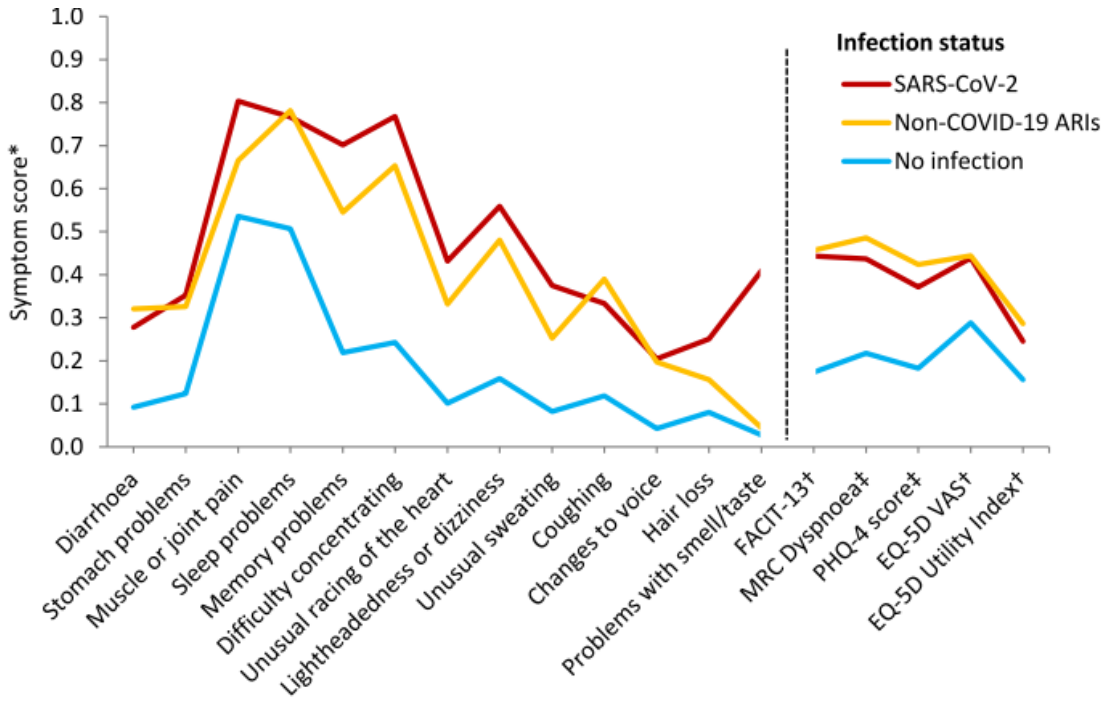
doi.org/10. 1016/j.eclinm.2023. 102251

Acute respiratory infections (ARIs) due to other pathogens other than Covid-19 may cause long-term symptoms, but few studies compare post-acute sequelae between SARS-CoV-2 and other ARIs. The investigators set out to compare symptom profiles between people with previous SARS-CoV-2 infection, people with previous non-Covid-19 ARIs, and contemporaneous controls, and to identify clusters of long-term symptoms.

They used COVIDENCE UK a prospective, population-based UK study of ARIs in adults. They analyzed data for 16 potential long Covid symptoms and health-related quality of life (HRQoL), reported between January 21 and February 15, 2021, by participants unvaccinated against

SARS-CoV-2. They classified participants as having previous SARS-CoV-2 infection or previous non-COVID-19 ARI (≥4 weeks prior) or no reported ARI. They compared symptoms by infection status using logistic and fractional regression and identified symptom clusters using latent class analysis (LCA). Long term symptoms were defined as new or ongoing symptoms more than 4 weeks after the acute infection. They assessed the prevalence or severity of 16 potential Covid-19 symptoms: coughing, problems with sleep, memory problems, difficulty concentrating, muscle or joint pain, problems with sense of taste or smell, diarrhea, stomach problems (abdominal pains), changes to voice, hair loss, unusual racing of the heart, lightheadedness or dizziness, unusual sweating, breathlessness, anxiety or depression, and fatigue. They also assessed health-related quality of life (HRQoL) using the EQ-5D-3L, which covers five dimensions of health—mobility, self-care, usual activities, pain or discomfort, and anxiety or depression.

The study included 10,171 participants (1311 [12.9%] with SARS-CoV-2 infection, 472 [4.6%] with non-Covid-19 ARI). Both types of infection were associated with increased prevalence/severity of most symptoms and decreased HRQoL compared with no infection. Participants with SARS-CoV-2 infection had increased odds of problems with taste/smell (odds ratio 19.74, 95% CI 10.53–37.00) and lightheadedness or dizziness (1.74, 1.18–2.56) compared with participants with non-Covid-19 ARIs. Separate LCA models identified three symptom severity groups for each infection type. In the most severe groups (representing 22% of participants for both SARS-CoV-2 and non-COVID-19 ARI), SARS-CoV-2 infection presented with a higher probability of problems with taste/smell (probability 0.41 vs 0.04), hair loss (0.25 vs 0.16), unusual sweating (0.38 vs 0.25), unusual racing of the heart (0.43 vs 0.33), and memory problems (0.70 vs 0.55) than non-COVID-19 ARI.



Comment: The long-term symptoms experienced by some people with previous ARIs, including SARS-CoV-2, highlight the need to improve understanding on diagnosis, and treatment of postacute infection syndromes. As much-needed research into long Covid continues, we must take the opportunity to investigate and consider the post-acute burden of ARIs due to other

pathogens. As other studies have shown, taste and smell as well as memory problems seem to be associated more with Covid. They focused on symptoms for each individual at a single timepoint, and thus could not map the change in each participant's symptoms over time with repeated measures. They did not adjust for pre-Covid-19 symptom burden, as few participants had these data available, meaning that they could not know whether participants with previous infections had a higher baseline symptom burden than those without. Their findings are restricted to unvaccinated patients infected with either the wild-type or alpha strains of SARS-CoV-2. However, 29% of people in the UK reporting long Covid were infected with the wild-type strain, which dominated before the vaccination rollout in the UK, showing that participants represent an important and substantial subgroup with long-lasting symptoms. COVIDENCE UK is a self-selected cohort, and so certain groups—such as women, older age groups, and White ethnicity—are over-represented in our study, potentially limiting the generalizability of their results. Lastly, they defined long term symptoms as new or ongoing symptoms more than 4 weeks after the acute infection. Some have used more than 3 months to define long Covid.