ID WATCH

by Ed Septimus, MD

Editor's Choice

7 vs. 14 days of Antibiotic Treatment for Patients with Bloodstream Infections: The BALANCE Trial.

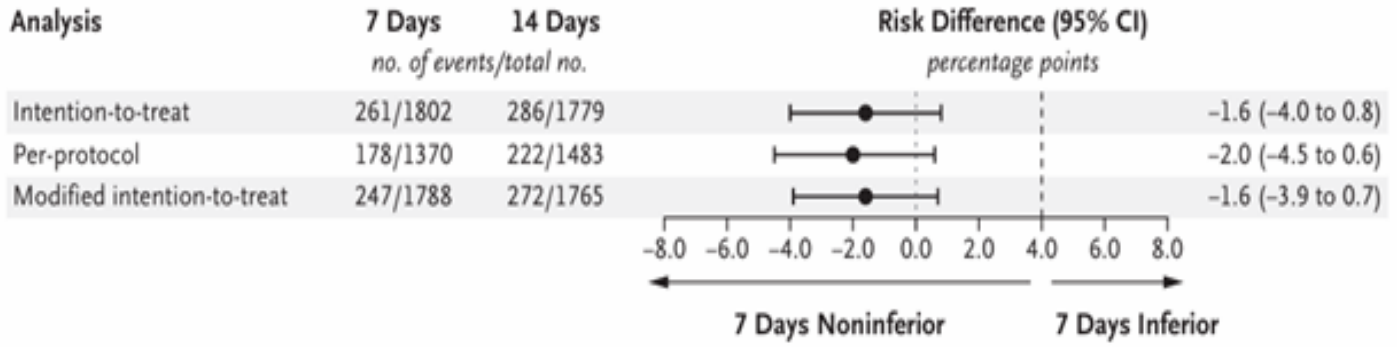
The New England Journal of Medicine published November 20, 2024
DOI: 10.1056/NEJMoa2404991

This was a multicenter, noninferiority trial involving 74 hospitals in seven countries. The investigators randomly assigned hospitalized patients (including patients in the intensive care unit [ICU]) who had a bloodstream infection (BSI) to receive antibiotic treatment for 7 days or 14 days. Antibiotic selection, dosing, and route were at the discretion of the treating team. They excluded patients with severe immunosuppression, (i.e., had neutropenia or were receiving immunosuppressive treatment after solid-organ transplantation or hematopoietic stem-cell transplantation), had prosthetic heart valves or endovascular grafts, had a documented or suspected infectious syndrome for which prolonged treatment was necessary (e.g. endocarditis, osteomyelitis, septic arthritis, undrained abscess, or unremoved prosthetic infection), foci requiring prolonged treatment, single cultures with possible contaminants, fungemia,or cultures yielding S aureus. The primary outcome was death from any cause by 90 days after diagnosis of the BSI, with a noninferiority margin of 4 percentage points.

3608 patients underwent randomization and were included in the intention-to-treat analysis; 1814 patients were assigned to 7 days of antibiotic treatment, and 1794 to 14 days. At enrollment, 55.0% of patients were in the ICU and 45.0% were in hospital wards. Infections were acquired in the community (75.4%), hospital wards (13.4%) and ICUs (11.2%). Bacteremia mostly originated from

the urinary tract (42.2%), abdomen (18.8%), lung (13.0%), vascular catheters (6.3%), and skin or soft tissue (5.2%). E coli, Klebsiella species, and Enterococcal species were the most pathogen in that order. By 90 days, 261 patients (14.5%) receiving antibiotics for 7 days had died and 286 patients (16.1%) receiving antibiotics for 14 days had died (difference, −1.6 percentage points [95.7% confidence interval {CI}, −4.0 to 0.8]), which showed the noninferiority of the shorter treatment duration. Per-protocol analysis also showed noninferiority (difference, −2.0 per centage points [95% CI, −4.5 to 0.6]). These findings were generally consistent across secondary clinical outcomes and across prespecified subgroups defined according to patient, pathogen, and syndrome characteristics.

C. difficile infections and infection or colonization with antimicrobial-resistant organisms were infrequent in this trial. Late C. difficile infections could have been missed if patients were treated in the ambulatory setting or readmitted to other facilities. Their approach to measuring antimicrobial-resistant organisms relied on routinely collected specimens rather than active surveillance. In addition, confidence intervals around the estimates of the treatment effect were wide, and therefore their data do not preclude the possibility of clinically important differences in these outcomes attributable to shorter or longer durations of antibiotic treatment.



Dr. Septimus's Annotations

Evidence to support shorter antibiotic regimens for patients with BSIs is growing. Before this trial three well-conducted, smaller, randomized, clinical trials have compared 7 days and 14 days of treatment in patients with bloodstream infection. [Clin Infect Dis 2019;69:1091-8; JAMA 2020;323:2160-9; Clin Microbiol Infect 2022;28:550-7] All three trials showed noninferiority of the shorter, 7-day duration of treatment. Their numbers were smaller and they used larger noninferiority margins (10 percentage points). In this randomized trial conducted in seven countries, investigators compared 7-day and 14-day antibiotic regimens in 3600 hospitalized patients with BSIs. About half the patients were in intensive care units, and more than 70 pathogens were represented. However, patients with S aureus or fungal BSIs were excluded, as were patients with severe immune compromise and prosthetic heart valves. Seven-day treatment was noninferior to 14-day for the primary outcome of 90-day mortality (14.5% vs. 16.1%). The length of stay was slightly but significantly shorter in the 7-day group.

BOTTOM LINE

There is a growing body of literature that supports the safety and efficacy of a shorter duration of antibiotic treatment for bloodstream infections. However, keep in mind that several high-risk patient groups (as noted above) were excluded from this study. This is another study which supports a shorter duration of therapy (7d vs 14d) for most patients with bloodstream infections.

2

Oral Versus Intravenous Antibiotic Therapy for *Staphylococcus aureus* Bacteremia or Endocarditis: A Systematic Review and Meta-Analysis of Randomized, Controlled Trials.

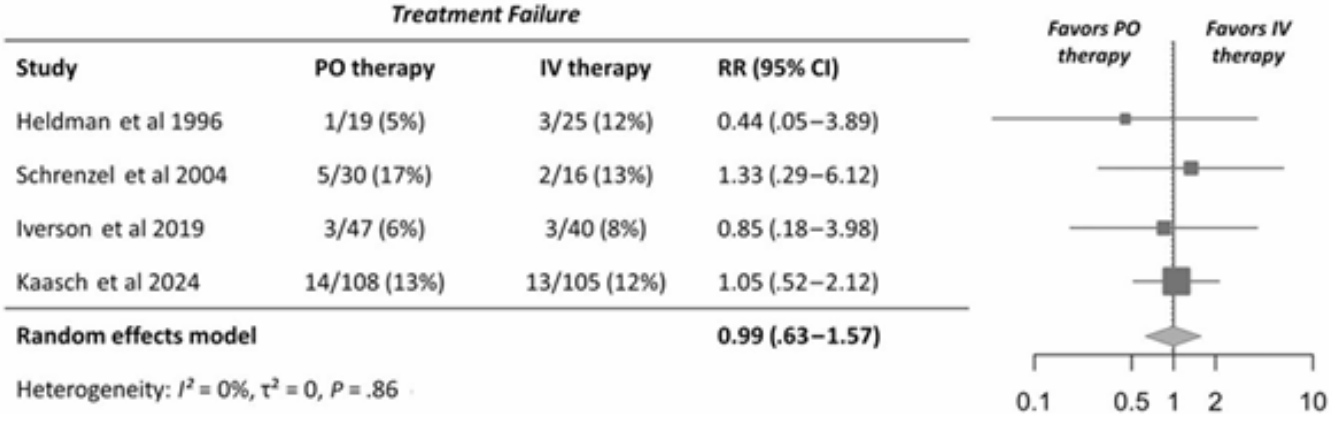
Clinical Infectious Diseases published online September 18, 2024
DOI: 10.1093/cid/ciae476

The question is for patients with bacteremia or endocarditis caused by S. *aureus*, what is the efficacy and safety of oral (or transition to oral) antibiotic therapy compared with all-intravenous therapy? To address this question the investigators conducted a systematic review of randomized, controlled trials (RCTs) to generate more precise estimates of the efficacy and safety of oral versus intravenous antibiotic therapy for S *aureus* bacteremia or endocarditis. They searched MEDLINE, Embase, the Cochrane Library, and Web of Science databases through February 2024. RCTs were included if they compared oral versus intravenous antibiotic therapy for S. *aureus* bacteremia or endocarditis and appropriately reported outcomes for each group. Risk of bias was assessed using the revised Cochrane tool for assessing risk of bias in randomized trials. Heterogeneity between studies was evaluated with Cochran's Q-statistic and I2 test. Treatment effects were summarized with pooled risk ratios using a random effects model meta-analysis.

Only four RCTs met criteria for inclusion in meta-analysis. Among participants assessed for treatment failure, there was no difference between oral and intravenous therapy groups (risk ratio [RR], 0.99; 95% confidence interval [CI], .63– 1.57; I2 = 0%). There was also no significant difference in adverse events between oral and intravenous therapy groups (RR, 0.65; 95% CI, .07–5.94; I2 = 74%); however, the confidence interval was wide, and heterogeneity was high.

		Participants With SAB/IE in Oral Therapy Arm			Participants With SAB/IE in Intravenous Therapy Arm		
Author	Total Participants Randomized	Total	MSSA	MRSA	Total	MSSA	MRSA
Heldman et al	93[a]	44	42	2	43	40	3
Schrenzel et al	130	30[b]	Unknown	Unknown	16[b]	Unknown	Unknown
Iversen et al	400	47	47	0	40	40	0
Kaasch at al	213	108	102	6	105	95	10

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; SAB/IE, *Staphylococcus aureus* bacteremia or infective endocarditis.
[a]Eighty-seven of 93 participants had SAB/IE, and 6 participants had coagulase-negative *Staphylococcus*; however, outcomes are not defined separately.
[b]Participants with catheter-related SAB or primary bacteremia; includes only clinically evaluable population that completed follow-up; intention-to-treat population not available.



Dr. Septimus's Annotations

This analysis of the four RCTs that met eligibility identified three key findings:

1. There is a dearth of high-quality evidence and reporting of oral versus intravenous therapy for the treatment of S. *aureus* bacteremia or endocarditis;
2. For a select group of patients, there is likely no difference in treatment failure in participants transitioned to oral therapy versus those who received all-intravenous therapy; and
3. There is also likely no difference in adverse events between these participants.

The available randomized trials and variability in disease states among the participants included across them (i.e., uncomplicated S. *aureus* bacteremia, right-sided endocarditis, and left-sided endocarditis) make definitive conclusions on the treatment effect difficult to accurately assess. A large portion of evidence for the use of oral therapy for S. *aureus* bacteremia or endocarditis has stemmed from observational studies. [OFID 2020; 7: ofaa151; Clin Infect Dis 2023; 77:672–9] These studies are limited by significant biases, such as confounding by indication (or contraindication). Few RCTs have focused on answering this question in such a manner that outcomes of participants transitioned to highly bioavailable oral agents for S. *aureus* bacteremia or endocarditis can be separately assessed and compared with those who received all-intravenous therapy. Additionally, S. *aureus* bacteremia is a disease with highly variable clinical manifestations that alter treatment strategies to a degree that randomizing these participants into conventional clinical trials often proves challenging.

Despite these weaknesses, in this meta-analysis, their findings contribute to the growing body of evidence in two important aspects. First, they demonstrate that among the more rigorously conducted and reported RCTs, and in a select group of patients, transitioning to oral therapy is as effective and safe as intravenous therapy. Second, their findings provide more robust and precise estimates of these effects, which have previously been limited by smaller sample sizes. However, the generalizability of these treatment effects is limited, and additional RCTs will be needed to confirm these findings.

BOTTOM LINE

In this systematic review of RCTs comparing oral with intravenous antibiotic therapy for S. *aureus* bacteremia or endocarditis, few studies met the eligibility criteria for inclusion. Meta-analysis of these studies suggests that transitioning from intravenous to oral therapy is likely effective in a subgroup of carefully selected patients. Additional randomized trials are necessary before transition to oral therapy can be routinely recommended.

3

Perioperative Antibiotic Prophylaxis Duration in Patients Undergoing Cystectomy With Urinary Diversion A Randomized Clinical Trial.

JAMA Network Open. 2024;7(10): e2439382.
DOI: 10.1001/jamanetworkopen.2024.39382

The purpose of this trial was to establish noninferiority of 24-hour perioperative antibiotic prophylaxis (PAP) vs extended-duration PAP in preventing surgical site infections (SSIs) within 90 days after cystectomy with urinary diversion. This was single center, noninferiority randomized clinical trial in patients aged older than 18 years undergoing elective open cystectomy with urinary diversion. Exclusion criteria were contraindications to administered drugs and inability to follow study procedures. PAP administered for 24 hours (24-hour PAP group) was compared to PAP administered until all catheters and stents were removed (extended PAP group). The primary end point was the rate of SSI, and the secondary end points included all-cause mortality, both within 90 days after surgery. Noninferiority of the 24-hour PAP treatment was assessed by comparing the 90% CI (corresponding to a significance level of $\alpha = .05$) with the predefined noninferiority margin of 10%. The

investigators selected a combination of tobramycin, metronidazole, and amoxicillin-clavulanate (with vancomycin instead of amoxicillin-clavulanate if patients were allergic to penicillin or β-lactam antibiotics).

A total of 95 patients were randomly assigned to the 24-hour PAP group (median [IQR] age, 69.3 [63.1-76.8] years; 66 males [69.5%]) and 98 to the extended PAP group (median [IQR] age, 69.5 [60.8-75.5] years; 68 males [69.4%]). Patients in the 24-hour PAP group received PAP for a median of 1 day (IQR, 1-1 day), and patients in the extended PAP group received PAP for a median of 8 days (IQR, 7-10 days). No significant differences in SSIs occurring within 90 days were found (24-hour PAP group, 8 patients [8.4%]; extended PAP group, 12 patients [12.2%]; P = .53). The risk difference for 90-day cumulative SSI incidence was -3.8% (90% CI, -11.1% to 3.4%), establishing noninferiority of 24-hour PAP vs extended PAP to prevent SSI. Mortality was not significantly different between groups.

Table 2. SSIs and Death

Variable	24-h PAP (n = 95)	Extended PAP (n = 98)	P value
Summary measures			
Any SSI during follow-up, No. (%; 95% CI)	8 (8.4; 95% CI, 3.7-15.9)	12 (12.2; 95% CI, 6.5-20.4)	.53
Type of SSI, No. (%)			
Superficial	5 (5.3)	4 (4.1)	.43
Deep	2 (2.1)	5 (5.1)	
Organ or space	1 (1.1)	3 (3.1)	
Time after surgery to SSI, median (IQR), d	11 (8-22)	14 (8-23)	.76
PAP duration, median (IQR), d	1 (1-1)	8 (7-10)	<.001
Length of hospital stay, median (IQR), d	15 (12-17)	15 (12-17)	.40
Length of hospital stay with SSI, median (IQR), d	19 (17-30)	22 (14-30)	.87
Death during follow-up, No. (%; 95% CI)	6 (6.3; 95% CI, 2.4-13.2)	5 (5.1; 95% CI, 1.7-11.5)	.96
Cause of death, No. (%)			
Unclear, after discharge	1 (11.7)	3 (60.0)	NA
Respiratory failure and/or cardiac arrest	2 (33.3)	1 (20.0)	
Tumor progression	3 (50.0)	1 (20.0)	
Competing-risk regression, HR (95% CI)			
SSI[a]	0.68 (0.28-1.64)	1 [Reference]	.39
Death	1.29 (0.35-4.75)	1 [Reference]	.70

Abbreviations: HR, hazard ratio; NA, not applicable; PAP, perioperative antibiotic prophylaxis; SSI, surgical site infection.

[a] For the primary outcome of SSI, the risk difference (90-day cumulative incidence) between 24-hour PAP and extended PAP was −3.8% (90% CI, −11.1% to 3.4%), establishing noninferiority at a margin of 10.0%.

Dr. Septimus's Annotations

Historically, patients undergoing cystectomy and urinary diversion received extended courses of intravenous antibiotics given the high rate of infectious complications. However, based on studies from other clean-contaminated open abdominal surgical procedures, perioperative antibiotic practices for cystectomy now recommend a shorter perioperative antibiotic duration. [Eur Urol Focus. 2023;9(4):631-636] The American Urological Association (AUA) guidelines, now recommend single-dose cefazolin for cystectomy with small-bowel urinary diversion (alternative agents include single-dose clindamycin and aminoglycoside, second-generation cephalosporin, or aminopenicillin and β-lactamase inhibitor and metronidazole). [J Urol. 2020;203(2):351-356] The European Association of Urology makes no recommendations for specific agents or duration of perioperative antibiotics for cystectomy and leaves the decision to the clinician. [European Association of Urology. Urological infections: guidelines. 2024. https://uroweb.org/guidelines/urological-infections] Due to the lack of high-quality randomized data to support optimal duration of antibiotic prophylaxis for cystectomy many surgeons still administer PAP for greater than 24 hours. The current randomized clinical trial supports the recommendation for shorter course prophylaxis. A recent retrospective study of a database of patients undergoing robotic-assisted radical cystectomy at a single institution compared AUA guideline recommendations of single-dose cephalosporin

for perioperative antibiotic prophylaxis with a modified protocol based on the hospital's antibiogram (ampicillin-sulbactam, gentamicin, and fluconazole for 24 hours). [Eur Urol Focus. Published online October 12, 2023] The study found that patients who received the antibiogram-based prophylaxis protocol had significantly lower rates of urinary tract infection (UTIs) and SSIs at 30 days compared with those who received the single-dose cephalosporin. Unfortunately, the 2 groups received different durations of antibiotics, leaving the question of single-dose vs 24 hours of antibiotics unanswered. Regardless, this study supports a patient-specific and population-specific perioperative antibiotic prophylaxis protocol for cystectomy, which I believe may provide the best means of infection prevention while selecting the narrowest antibiotic coverage based on local susceptibilities. In addition, in the current study the investigators inclusion and focus on asymptomatic bacteriuria (ABU) in this study is questionable. ABU is expected following urinary diversion. It is unclear why urine cultures were routinely obtained postoperatively. In addition, the investigators state that although neither specified nor recommended by the protocol, antibiotic treatments for asymptomatic bacteriuria were prescribed at the discretion of the treating practitioner at their institution. There was no significant difference in rates of febrile UTIs between the 24-hour and extended prophylaxis groups, despite the higher rate of asymptomatic bacteriuria in the 24-hour prophylaxis group. This supports the well-recognized recommendation to refrain from treatment of asymptomatic bacteriuria. [Clin Infect Dis. 2019; 68: e83–e110]

"Based on current evidence, patients undergoing cystectomy with urinary diversion should receive perioperative antibiotic prophylaxis for 24 hours or less, because longer courses have not been shown to provide additional benefit and are associated with increasing adverse events."

BOTTOM LINE

Based on current evidence, patients undergoing cystectomy with urinary diversion should receive perioperative antibiotic prophylaxis for 24 hours or less, because longer courses have not been shown to provide additional benefit and are associated with increasing adverse events. I want to emphasize that routine postoperative urine cultures and treatment of asymptomatic bacteriuria are not recommended unless infectious signs and symptoms are present.

4 CDC Report Mycoplasma pneumoniae on the Rise: CDC: "Mycoplasma pneumoniae Infection Surveillance and Trends," "Clinical Features of Mycoplasma pneumoniae Infection."

Young children are increasingly infected with Mycoplasma pneumoniae sometimes called walking pneumonia. A hallmark symptom is a cough that starts out dry but eventually produces moderate amounts of thick, non-bloody mucus. The cough can last for weeks. It's an unexpected trend, since Mycoplasma pneumoniae was so uncommon during the height of the Covid-19 pandemic that one medical journal ran an article suggesting that it may be gone forever. And the increase in illnesses among young children is also unusual, since documented cases usually occur among school-age kids or adolescents. Mycoplasma pneumoniae typically causes respiratory tract infections and can cause damage to the pharynx, trachea, and lungs. Most illnesses are mild, starting with a fever, sore throat, and cough and evolving into what may be viewed as a chest cold. The symptom onset is very gradual.

The CDC issued an alert about the bacteria after noticing an increase in emergency room data listing Mycoplasma pneumonia as a diagnosis. The increase was first detected in the spring, and cases appear to have peaked in August but remain elevated. The most surprising increase was seen among 2- to 4-year-olds, but a sizable jump was also recorded among 5- to 17-year-olds.

The bacteria spread through respiratory droplets, such as from a cough or sneeze. The long incubation period (1-4 weeks) makes the bacteria prone to causing outbreaks, such as in-residence halls, schools, and nursing homes. Coughing symptoms often last a long time, as well.

Dr. Septimus's Annotations

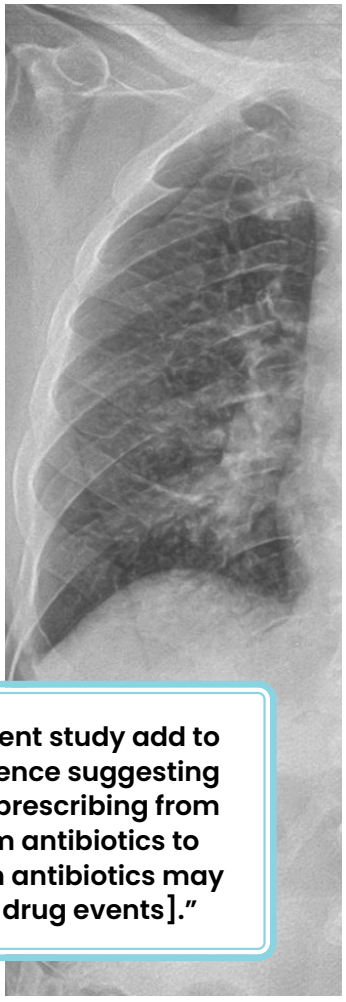
A nasal or throat swab for PCR can test for bacteria, but this test is not as commonly offered by labs as the tests for influenza, Covid-19, and RSV. A chest x-ray can be obtained to check for pneumonia. About 10% of people go on to develop a true case of pneumonia. Doxycycline is preferred over azithromycin due to increasing reports of macrolide-resistant strains and better outcomes with tetracyclines. [BMC Infect Dis 2021; 21:1003] Levofloxacin is an alternative regiment. Doxycycline can be safely administered for durations <21 days regardless of age. [AAP Red Book]

5

Comparative safety of different antibiotic regimens for the treatment of outpatient community-acquired pneumonia among otherwise healthy adults

Clinical Infectious Diseases published online October 23, 2024
DOI: 10.1093/cid/ciae519

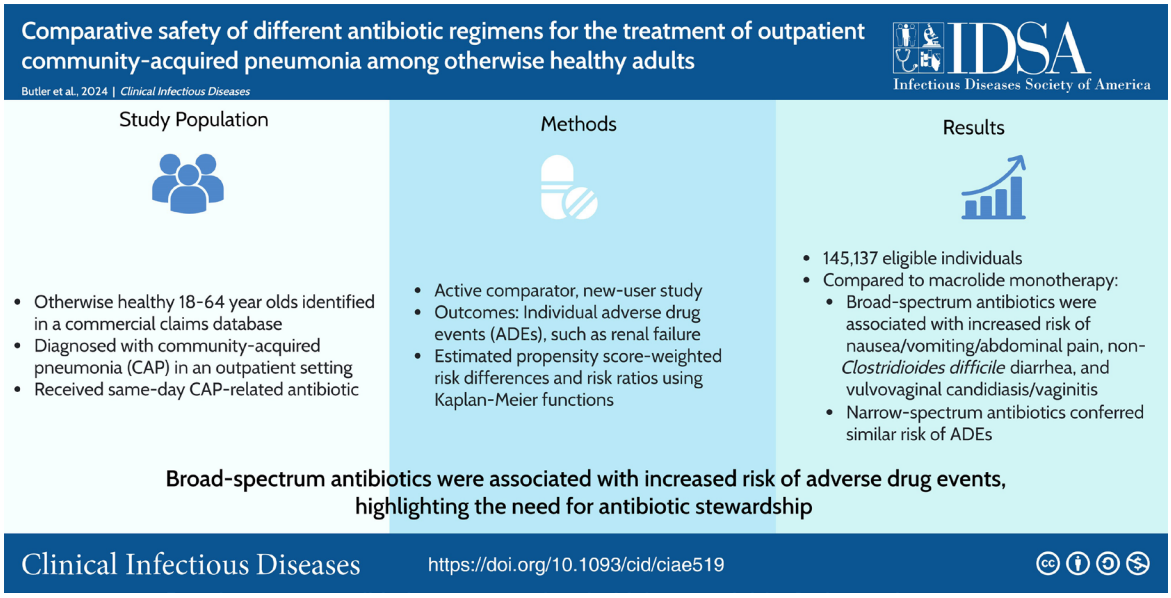
The investigators set out to compare the risk of adverse drug events (ADEs) associated with antibiotic regimens for CAP treatment among otherwise healthy, non-elderly adults. They conducted an active comparator new-user cohort study (2007-2019) of commercially-insured adults 18–64 years diagnosed with outpatient CAP, evaluated via chest x ray, and dispensed a same-day CAP-related oral antibiotic regimen. ADE follow-up duration ranged from 2–90 days (e.g., renal failure [14 days]). They estimated risk differences [RD] per 100 treatment episodes and risk ratios using propensity score weighted Kaplan-Meier functions. Ankle/knee sprain and influenza vaccination served as negative control outcomes. They did not include amoxicillin monotherapy in the primary analysis, as this new recommendation from the 2019 guidelines occurred very late in the study period. [Am J Respir Crit Care Med. 2019;200(7): e45 e67] They used ICD-9-CM and ICD-10-CM diagnosis codes to identify individual ADE outcomes. Potential confounders of the association between antibiotic exposure and ADE outcomes were identified a priori based on clinical knowledge. The following patient- and provider-level characteristics were assessed at index: age, sex, geographic region, health insurance plan type, urban residence, calendar month, calendar year, provider specialty, provider outpatient location (i.e., office, emergency department, urgent care center), and ceftriaxone administration on the date of CAP diagnosis (since CAP patients frequently receive a one-time dose of IV ceftriaxone). The presence of baseline emergency department encounters, number of physician office visits (0, 1, 2, 3+), were assessed during the 180-day baseline period.



"Results of the present study add to accumulating evidence suggesting that efforts to shift prescribing from broader-spectrum antibiotics to narrower-spectrum antibiotics may prevent [adverse drug events]."

Of 145,137 otherwise healthy CAP patients without comorbidities, 52% received narrow spectrum regimens (44% macrolide, 8% doxycycline) and 48% received broad-spectrum regimens (39% fluoroquinolone, 7% β-lactam, 3% β-lactam + macrolide). Compared to macrolide monotherapy, each broad-

spectrum antibiotic regimen was associated with increased risk of several ADEs (e.g., β-lactam: nausea/vomiting/abdominal pain [RD per 100, 0.32; 95% CI, 0.10 0.57]; non-Clostridioides difficile diarrhea [RD per 100, 0.46; 95% CI, 0.25–0.68]; vulvovaginal candidiasis/vaginitis [RD per 100, 0.36; 95% CI, 0.09–0.69]).



Dr. Septimus's Annotations

Broad-spectrum antibiotics were associated with increased risk of ADEs among otherwise healthy adults treated for CAP in the outpatient setting. Their findings are consistent with previous studies that broader spectrum antibiotic regimens for common outpatient conditions are associated with increased risks of adverse effects in both adults and children. [JAMA Network Open. May 2, 2022;5(5): e2214153] Results of the present study add to accumulating evidence suggesting that efforts to shift prescribing from broader-spectrum antibiotics to narrower-spectrum antibiotics may prevent ADEs. Unlike the 2007 guidelines, the updated 2019 guidelines give a strong recommendation for routine use of doxycycline, based on limited data, mostly involving small numbers of patients. [Am J Respir Crit Care Med. 2019;200(7): e45 e67] The current study findings of similar risk of ADEs compared to macrolide monotherapy support the safety of doxycycline for treatment of outpatient CAP. Doxycycline is also associated with reduced risk of C. difficile infection Additionally; the updated guidelines newly recommend amoxicillin monotherapy.

This study inclusion was based on diagnosis codes for pneumonia that have not been validated in the outpatient setting. Antibiotic exposure was based on pharmacy-dispensing billing claims. While this is the gold standard of prescription drug ascertainment, information on adherence was not available. Claims-based algorithms to identify ADEs have not been validated. This study was restricted to otherwise healthy, commercially insured adults aged 18-64 years; thus, results may not be generalizable to other populations such as adults with comorbidities who may be at increased risk for ADEs due to underlying health conditions or drug interactions.

BOTTOM LINE

Among healthy, non-elderly adults treated for community acquired pneumonia in the outpatient setting, each broad-spectrum antibiotic regimen was associated with increased risk of adverse drug events versus macrolide monotherapy. Risk was generally similar between narrow-spectrum antibiotic regimens (doxycycline, macrolide monotherapy). Antimicrobial stewardship is needed to promote judicious use of broad-spectrum antibiotics and ultimately decrease antibiotic related adverse drug events (ADEs) in the outpatient setting.

6

Empirical antibiotic therapy for sepsis: save the anaerobic microbiota

The Lancet: Respiratory Medicine published online October 11, 2024
DOI: 10.1016/ S2213-2600(24)00257-1

Key points:

- Although anaerobes are infrequently the causative pathogen in sepsis, patients with sepsis often receive antibiotic treatment that covers anaerobic bacteria.
- Most antibiotics decrease gut microbiome diversity and deplete obligate anaerobic commensals, but important differences between antibiotics exist.
- Depletion of obligate anaerobic gut bacteria might result in intestinal pathogen overgrowth and subsequent systemic translocation, diminished systemic immune responses, and an increased risk of nosocomial infections.
- Observational cohort studies have suggested that exposure to anti-anaerobic antibiotics in patients with sepsis in the ED and ICU is associated with increased mortality.
- Reducing the unnecessary usage of anti-anaerobic antibiotics and saving anaerobic gut microbiota might improve sepsis outcomes.

Figure 1

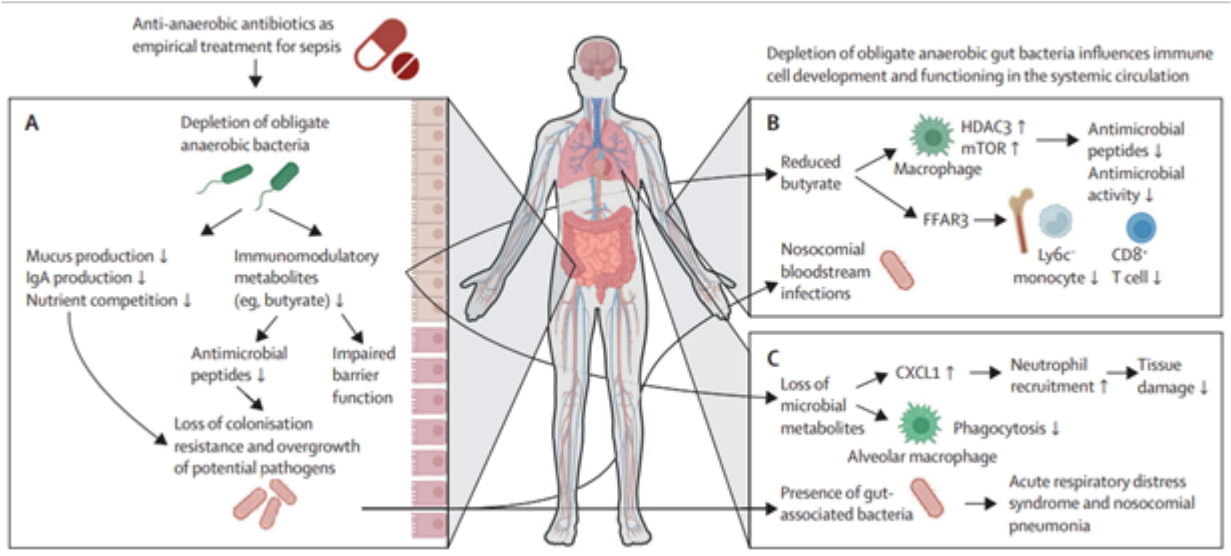
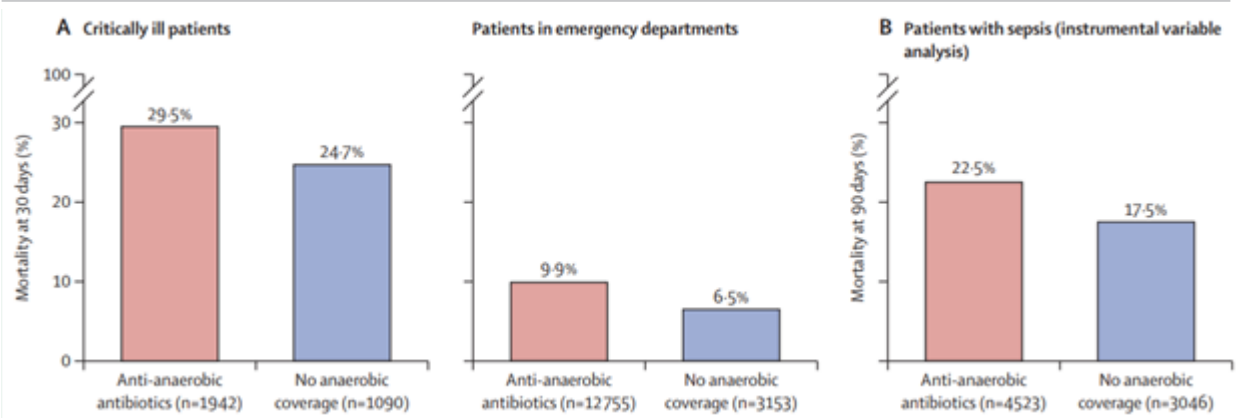


Figure 2



Dr. Septimus's Annotations

Antibiotics often decrease gut microbiome diversity and deplete obligate anaerobic commensals (e.g., Lachnospiraceae and Ruminococcaceae families, and Bacteroidetes), which produce health-associated metabolites, such as butyrate. [N Engl J Med 2016; 375: 2369–79] Depletion of this normal flora opens nutritional niches and allows for the overgrowth of potentially pathogenic bacteria, such as Enterococcus and Enterobacteriaceae. [Nat Rev Microbiol 2023; 21: 772–88] Depletion of obligate anaerobic commensals by antianaerobic treatment might increase sepsis severity through multiple mechanisms (figure 1 above). Obligate anaerobes result provides colonization resistance against possibly harmful (mostly aerobic) microorganisms through competition for nutrients, maintenance of the anaerobic environment, production of the short-chain fatty acid butyrate, and enhancement of immunoglobulin-A production. [Nat Rev Immunol 2024; 24: 577–95] Butyrate serves as the main energy source of enterocytes, thereby ensuring intestinal barrier function and preventing systemic translocation of pathogens. Loss of anaerobic commensals results in expansion of Enterococcus and Enterobacteriaceae, which is associated with adverse sepsis outcomes. [Lancet Gastroenterol Hepatol 2017; 2: 135–43] In the past 2 years, the observation that anti-anaerobic antibiotics were associated with worse outcomes after stem-cell transplantation was expanded to patients with suspected infections (figure 2 above). In 3032 mechanically ventilated patients treated with intravenous antibiotics, early anti-anaerobic antibiotics (within 72 h of mechanical ventilation initiation) were associated with higher 30-day mortality, increased frequency of ventilator-associated pneumonia caused by Enterobacteriaceae, and fatal Enterobacteriaceae infections (29.0% vs 3.0% of all fatal infections). [Eur Respir J 2023; 61: 2200910]

A recent retrospective cohort study compared piperacillin–tazobactam versus cefepime— both combined with intravenous vancomycin, for empirical treatment for undifferentiated sepsis. Among 7569 patients who did not have clear indications for anti-anaerobic coverage (e.g., necrotizing, intra-abdominal, or head and neck infections) piperacillin–tazobactam was associated with a 2·6% increase in 90-day mortality in unadjusted analysis and a 5% increase in the instrumental variable analysis. [reviewed in December 2023 ID Watch] [JAMA Intern Med 2024; 184: 769–77]

BOTTOM LINE

In summary, obligate anaerobic gut bacteria provide direct and indirect mechanisms that protect against pathogen overgrowth and subsequent systemic translocation of pathogens, and enhance immune responses in distant organs. In empiric therapy for sepsis, coverage of anaerobic bacteria is often unnecessary, and accumulating evidence shows that the depletion of anaerobic gut commensals results in intestinal pathogen overgrowth, diminished systemic immune responses, and a subsequent increased risk of nosocomial infections, ARDS, and mortality.

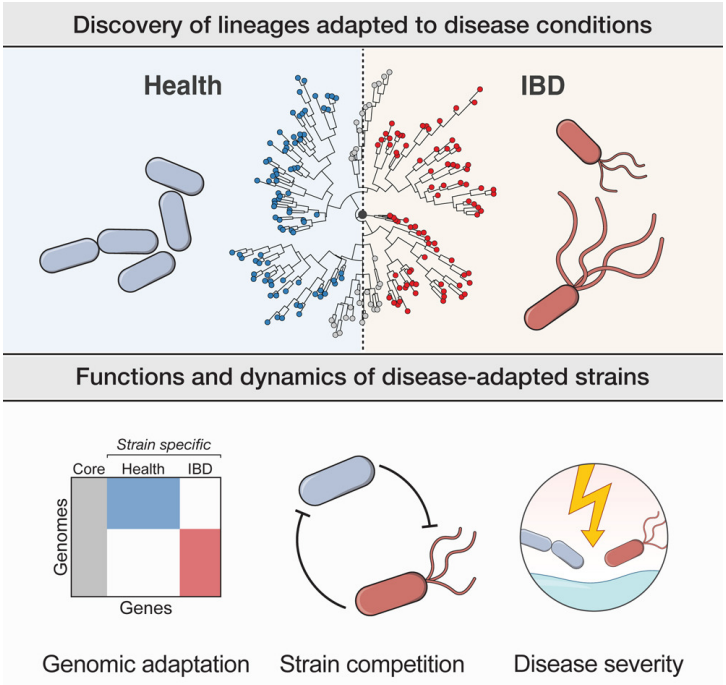
Discovery of disease-adapted bacterial lineages in inflammatory bowel diseases

Cell Host & Microbe published July 10, 2024, Volume 32, Issue 7, p1147-1162.e12
DOI: 10.1016/j.chom.2024.05.022

The recent availability of fecal metagenomes from thousands of individuals in health and inflammatory bowel disease (IBD) enables large-scale evolutionary analyses to map the bacterial strains that underlie inflammation. To this end, the investigators leveraged a vast resource of 6,138 metagenomes to infer 142,022 strain genotypes within 822 people with IBD and 1,257 non-IBD controls. By analyzing stool samples from individual IBD patients over time, the investigators found that these disease-associated strains outcompeted their healthy counterparts during bouts of heightened inflammation, implying that they had acquired genetic changes granting them a survival advantage during IBD. They looked at genetic

differences in the disease-associated strains (compared with health-associated strains) mapped to known aspects of inflammation, including oxidative stress, nutrient synthesis and immune system evasion. They also found that the loss of health-associated strains predicted higher fecal levels of calprotectin, a marker of inflammation severity including the loss of health-associated strains of Eggerthella lenta was predictive of fecal calprotectin a biomarker of disease severity.

Dr. Septimus's Annotations



Disruptions to the human gut microbiota are associated with a range of immunological diseases, including IBD, rheumatoid arthritis, and type 1 diabetes mellitus. Among these, IBD is one of the best-characterized diseases and consists of two major subtypes, Crohn's disease (CD) and ulcerative colitis (UC), which are clinically and molecularly distinct, with compelling evidence of microbiome-based etiology. [Nat. Rev. Microbiol. 2019; 17:497-511] A hallmark of the IBD gut microbiota is reduced species diversity, driven by a shift from obligate anaerobes, including the Clostridia, to facultative aerobes such as the Enterobacteriaceae. The next major challenge for microbiome research is to advance from these associative findings to the causal mechanisms that underlie disease. [Cell. 2018; 174:785-790] In this study the investigators used stool metagenomes of thousands of IBD patients and healthy controls to reconstruct 140,000 strain genotypes, revealing hundreds of lineages enriched in IBD. Disease-associated strains outcompete their healthy counterparts during inflammation, implying long-term adaptation to disease. Strain genetic differences map onto known axes of inflammation, including oxidative stress, nutrient biosynthesis, and immune evasion. Lastly, the loss of health-associated strains of Eggerthella lenta was predictive of fecal calprotectin, a biomarker of disease severity. Remarkably, both health- and disease-associated strains responded to changes in fecal calprotectin. During bouts of inflammation, fecal calprotectin levels increased by over 73-fold, and IBD-associated strains outcompeted health-associated strains. Strikingly, this effect was most pronounced in IBD patients. Conversely, when inflammation activity receded, fecal calprotectin levels decreased by 50-fold. Overall, this work identified reservoirs of strain diversity that may impact inflammatory disease and can be extended to other microbiome-associated diseases.

BOTTOM LINE

Key findings in this study were:

1. **The human gut microbiome contains hundreds of lineages that are associated with IBD**
2. **IBD-associated lineages outcompete their healthy counterparts during inflammation**
3. **The loss of health-associated strains is predictive of a biomarker of inflammation. The findings in this study could have diagnostic utility and also have the potential to guide tailored interventions for inflammatory bowel disease and other immune-mediated diseases. [see next review]**

7

Antibiotics damage the colonic mucus barrier in a microbiota-independent manner.

Science Advances published September 11, 2024, Vol. 10, Iss. 37
DOI: 10.1126/sciadv.adp4119

The investigators hypothesized that antibiotics affect the integrity of the mucus barrier, which allows bacterial penetrance and predisposes to intestinal inflammation. To determine whether antibiotic treatment affects the mucus barrier, the investigators orally treated mice with antibiotics. They aimed to mimic short- term antibiotic treatment in patients; thus, they treated the mice twice a day for only 3 days. They used four different antibiotics, each belonging to a different class of antibiotics: ampicillin (aminopenicillin class), metronidazole (nitroimidazole class), neomycin (aminoglycoside class), and vancomycin (glycopeptide class). To quantify bacterial penetration into the colonic mucus barrier, they fixed the tissues in Carnoy's fixative, which preserves the mucus barrier and the native bacterial spatial localization, and stained bacteria using a pan- bacterial fluorescent in situ hybridization (FISH) probe.

Using fecal microbiota transplant, RNA sequencing followed by machine learning, ex vivo mucus secretion measurements, and antibiotic treatment of germ- free mice, they determined that antibiotics induce endoplasmic reticulum stress in the colon that inhibits colonic mucus secretion in a microbiota- independent manner. This antibiotic-induced mucus secretion flaw led to penetration of bacteria into the colonic mucus layer, translocation of microbial antigens into circulation, and exacerbation of ulcerations in a mouse model of IBD.

Dr. Septimus's Annotations

The colonic mucus layer separates the host from the trillions of microbes that inhabit the gut lumen. If this mucus barrier is breached, bacteria can encroach on the host intestinal epithelium and trigger a proinflammatory response. [Gastroenterology 2006; 131, 117–129] Breakdown of this barrier is a hallmark of IBDs and perhaps a driving factor in the development of these diseases. [Gut 2014; 63, 281–291] Antibiotic treatment in mice leads to translocation and uptake of bacteria to gut- draining lymph nodes while predisposing to development of intestinal inflammation. [Gut 2016; 65, 1100–1109] The question is whether antibiotics directly damage the mucus barrier. They found that all four antibiotics tested led to breakdown of the colonic mucus barrier and penetration of bacteria into the mucus layer.

The consequences of overuse of antibiotics have led to the rise of antimicrobial resistance, and the development of some chronic diseases. Diseases such as diabetes, growth defects, and chronic inflammations have been linked in multiple studies to antibiotic use. [Nat. Commun. 2021;12, 443] As antibiotics target microbes directly, it was assumed that the effects of antibiotics on the gut microbiota may be a main driver of these diseases. [Nat. Rev. Microbiol.2023; 21, 789–804] While antibiotic use affects the host by disrupting its microbiota, recent evidence suggests that antibiotics might act directly on host cells.

Another group of chronic diseases that are linked to antibiotic use are IBDs. Recent epidemiological studies have provided a strong link between antibiotic use and risk for development of IBD [Lancet Gastroenterol. Hepatol. 2020; 5, 986–995], in a dose- dependent manner. [see review above] Here, the investigators hypothesized that antibiotic use might lead to development of intestinal inflammation by affecting the colonic mucus barrier. The ability of the mucus barrier to provide separation between the host and its gut microbiota is crucial for maintaining gut homeostasis. Breakdown of this barrier is observed both in animal models of IBD and in patients with IBD. [Gut 2019;68, 2142–2151]

BOTTOM LINE

The investigators found that antibiotic treatment led to breakdown of the colonic mucus barrier and penetration of bacteria into the mucus layer predisposing to intestinal inflammation by impeding mucus production.

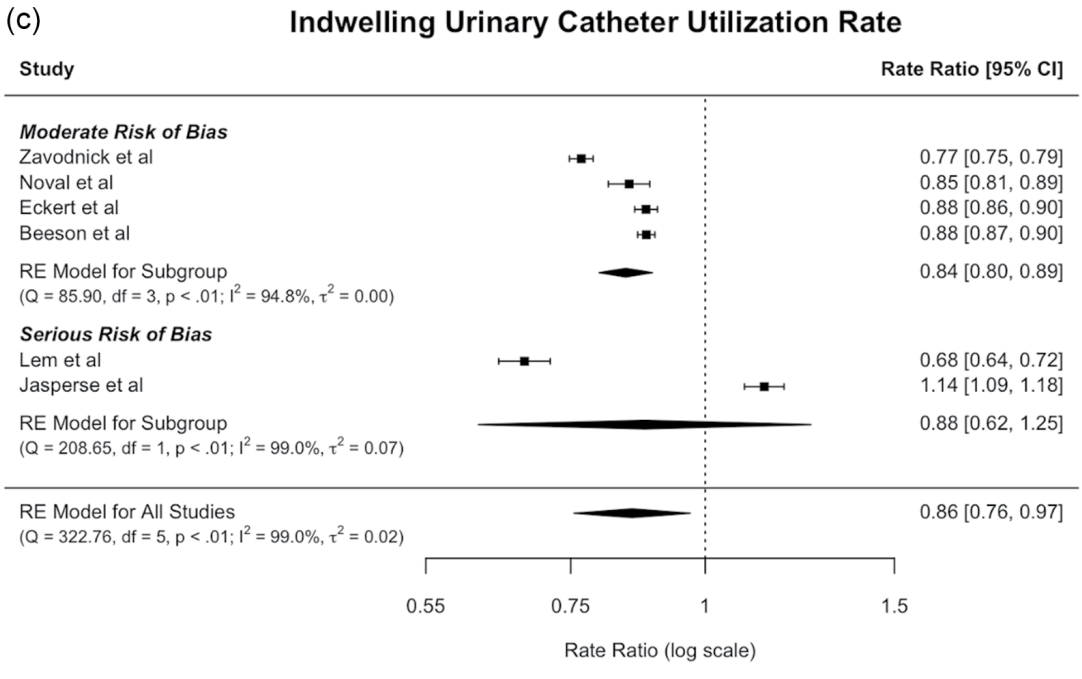
Clinical outcomes of female external urine wicking devices as alternatives to indwelling catheters: a systematic review and meta-analysis.

Infection Control & Hospital Epidemiology published May 6, 2024, Vol. 45, Iss. 9
DOI: 10.1017/ice.2024.73

Female patients using indwelling urinary catheters (IUCs) have a higher risk for developing catheter-associated urinary tract infections (CAUTIs) compared to males. Female external urine wicking devices (FEUWDs) have emerged as potential alternatives to IUCs for incontinence management. IUC alternatives for male patients have existed for quite some time. Recently, a noninvasive collection device designed for female genitalia was developed and trademarked as PureWick. Utilizing a soft and flexible wicking material to absorb urine, which is gently drawn away from the body using low, continuous suction. These devices have the potential to reduce indwelling CAUTI incidence in females. Current research has examined two similar female external urine wicking devices (FEUWDs) that differ only slightly in shape and options for securing the device to the patient: PureWick (Becton, Dickinson) and PrimaFit (Sage Products). In this article the authors performed a systematic review and meta-analysis of the existing literature to assess the clinical risks and benefits of FEUWDs, hypothesizing that FEUWD use would result in reduced CAUTI rates (without increasing non-indwelling catheter-associated UTIs) due to their less invasive technology than traditional indwelling catheters.

The following databases were searched from inception to July 12, 2022, to identify relevant articles, trials, or meeting abstracts describing alternatives to indwelling catheters: Ovid Medline (Ovid Medline, Embase.com, Scopus, Web of Science Core Collection, CINAHL Complete, and ClinicalTrials.gov. Included studies used FEUWDs as an intervention and reported measures of urinary tract infections (UTIs) and secondary outcomes related to incontinence management.

Of 2,580 returned records, 50 were systematically reviewed. Meta-analyses assessed rates of indwelling CAUTIs and IUC utilization. Following FEUWD implementation, IUC utilization rates decreased 14% (RR=0.86, 95% CI = [0.76, 0.97]) and indwelling CAUTI rates nonsignificantly decreased up to 32% (IRR =0.68,95%CI=[0.39,1.17]). However, limited only to studies that described protocols for implementation, the incidence rate of indwelling CAUTIs decreased significantly up to 54% (IRR =0.46, 95% CI = [0.32, 0.66]). Secondary outcomes were reported less routinely.



This is the first systematic review and meta-analysis of clinical outcomes associated with FEUWDs, which have the potential to supplement existing CAUTI prevention initiatives. The results of this meta-analysis suggest that rigorously protocolized implementations of FEUWDs can significantly reduce indwelling urinary catheter (IUC) utilization and indwelling CAUTI rates in hospitals. It appears that the process by which FEUWDs are implemented is an important determinant of their effect on IUC utilization and indwelling CAUTI rates. Implementation of FEUWDs may reduce CAUTIs through two paths: (1) by reducing IUC utilization—patients never catheterized cannot, by definition, have a CAUTI, while patients with fewer catheter-days are at lower risk of CAUTIs—and (2) by reducing CAUTI rates among those catheterized if FEUWD roll-out was part of a "bladder bundle" that optimizes CAUTI prevention practices. Secondary outcomes like skin injury and mobility-related complications were reported rarely and with varied or unspecified definitions.

There were a few limitations to this review. All studies included in meta-analyses demonstrated a moderate to serious risk of bias. Because several studies were conducted as QI projects rather than controlled interventions, implementation protocols varied across sites, which contributed to heterogenous effects. Another limitation is that some studies calculated rates based on total (male and female) patient-days.

Moving forward the authors make several recommendations. First, they recommend developing a standardized definition of female external urine wicking device-associated urinary tract infections (FEUWD-UTIs) to facilitate comparison across future studies. In addition to the joint reporting of IUC utilization and indwelling CAUTI rates, FEUWD utilization and FEUWD-UTI rates should be reported, as well as skin- and mobility-related complications associated with FEUWD use. It would also be useful for investigators to report IUC utilization and indwelling CAUTI rates among female patients only so that evaluations of the relationship between FEUWD and IUC use are specific to the patient population of interest.

In addition, FEUWD implementation protocols should include:

1. Standardized guidelines for FEUWD use rather than clinician discretion only,
2. Consistent and standardized charting,
3. Maintained attention to local hygiene as would be expected for IUCs, and
4. Documentation of all potential FEUWD-associated complications.

BOTTOM LINE

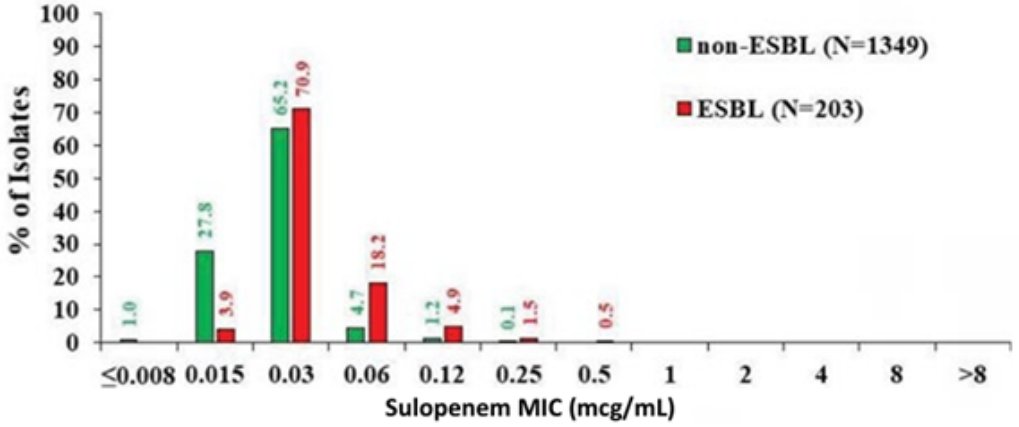
FEUWDs (female external urine wicking devices) have the potential to significantly reduce IUC (indwelling urinary catheters) utilization and indwelling CAUTI(catheter-associated urinary tract infections) rates in hospital settings when introduced with a protocol to guide use.

10 FDA approves sulopenem etzadroxil/ probenecid a new oral antibiotic for urinary tract infections

The FDA approved a new oral antibiotic, sulopenem etzadroxil/ probenecid, for treating uncomplicated urinary tract infections (uUTIs). Sulopenem etzadroxil/ probenecid (Orlynvah) is a broad-spectrum oral penem antibiotic that's indicated for treating uUTIs caused by certain bacteria (E coli, K pneumoniae, or Proteus mirabilis) in adult women who have limited or no alternative treatment options. Sulopenem etzadroxil/ probenecid has activity against ESBL producing pathogens. [see below]

The FDA says the approval was based in part on two phase 3 randomized controlled trials in which Orlynvah was compared with standard treatment options for uUTIs. In a trial involving 2,241 adult women who had uUTI (the REASSURE trial), patients with amoxicillin/clavulanate-susceptible pathogens who received Orlynvah had a 62% composite response rate (combined microbiologic and clinical response), compared with a 55% composite response rate in patients treated with amoxicillin/clavulanate—a finding that demonstrated non-inferiority. In another trial (SURE-1), conducted in 1,660 adult women with uUTIs caused by ciprofloxacin-resistant pathogens, Orlynvah was found superior to ciprofloxacin, with a 48% composite response rate compared with 33% in the ciprofloxacin group. The most common side effects of Orlynvah in trial participants were diarrhea, nausea, vaginal yeast infection, headache, and vomiting.

Figure 2. Sulopenem MIC Distribution Against Non-ESBL and ESBL *E. coli*



Dr. Septimus's Annotations

At a meeting of the FDA's Antimicrobial Drugs Advisory Committee in September committee members agreed that Orlynvah could be beneficial for some patients, but some expressed concern that off-label use could amplify resistance to carbapenems, which are closely related to penems. That concern was shared by the FDA. The FDA added that careful antimicrobial stewardship and consideration by guidelines committees are critical to ensure appropriate positioning of sulopenem etzadroxil/probenecid in the choice of treatment options for uUTI.

BOTTOM LINE

An oral penem(sulopenem etzadroxil/probenecid) for treatment of resistant bacteria causing uUTI potentially addresses an unmet need in the ambulatory setting.

Guidelines for the Prevention, Diagnosis, and Management of Urinary Tract Infections in Pediatrics and Adults. A WikiGuidelines Group Consensus Statement.

JAMA Network Open. 2024;7(11):e2444495.
DOI: 10.1001/jamanetworkopen.2024.44495

The purpose of this review was to create a clinical guideline for the diagnosis and management of urinary tract infections that addresses the gap between the evidence and recommendation strength. This consensus statement and systematic review applied an approach previously established by the WikiGuidelines Group to construct collaborative clinical guidelines. In May 2023, new and existing members were requested for questions on urinary tract infection prevention, diagnosis, and management. For each topic, literature searches were conducted up until early 2024 in any language. Evidence was reported according to the WikiGuidelines charter: clear recommendations were established only when reproducible, prospective, controlled studies provided hypothesis-confirming evidence. In the absence of such data, clinical reviews were developed discussing the available literature and associated risks and benefits of various approaches. A total of 54 members representing 12 countries reviewed 914 articles and submitted information relevant to 5 sections: prophylaxis and prevention (7 questions), diagnosis and diagnostic stewardship (7 questions), empirical treatment (3 questions), definitive

treatment and antimicrobial stewardship (10 questions), and special populations and genitourinary syndromes (10 questions). Of 37 unique questions, a clear recommendation could be provided for 6 questions. In 3 of the remaining questions, a clear recommendation could only be provided for certain aspects of the question. Below is a summary of the six recommendations and three partial recommendations followed by some additional comments.

Six recommendations

Q ***Is there a role for cranberry juice or supplements in the prevention of UTIs?***

Cranberry juice or supplements reduce the risk of symptomatic, culture-verified UTIs in women and children. However, evidence for their use in older adults, those with bladder emptying problems or pregnant women is insufficient to make a clear recommendation for or against its use.

Q ***Is there a role for topical estrogen in the prevention of UTIs?***

Based on available evidence from 30 randomized clinical trials and one large retrospective observational study, topical estrogen is effective at reducing recurrent UTIs in postmenopausal women.

Q ***Is there a role for methenamine hippurate in the prevention of UTIs?***

A systematic review, which included a multicenter, open-label, randomized noninferiority trial conducted in the United Kingdom from June 2016 to June 2018, compared the efficacy of methenamine with daily low-dose antibiotics in preventing recurrent UTIs in women aged 18 years and older and found that methenamine was noninferior to antibiotics for the prevention of UTIs.

Table 1. Strategies to Prevent UTIs

Strategy	Level of evidence	Intervention	Comments
Continuous or postcoital antimicrobial prophylaxis	Clinical review	TMP/SMX: continuous, 40 mg/200 mg once daily or 40 mg/200 mg 3 times weekly; postcoital, 40 mg/200 mg or 80 mg/200 mg once postcoitus; Nitrofurantoin: continuous, 50 mg or 100 mg daily; postcoital, 50 mg or 100 mg once postcoitus	The decision to use antibiotic prophylaxis must balance the need for prevention against the risk of adverse drug events, antimicrobial resistance, and microbiome disruption.[a]
Cranberry products	Clear recommendation	Cranberry products containing proanthocyanidin levels of 36 mg	Cranberry products can reduce the recurrent UTIs in women, children, and individuals susceptible to UTIs. Data for older people, those with bladder emptying problems, or pregnant women is insufficient.
Probiotics	Clinical review	No recommendation	Studies were heterogenous with regard to patient populations, specific probiotics, route of administration, and study design.
Vaginal estrogen	Clear recommendation	Vaginal estrogen, such as vaginal rings, vaginal insert or vaginal cream	There is a wide variety of formulations and local delivery methods. Availability may vary in different countries or geographic regions.
Increased water intake	Clinical review	Additional 1.5L of water	Water intake was shown to decrease UTIs in 1 RCT among healthy women. Given the low-risk nature of the intervention, pending a confirmatory study, it is reasonable to offer this intervention to healthy women with recurrent UTIs.
Methenamine hippurate	Clear recommendation	Methenamine hippurate: 1 g twice daily; methenamine mandelate: 1 g every 6 hours	Methenamine is an appealing antimicrobial-sparing intervention to reduce UTIs in patients without incontinence and a fully functional bladder.

Abbreviations: RCT, randomized clinical trial; TMP/SMX, trimethoprim sulfamethoxazole; UTI, urinary tract infection.

[a] Consider use of other options reviewed in eAppendix 1 of the Supplement in more detail prior to continuous or postcoital antimicrobials.

Q ***What are reasonable empirical treatment regimen(s) for pediatric or adult patients diagnosed with a UTI?***

Empirical treatment regimens for pediatric and adult patients should contain antimicrobials that historically demonstrated efficacy and safety in the treatment of UTIs, achieve adequate urinary concentrations and provide reliable activity against the most common pathogens based on local resistance rates.

Q ***What are optimal oral agents and an appropriate duration of treatment for gram-negative bacteremia from a urinary source?***

Multiple randomized clinical trials composed of patients with gram-negative bacteremia from predominantly urinary sources demonstrate noninferiority of 7 days compared with 14 days of treatment for a variety of patient-oriented outcomes, including clinical cure, clinical failure, relapse and all-cause mortality. [see review above from ID Week]

Q ***What is the optimal clinical approach for patients with nephrolithiasis, foreign objects, nephrostomy tubes and/or ureteral stents?***

Routine cystoscopy and urodynamic studies do not require antimicrobial prophylaxis in asymptomatic patients. Preoperative antibiotics do not appear to reduce infectious complications from routine cystoscopic stent removal or nephrostomy tube placement.

In most patients with uncomplicated urologic cases undergoing percutaneous nephrolithotomy, a single dose of antimicrobial prophylaxis appears to reduce the risk of infection.

Table 2. Clinical Practice Guideline Definitions of UTI Syndromes in Adults[a]

Defining term(s)	Proposed IDSA	Current IDSA	EAU	AUA, CUA, and SUFU
Complicated UTI and acute pyelonephritis	Any infection beyond the bladder, includes pyelonephritis, CAUTI, febrile or bacteremic patients	Urinary symptoms plus functional or structural abnormalities of the urinary tract. CVA pain and tenderness, often with fever (pyelonephritis)	Dysuria, urgency, frequency, flank pain, CVA tenderness, suprapubic pain, fever, chills, nausea, vomiting; anatomical or functional abnormalities of the urinary tract (eg, obstruction, incomplete voiding due to detrusor muscle dysfunction; presence of diabetes or immunosuppression	Anatomical or functional abnormality of the urinary tract (eg, stone disease, diverticulum, neurogenic bladder); immunocompromised host; multidrug resistant bacteria
Uncomplicated UTI	All other infections not defined as complicated	Frequency, urgency, dysuria, or suprapubic pain in a woman with a normal genitourinary tract	Dysuria, frequency and urgency and the absence of vaginal discharge; limited to nonpregnant women with no known relevant anatomical and functional abnormalities or comorbidities	Dysuria in conjunction with variable degrees of increased urinary urgency and frequency, hematuria, or new or worsening incontinence; female host; no known factors that would increase susceptibility to develop UTI

Abbreviations: AUA, American Urological Association; CAUTI, catheter-associated urinary tract infection; CUA, Canadian Urological Association; CVA, costovertebral angle; EAU, European Association of Urology; IDSA, Infectious Disease Society of America; SUFU, Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction; UTI, urinary tract infection.

[a] See eAppendix 2 of the Supplement for detailed supporting information.

Three partial recommendations

Q ***What is the appropriate duration of treatment for acute cystitis in adults?*** See table 4 below

The collaborative made recommendations for the optimal treatment duration for cystitis, regardless of biological sex, for six antimicrobial classes, all ranging between 3 to 5 days — except for oral fosfomycin, which is given as one dose. The researchers found insufficient data to make recommendations on other classes, including beta lactams and parenteral aminoglycosides.

Q ***What is the appropriate duration of treatment for acute pyelonephritis and/or febrile UTI in adults?*** See table 4 below

Although duration recommendations were made by the collaborate for fluoroquinolones (5 to 7 days) and dose-optimized beta lactams (7 days), it found insufficient evidence to make recommendations for several other antimicrobials, or to provide a clear recommendation on how long to treat febrile UTIs.

Table 4. Duration of Treatment Based on Syndrome and Antimicrobial Class Used

Syndrome and antimicrobial class	Duration of therapy (level of evidence)	Comments
Adult cystitis[a]		
Aminoglycosides	Clinical review, not enough evidence to provide a clear recommendation for duration of treatment	Multiple observational studies suggest a single dose of an aminoglycoside achieve high clinical and/or microbiological cure rates; no comparative literature exists
β-lactams	Clinical review, not enough evidence to provide a clear recommendation for duration of treatment	Optimal duration may depend on the specific agent and dosing used. Heterogeneity in study design and β-lactam agent and dose used in studies precludes a clear recommendation
Fluoroquinolones	3 d (clear recommendation)	Due to risk of individual and ecological collateral damage, should not be used if other treatment options exist.
Fosfomycin (oral)	Single dose (clear recommendation)	Alternative dosing strategies have only been studied in RCTs and observational studies of febrile UTI, bacteremic UTI, and pyelonephritis
Nitrofurantoin	5 d (clear recommendation)	5-d and 7-d Courses result in comparable clinical outcomes; may use with CrCl as low as 30 mL/min

Abbreviations: ABP, acute prostatitis; CBP, chronic prostatitis; CrCl, creatinine clearance; IV, intravenous; RCT, randomized clinical trials; TMP/SMX, trimethoprim sulfamethoxazole; UTI, urinary tract infection.

Table 4. Duration of Treatment Based on Syndrome and Antimicrobial Class Used

Syndrome and antimicrobial class	Duration of therapy (level of evidence)	Comments
Adult cystitis[a]		
Pivmecillinam	3 d (clear recommendation)	3 d Regimens appear to have comparable efficacy as longer regimens and various regimens of comparators commonly used in contemporary practice.
TMP/SMX	3 d (clear recommendation)	Contemporary *Escherichia coli* resistance rates in most geographical regions limit utility as first-line treatment.
Adult pyelonephritis[b]		
Aminoglycosides	Clinical review, not enough evidence to provide a clear recommendation for duration of treatment	Multiple observational studies suggest monotherapy may be effective, however the optimal duration is unknown.
β-lactams	7 d (clear recommendation)	Dose optimization is critical based on analogous data supporting β-lactam use in the treatment of gram-negative bloodstream infection and outcomes of RCTs using IV β-lactams. 3 RCTs demonstrate comparable outcomes with 7 d of treatment vs 2-, 3-, and 6- wk regimens.
Fluoroquinolones	5 to 7 d (clear recommendation)	RCTs supporting 5 d of treatment used ofloxacin or levofloxacin; RCTs supporting 7 d of treatment used ciprofloxacin or fleroxacin. Ofloxacin is a second generation fluoroquinolone similar to ciprofloxacin, so may be reasonable to use 5 d of treatment when using ciprofloxacin as well.
Fosfomycin	Clinical review, not enough evidence to provide a clear recommendation for duration of treatment	IV fosfomycin available in some countries may be reasonable empirical treatment for pyelonephritis, but there is a lack of strong data supporting the use of oral fosfomycin for the treatment of pyelonephritis.
TMP/SMX	Clinical review, not enough evidence to provide a clear recommendation for duration of treatment	Historical durations of 14 d were used based on a series of very small RCTs in the 1970s to 1990s; outcomes of patients who received TMP/SMX in more recent RCTs suggest 7 d may be adequate, but further prospective investigation is needed.
Adult febrile UTI[b]	Clinical review, not enough evidence to provide a clear recommendation for duration of treatment	When considering the available data for pyelonephritis and gram negative bacteremia from a urinary source, it may be reasonable for febrile UTI to be treated in a similar fashion to pyelonephritis.
Catheter-associated UTI[c]	Clinical review, not enough evidence to provide a clear recommendation for duration of treatment	Data are limited to observational studies and small subgroups of RCTs, precluding a clear recommendation. Observational data suggest 5 to 7 d may be as effective as longer durations.
Gram-negative bacteremia from a urinary source[d,e]	7 d (clear recommendation)	Heterogeneity in trial design and selection and dosing of antimicrobials used limits ability to recommend specific antimicrobial classes. Fluoroquinolones, TMP/SMX, and β-lactams were included in published RCTs demonstrating noninferiority of 7 d to 14 d.
Prostatitis[f]	Clinical review, not enough evidence to provide a clear recommendation for duration of treatment for either ABP or CBP.	There is a dearth of data for both acute and chronic bacterial prostatitis that precludes a clear recommendation for duration of treatment in either scenario. Historical durations range from 14 d for ABP to 6 weeks or longer for CBP.
Pediatric cystitis (>2 mos of age)[g]	Clinical review, not enough evidence to provide a clear recommendation for duration of treatment	Heterogeneity in trial design, inclusion of clinically relevant outcomes precludes a clear recommendation. Numerous RCTs suggest shorter durations are likely effective (3 to 5 d).
Pediatric pyelonephritis (age >2 y)[h]	Clinical review, not enough evidence to provide a clear recommendation for duration of treatment	Quantity and heterogenity of existing data preclude a clear recommendation. Observational data suggest comparably high rates of clinical success when patients are treated for 5 to 9 d compared with longer (10 to 14 d) durations.
Kidney and perinephric abscess[i]	Clinical review, not enough evidence to provide a clear recommendation for duration of treatment	Source control is of utmost importance. Expert opinion does not distinguish between 14 and 21 d of treatment.
Emphysematous cystitis and pyelonephritis[j]	Clinical review, not enough evidence to provide a clear recommendation for duration of treatment or emphysematous cystitis or pyelonephritis	May vary widely depending on clinical response and whether percutaneous drainage was performed. When considering the available data for pyelonephritis and Gram-negative bacteremia from a urinary source, it may be reasonable for emphysematous cystitis and pyelonephritis to be treated in a similar fashion to other more clinically severe UTIs, such as febrile UTI, pyelonephritis, and gram negative bacteremia from a urinary source.

Abbreviations: ABP, acute prostatitis; CBP, chronic prostatitis; CrCl, creatinine clearance; IV, intravenous; RCT, randomized clinical trials; TMP/SMX, trimethoprim sulfamethoxazole; UTI, urinary tract infection.

Q ***What are effective antimicrobial stewardship strategies that can optimize the rational and sustainable use of antimicrobials in the setting of treatment of UTIs?***

The collaborative was able to make specific recommendations that encouraged de-escalation and using mostly or all oral treatment, which can reduce hospital stays and lower the risk for adverse events linked to IV antibiotic treatment, according to the guideline.

Additional comments

Q ***What Is the Role and the Sensitivity and Specificity of a Urinalysis (UA) for the Diagnosis of UTIs and When Should Clinicians Order Urine Cultures?***

While the absence of pyuria can help rule out infection in most patient populations, the positive predictive value of pyuria for diagnosing infection is low as it often indicates the presence of genitourinary inflammation due to many other possible noninfectious reasons and can be present in asymptomatic bacteriuria (ABU). The authors believe that evidence-based diagnosis of UTI should be primarily based on clinical symptoms. Clinical symptoms should be integrated with UA findings, but authors caution clinicians to not rely solely on the UA alone.

Q ***What Is the Role of UA and Urine Culture Testing for the Workup of Fever?***

Routine use of UA and urine cultures for the workup of fever in hospitalized patients leads to unnecessary testing and antimicrobial use.[Cleve Clin J Med. 2022;89:581-587] Studies show that UTIs, including catheter-associated UTIs (CAUTI), are infrequently the source of fever, particularly in the absence of urinary tract obstruction, recent urological procedures, or immunocompromise.[Crit Care Med. 2023;51:1570-1586] Consequently, urine testing should not be automatic in febrile patients, and should be reserved for cases with specific urinary or related symptoms. Effective management of UTI hinges on appropriate diagnostic testing and antimicrobial stewardship, aiming to prevent the misuse of antibiotics for ASB. Symptom-based testing is key to ensure appropriate urine culture testing and proper diagnosis of UTI. [Clin Infect Dis. 2019; 68:1611-1615]

BOTTOM LINE

This consensus review presents evidence-based strategies for managing UTIs and clinical reviews in areas where strong evidence is lacking. The guidance is based on information available up to early 2024. Pressing research gaps remain, including the need for high-quality studies to validate novel diagnostic methods, optimize treatment durations, establish standard definitions, and refine antimicrobial stewardship strategies for asymptomatic bacteriuria and MDROs.

12

A Comparison of Different Strategies for Optimizing the Selection of Empiric Antibiotic Therapy for Pneumonia Caused by Gram-Negative Bacteria in Intensive Care Units (icus): Unit-Specific Combination Antibiograms Versus Patient-Specific Risk Factors

Open Forum Infectious Diseases published online October 30, 2024, Vol. 11, Iss. 11
DOI: 10.1093/ofid/ofae643

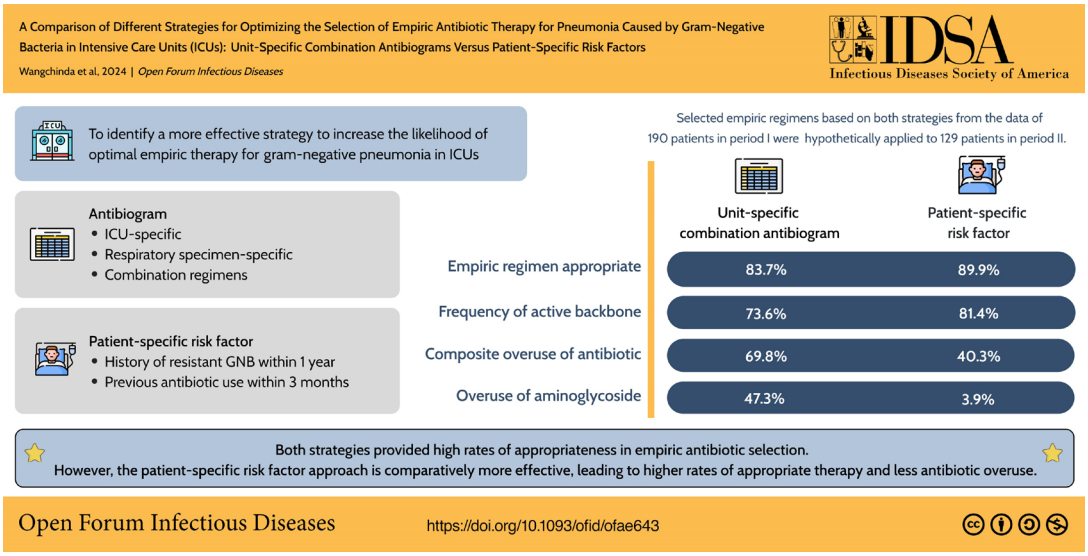
This was a retrospective study divided into two periods. In period I, gram-negative respiratory cultures from ICU patients were used to develop unit-specific combination antibiograms, and individual patient charts were reviewed to assess the impact of risk factors on antimicrobial susceptibility to develop a risk-factor based treatment algorithm. Optimal empiric regimens based on these two strategies were then defined. In period II, these regimens were hypothetically applied to patients to compare rates of appropriate empiric therapy and overuse by the two methods. The most used anti pseudomonal agents, including cefepime, piperacillin-tazobactam, meropenem, levofloxacin, ciprofloxacin, amikacin, gentamicin, and tobramycin. Two combination antibiograms were then constructed, one for each unit (i.e., MICU and SICU), by assessing the activity of β-lactam monotherapy, and

β-lactams with their potential combination partner agents (i.e., aminoglycosides and fluoroquinolones). The empiric regimen was considered appropriate if the isolated gram-negative bacteria was susceptible to at least one empiric antibiotic. Overuse was defined as unnecessary use of carbapenems when a narrower spectrum β-lactam (i.e., cefepime or piperacillin-tazobactam) could have been utilized or a novel β-lactam was administered when a traditional agent (i.e., a carbapenem, cefepime, or piperacillin-tazobactam) would have provided appropriate coverage. Addition of fluoroquinolone or an aminoglycoside when the β lactam backbone was active was also considered overuse.

Risk factors collected for analysis included a previous positive culture with a Gram-negative organism resistant to at least one traditional anti-pseudomonal β-lactam recommended for empiric therapy for ICU pneumonia (i.e., cefepime, piperacillin-tazobactam, meropenem, or imipenem) within 1-year, previous antibiotic exposures within 3 months, admission from an outside healthcare facility, and a prolonged ICU stay (≥ 5 days prior to index culture). Sensitivity analyses were also performed to compare results for other "at risk" time frames for previous antibiotic use and microbiological history.

Empiric antibiotic regimens included either monotherapy with a single anti-pseudomonal β-lactam or combination therapy with an antipseudomonal β-lactam paired with either an aminoglycoside or fluoroquinolone. The selected empiric regimens were chosen to achieve expected antibiotic coverage for at least 85% of patients. This was selected to balance appropriateness with minimizing antibiotic overuse.

Risk factor-based regimens had a higher appropriateness rate compared to regimens derived from antibiograms (89.9% vs 83.7%). Additionally, applying antibiogram based regimens resulted in a higher prevalence of antibiotic overuse than a patient-specific risk factor-based approach (69.8% vs. 40.3%), with excess overuse driven by a higher frequency of unnecessary use of combination therapy.



Dr. Septimus's Annotations

Pneumonia, particularly hospital-acquired pneumonia and ventilator-associated pneumonia (HAP/VAP) are common infections in ICUs and are associated with high morbidity and mortality. Inappropriate empiric antibiotic treatment, meaning regimens lacking in vitro activity against causative pathogens, is the most important modifiable risk factor contributing to poor outcomes. [J Crit Care 2008; 23:91-100] It has become common practice to administer two antipseudomonal agents empirically to patients to increase the likelihood of providing adequate coverage. In fact, this strategy is a guideline recommended in ICU patients with pneumonia who have risk factors for multidrug-resistant (MDR) pathogens, in those who reside in units with high rates of antibiotic resistance,

and in patients who are critically ill. [Clin Infect Dis 2016;63: e61-e111] Treatment guidelines also recommend incorporating local epidemiology and patient risk factors for antimicrobial resistance into empiric treatment decisions, but little guidance on how to do it. Therefore, optimal strategies to promote appropriate and optimal empiric antibiotic therapy are needed. Given limitations of using unit-specific combination antibiograms suggest the potential advantages of developing more personalized empiric regimens based on patient-specific risk factors. Significant risk factors for MDR-Gram-negative pathogens in respiratory cultures include prior colonization or infection by a MDR organism [Am J Respir Crit Care Med 1996; 154:1339-46], prior antibiotic use [Infection 2005;33:129-35], prolonged hospitalization [Intensive Care Med 2013;39:672-81], and patient's location prior to admission. [Arch Intern Med 2008; 168:2205-10] Evaluating these risk factors in individual patients could improve the appropriateness of empiric antibiotic therapy. This study was designed to examine two main objectives to optimize the selection of empiric antibiotic therapy for Gram-negative pneumonia in ICUs.

While these cultures were typically collected for the diagnosis of pneumonia, not all these cultures necessarily indicated true infections. Prospective validation of a risk-factor based approach is needed.

BOTTOM LINE

Both patient-specific risk factors and unit-specific combination antibiogram approaches were useful and can be used in empiric antibiotic selection. However, the patient specific risk factor-based approach offers a higher rate of appropriateness therapy and advantages in reducing the overuse of combination agents.

13

Risk of invasive MDRO infection in MDRO-colonized patients

Infectious Control & Hospital Epidemiology published online October 14, 2024
DOI: 10.1017/ice.2024.156

In this retrospective study, the investigators set out to estimate the risk of developing clinical multidrug-resistant organism (MDRO) infection with carbapenem resistant Enterobacterales (CRE), methicillin-resistant Staphylococcus aureus (MRSA), or vancomycin-resistant enterococci (VRE) in colonized patients compared with non-colonized admitted to high-risk areas with a focus on CRE colonization/infection.

This study included patients enrolled in active surveillance testing (AST) for CRE, MRSA, or VRE during the year 2021. Development of relevant invasive infection within 365 days of the AST result was collected as the primary outcome. The association between MDRO colonization and infection was calculated using the risk ratio. The prevalence of CRE organisms and carbapenemase genes was evaluated as well.

A total of 19,134 ASTs were included in the analysis (4,919 CRE, 8,303 MRSA, and 5,912 VRE). Patient demographics were similar between colonized and non-colonized groups. Colonization was associated with an increased risk of infection in the 3 cohorts (CRE, MRSA, and VRE), with risk ratios reported as 4.6, 8.2, and 22, respectively. Most patients (88%) develop CRE infection with the same colonizing carbapenemase gene. Oxa-48/NDM Klebsiella pneumoniae was the most common organism detected in CRE infection.

Dr. Septimus's Annotations

MDRO infections present a significant challenge in healthcare. It has been established that prior MDRO colonization correlates with an increased risk of subsequent infection. A systematic review found that 7.6%–44.4% of 1,806 CRE-colonized patients developed clinical CRE infections. [Am J Infect Control 2016; 44:539–43] Colonization with MRSA or VRE increased the risk of related infection by 2.7–3.6 (RR) and 14.3 (OR), respectively. [Am J Infect Control 2013; 41:405–10; Infection 2014; 42:1013–22]

This study was conducted within a specific hospital environment, and the sample was selected based on surveillance tests applied only in critical care settings, hence limiting the generalizability of the findings to other settings characterized by different patient demographics and infection prevention protocols.

BOTTOM LINE

This study supports the need to implement active surveillance testing (AST) for multidrug-resistant organism (MDRO) colonization to identify patients who are at an increased risk of developing MDRO infections. This study also highlights the need of implementing rigorous infection prevention measures to reduce transmission and antimicrobial stewardship to reduce selection of MDROs.

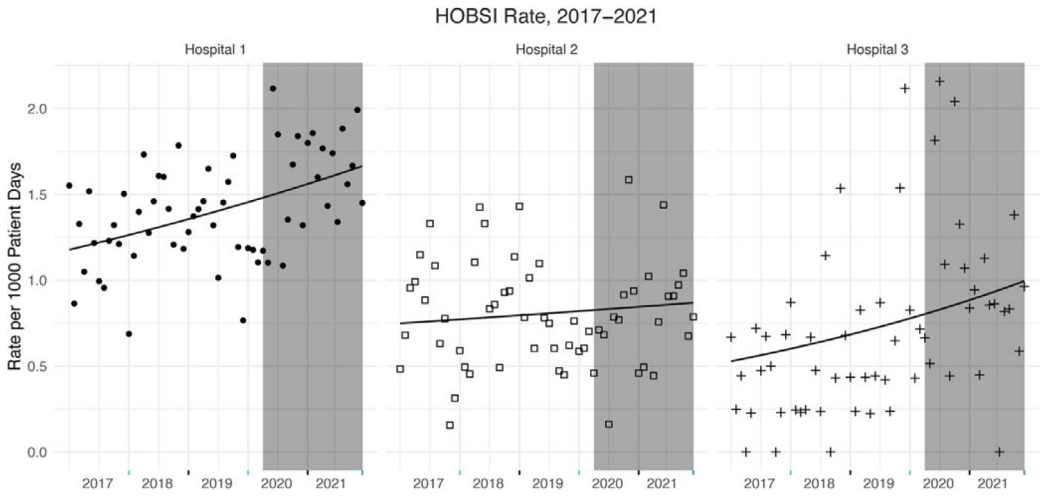
Comparative epidemiology of hospital-onset bloodstream infections (HOBSIs) and central line-associated bloodstream infections (CLABSIs) across a three-hospital health system

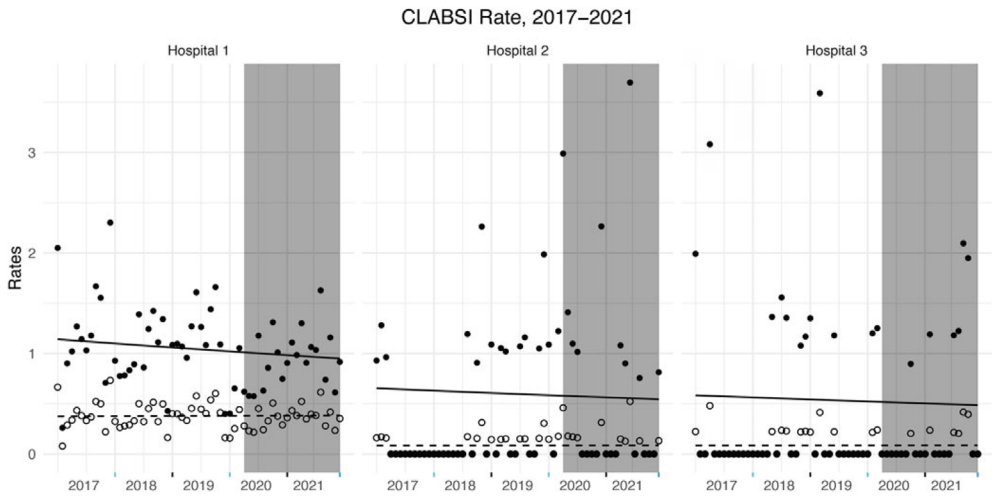
Infect Control Hosp Epidemiol 2024, 45,952–958
DOI: 10.1017/ice.2024.38

Over the past several years, a new quality metric- hospital onset bloodstream infection (HOBSI)- has been proposed. Given its simpler definition, HOBSI may serve as a more objective and easily automated metric compared to its central line-associated bloodstream infection (CLABSI) counterpart. Furthermore, previous studies have suggested that HOBSI surveillance is able to better discriminate between the quality of care provided across units or facilities compared to CLABSI surveillance. [Infect Control Hosp Epidemiol 2016; 37:143–148]

The investigators set out to evaluate the comparative epidemiology of HOBSI and CLABSI. To evaluate they designed a retrospective observational study of HOBSI and CLABSI across a three-hospital healthcare system from 01/01/2017 to 12/ 31/2021. HOBSIs were identified as any non-commensal positive blood culture event on or after hospital day 3. CLABSIs were identified based on National Healthcare Safety Network (NHSN) criteria. They performed a time-series analysis to assess comparative temporal trends among HOBSI and CLABSI incidence. Using univariable and multivariable regression analyses, they compared demographics, risk factors, and outcomes between non-CLABSI HOBSI and CLABSI.

HOBSI incidence increased over the study period (IRR 1.006 HOBSI/1,000 patient days; 95% CI 1.001–1.012; P = .03), while no change in CLABSI incidence was observed (IRR .997 CLABSIs/1,000 central line days, 95% CI .992–1.002, P = .22). Differing demographic, microbiologic, and risk factor profiles were observed between CLABSIs and non-CLABSI HOBSIs. Multivariable analysis found lower odds of mortality among patients with CLABSIs when adjusted for covariates that approximate severity of illness (OR .27; 95% CI .11–.64; P < .01). They compared microbiologic data, demographic data, and comorbidity profiles across CLABSI and non-CLABSI HOBSI in their cohort. Gram-negative pathogens constituted proportionally more non-CLABSI HOBSIs as compared to CLABSIs, while common line-associated pathogens such as Candida, Enterococcus, and coagulase-negative Staphylococcal species comprised a larger proportion of CLABSIs than non-CLABSI HOBSIs.





Dr. Septimus's Annotations

CLABSI incidence has been one of the reportable measures of infection prevention monitored by the CDC's NHSN. Though CLABSIs remain a major cause of morbidity and mortality [Cureus 2022;14: e22809] there are drawbacks in utilizing CLABSIs as a quality metric alone. First, CLABSI criteria as defined by the NHSN can be complex, subjective, and labor intensive for infection preventionists. Second, NHSN-defined CLABSI criteria are imperfect measures of true clinical diagnoses of central line associated bacteremia, with limited sensitivity and specificity. [Infect Control Hosp Epidemiol 2023; 44:2062–2064] HOBSI may provide a more complete assessment of overall quality of care compared to CLABSI: while CLABSI diagnoses are limited to those with a central line, HOBSI diagnoses include bacteremia from all potential healthcare related infections (e.g. non central lines, ventilator-associated pneumonia or urinary tract infection), each of which have important infection prevention measures whose adherence may be better captured by HOBSI compared to CLABSI.

This study found the incidence rate of HOBSI increased over time, but did not find a coincident increase in CLABSI incidence in their hospital system from 2017 to 2021, which was an unexpected finding based on recent literature which included the years of Covid-19 which found an increase in CLABSIs. [Infect Control Hosp Epidemiol 2016; 37:143–148] HOBSI incidence- in certain settings may measure quality of care in a manner different from CLABSI incidence alone. Compared to the restrictive criteria required for diagnosis of CLABSI by NHSN criteria, the utilized HOBSI definition captures bacteremia of all potential hospital-acquired sources. Accordingly, HOBSI incidence may reflect how well other infection prevention measures (e.g. midline catheters, peripheral IVs, urinary catheter- or ventilator-related care) are implemented on a consistent basis. This finding is an important consideration for institutions as HOBSI is implemented as a quality metric, since it may guide where infection prevention teams should focus their efforts beyond central lines. Non-CLABSI HOBSI events occur in substantially greater numbers than CLABSI events. [Clin Infect Dis, published online May 6, 2024, DOI: 10.1093/cid/ciae245] They relied upon an electronic method for HOBSI identification of blood culture contamination based on CDC NHSN commensal organisms, which may have resulted in exclusion of true HOBSIs. Future work examining the preventability of HOBSI needs to be assessed.

BOTTOM LINE

Hospital onset bloodstream infection (HOBSI) may serve as a more objective and easily automated metric compared to its central line-associated bloodstream infection (CLABSI). In addition, HOBSI incidence may reflect how well other infection prevention measures (e.g. midlines, peripheral IVs, urinary catheter- or ventilator-related care) are implemented on a consistent basis.

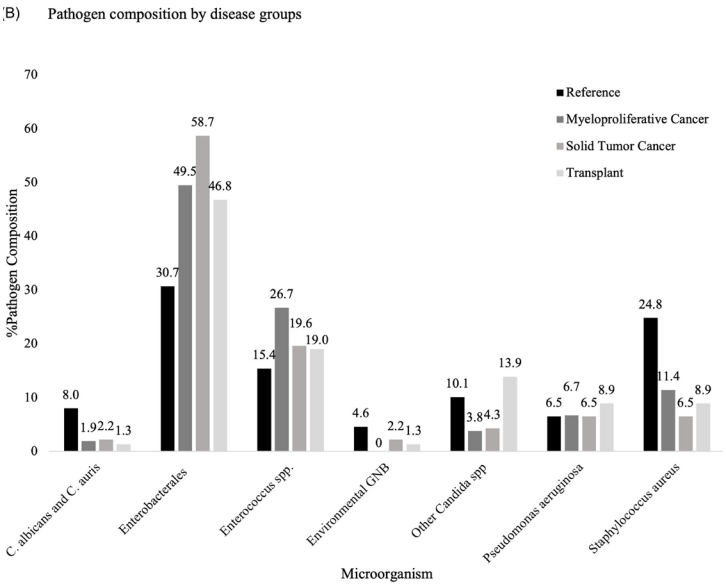
15

Clinical characteristics associated with hospital-onset bacteremia and fungemia among cancer and transplant patients.

Infectious Control & Hospital Epidemiology published online October 23, 2024, Vol. 45, Iss. 8
DOI: 10.1017/ice.2024.160

This study quantified the burden of hospital-onset bacteremia and fungemia (HOB) among cancer and transplant patients compared to other patients. This paper was a retrospective cross-sectional study using data from 41 hospitals between October 2015 and June 2019. Hospitalizations were segmented into categories using diagnosis-related groups (DRG): myeloproliferative (MP) cancer, solid tumor cancer, transplant, and noncancer/non-transplant ("reference group"). Analyses were stratified by length of stay (LOS). Reportable HOB cases were defined by the currently available definition per the CDC (i.e., a first positive blood culture and was collected in the hospital-onset period, on or after day 4 of hospitalization) for an eligible BSI organism as defined by the NHSN bloodstream pathogen list. Sex, age, LOS, DRG, 30-day readmissions, ICU during hospitalization, hospital cost per admission, in-hospital mortality, insurance payor, and hospital by demographics, staffed bed size, teaching status, and urban/rural location were variables collected in administrative data.

Of 645,315 patients, 59% were female and the majority 41 years of age or older (76%). Hospitalizations with MP cancer and transplant demonstrated higher HOB burden compared to the reference group, regardless of LOS category. For all hospitalizations, the >30 days LOS category had a higher burden of HOB. The median time to reportable HOB was within 30 days regardless of duration of hospitalization (reference, 8 days; solid tumor cancer, 8 days; transplant, 12 days; MP cancer, 13 days). The top three prevalent pathogens were Enterobacteriaceae, Enterococcus spp., and S aureus in both LOS groups and DRG groups. Enterobacteriaceae was the most prevalent pathogen for both LOS groups (34.6% in LOS ≤30 days and 28.5% in LOS >30 days). In LOS ≤30 days, S. aureus was the second most prevalent pathogen followed by Enterococcus spp. (25.2% and 13.7%, respectively. Whereas in the LOS >30 days, Enterococcus spp. was more prevalent than S. aureus (24.2% vs 15.8%). The most prevalent pathogen for all DRG groups was Enterobacteriaceae. The second most prevalent pathogen for MP cancer, solid tumor cancer, and transplant groups was Enterococcus spp.; however, S. aureus was the second most prevalent for the reference group.



Dr. Septimus's Annotations

Key findings from this study include a higher burden of HOB and admission rates in MP cancer and transplant groups compared to the reference group. There were more cases of cancer and transplant patients which make clinical sense as both populations are at higher risk for complicated hospitalizations. This analysis focused on these patient populations compared to a reference group with further stratification of cancer patients into those with solid tumor vs MP cancer types. MP cancer and transplant patient populations have several clinical features in common that increase susceptibility to infection. Both groups are likely to be immunocompromised: transplant patients by intentional immune suppressive

agents to enhance transplanted organ viability, and MP cancer by the underlying illness and chemotherapy. Solid tumor cancer patients were more likely to have more admissions and may not be as chronically immune compromised until after they received chemotherapy or immunomodulating therapy. This may be why the HOB rates are similar between the MP cancer and transplant patients but also similar between solid tumor and reference patients.

"Hospitalizations with [myeloproliferative] cancer and transplant demonstrated higher [hospital-onset bacteremia and fungemia] burden compared to the reference group, regardless of [length of stay] category."

A recent study evaluating HOB prevention in a tertiary care hospital setting determined that ~56.0% of HOBs were not preventable by providers. The study attributed this to patients with HOB presenting with more complex disease states. [Am J Infect Control 2024; 52:195–199] Understanding the pathogens associated with HOB in at-risk populations can further direct efforts as certain organisms can originate from known reservoirs (i.e., Enterobacteriaceae from GI sources, S. aureus from skin or soft tissue, etc.). The goal of HOB is to provide additional opportunities to improve patient safety.

BOTTOM LINE

MP (myeloproliferative) cancer, and transplant patients had a higher burden of HOB (hospital-onset bacteremia) compared to other hospitalized patients regardless of LOS. What percentage of these infections are preventable should be further evaluated to inform quality metrics involving reportable bacteremia and fungemia. This study underscores the critical need for targeted infection prevention strategies in cancer and transplant patients.

16

Incidence and risk factors for central venous access device failure in hospitalized adults: A multivariable analysis of 1892 catheters

Journal of Hospital Medicine published May 27, 2024, Vol. 19, Iss. 10, p. 905-917
DOI: 10.1002/jhm.13414

Investigators in Australia performed a secondary analysis of a multicenter randomized trial originally published in 2021. [Lancet 2021; 397:1447-1458] to determine the incidences of all-cause central line failure and specific complications (central line–associated bloodstream infections, catheter occlusion, dislodgement, fracture, thrombosis, and pain). The original trial in 2021 studied infusion set replacement every 7 days versus every 4 days. In both central lines (CVAD) and peripheral line (PAC) patients, rates of catheter-related bloodstream infections (CLABSIs) were similar with infusion set replacement every 7 days or every 4 days (1.8% and 1.5% for CVADs; 0.3% and 0% for PACs).

In this current study almost 1900 CVADs (43% nontunneled CVADs[NTCVAD], 40% PICCs, 17% tunneled CVADs[TCVAD]) in adult patients were included in the analysis. Overall, the failure rate was 10%, and more than half of failures were CLABSIs. Catheter occlusion and dislodgement each caused ≈17% of failures. Per 1000 catheter-days, failure incidences were 8, 8, and 6 in PICCs, nontunneled CVADs, and tunneled CVADs, respectively. Antimicrobial nontunneled CVADs were associated with significantly fewer CLABSIs than were other CVADs (hazard ratio, 0.23), but they were used in only 50% of patients with nontunneled CVADs. Nontunneled CVADs that were inserted at nonstudy hospitals were 7 times more likely to become dislodged than those placed at study hospitals.

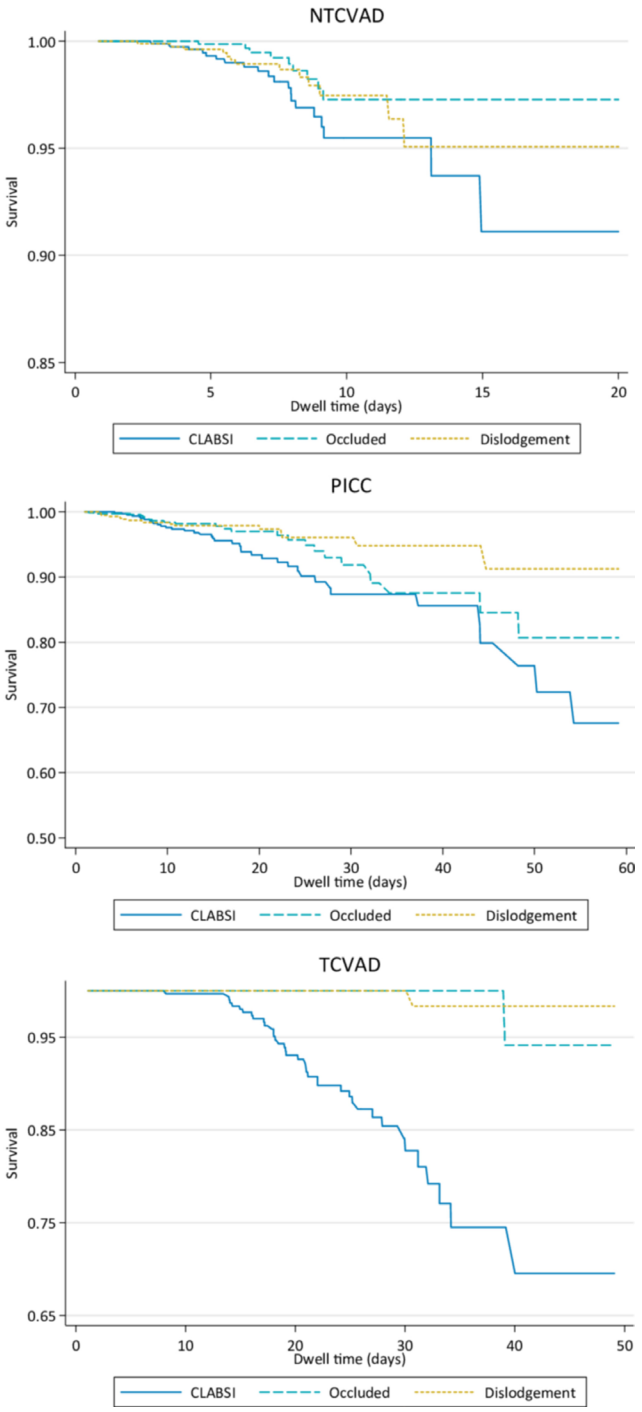
Patients at highest risk of CLABSI are those with PICCs receiving blood products or without antimicrobial (nontunneled) NTCVADs, and hematology/oncology patients with diabetes, chemotherapy treatment, no lipid treatment, and ≤2 lumen (tunneled) TCVADs.

CLABSI has the highest attributable patient risk of any CVAD complication with significant mortality and costs US $45,814 per case. [JAMA Int Med. 2013; 173:2039-2046] This data suggests that clinicians should consider using antimicrobial nontunneled CVADs to prevent CLABSI. Antimicrobial CVADs have been recommended for patients who are immunocompromised or have substantial risk for infection, particularly if catheters will be in place for longer than 5 days. Additionally, this study implies that nurses and clinicians should have heightened awareness about securing nontunneled CVADs especially when patients are transferred.

In the Compendium's "Strategies to prevent central line-associated bloodstream infections in acute-care hospitals: 2022 Update" use antiseptic- or antimicrobial-impregnated central venous catheter is listed as an additional approach (Quality of Evidence: HIGH in adult patients and Quality of Evidence: MODERATE in pediatric patients). In addition, based on the 2021 trial routine replacement of administration sets not used for blood, blood products, or lipid formulations can be performed at intervals up to 7 days (Quality of Evidence: HIGH) which is considered an essential practice. [Infect Control Hosp Epidemiol 2023;44: s31-s47]

BOTTOM LINE

This analysis of a large prospectively collected data set of central venous access devices (CVAD) outcomes in a hospitalized adult cohort has demonstrated that one in 10 CVADs failed prematurely with the most prevalent complication being central line-associated bloodstream infection (CLABSI) across all device types. Patients at highest risk of CLABSI are those with PICCs receiving blood products or without antimicrobial (nontunneled) NTCVADs, and hematology/oncology patients with diabetes, chemotherapy treatment, no lipid treatment, and ≤2 lumen (tunneled)TCVADs. Infection prevention practices are essential in reducing CLABSI.



NT: Nontunneled T: Tunneled

17

2023 National and State Healthcare-Associated Infections (HAI) Progress Report Shows Improvements in Preventing HAIs

CDC has released the 2023 National and State Healthcare-Associated Infections (HAI) Progress Report, which shows progress in preventing several important HAIs in acute care hospitals (ACHs) compared to 2022. This HAI Progress Report continues to show decreases in HAIs that align more closely with progress made prior to the start of the Covid-19 pandemic in 2020.

Decreases in national standardized infection ratio (SIR) from 2022 to 2023 for some HAIs in ACHs included:

- 16% decrease in hospital-onset methicillin-resistant Staphylococcus aureus (MRSA) bacteremia
- 15% decrease in central line-associated bloodstream infections (CLABSI)
- 13% decrease in hospital-onset Clostridioides difficile (C. difficile) infection
- 11% decrease in catheter-associated urinary tract infections (CAUTI)
- 5% decrease in ventilator-associated events (VAE)
- 8% Increase in surgical site infections (SSIs) in abdominal hysterectomy.
- Among (rehab)IRFs, there was a 14% decrease in hospital-onset C. difficile infection and an 8% increase in CAUTI; otherwise, there were no significant changes in CLABSI and hospital-onset MRSA 2023 SIRs compared with 2022.
- Among LTACHs, there was a 13% decrease in hospital-onset C. difficile infection, otherwise, there were no significant changes in 2023 SIRs compared with 2022.

2023 National HAI SIRs compared to 2022 SIRs by Facility Setting

HAI Type	Acute Care Hospitals (ACH)	Inpatient Rehab Facilities (IRF)	Long-term Acute Care Hospitals (LTACH)
CLABSI, all locations	↓ 15%	No change	No change
CAUTI, all locations	↓ 11%	↑ 8%	No change
VAE, all locations	↓ 5%		No change
SSI: Colon surgery	No change		
SSI: Abdominal hysterectomy	↑ 8%		
LabID MRSA bacteremia	↓ 16%	No change	No change
LabID CDI	↓ 13%	↓ 14%	↓ 13%

Dr. Septimus's Annotations

This report shows a significant reversal from 2020-2021 report seen below.

	2020 Q1	2020 Q2	2020 Q3	2020 Q4
CLABSI	↓ -11.8%	↑ 27.9%	↑ 46.4%	↑ 47.0%
CAUTI	↓ -21.3%	No Change[1]	↑ 12.7%	↑ 18.8%
VAE	↑ 11.3%	↑ 33.7%	↑ 29.0%	↑ 44.8%
SSI: Colon surgery	↓ -9.1%	No Change[1]	↓ -6.9%	↓ -8.3%
SSI: Abdominal hysterectomy	↓ -16.0%	No Change[1]	No Change[1]	↓ -13.1%
Laboratory-identified MRSA bacteremia	↓ -7.2%	↑ 12.2%	↑ 22.5%	↑ 33.8%
Laboratory-identified CDI	↓ -17.5%	↓ -10.3%	↓ -8.8%	↓ -5.5%

The last few years have seen steady improvement, back in line with pre-Covid-19. Compared to 2022, 30 states improved performance on at least two HAIs, while two states performed worse, the report said. Against the 2015 baseline, a SIR of 1, 49 states performed better on at least three HAIs.

The Compendium Update published in 2023 provides a roadmap to eliminating preventable HAIs.

BOTTOM LINE

This report highlights substantial improvement in reducing healthcare-associated infections (HAIs) from 2020-2021 during Covid-19. While much progress has been made, more needs to be done to prevent healthcare-associated infections.

18 WHO Global Tuberculosis Report 2024

The global rise in the number of people diagnosed with TB (incident cases) that started during the Covid-19 pandemic has slowed and has started to stabilize. The total was 10.8 million in 2023, a small increase from 10.7 million in 2022 although still much higher than 10.4 million in 2021 and 10.1 million in 2020. Most of the global increase in incident cases between 2022 and 2023 reflects population growth. The TB incidence rate (new cases per 100,000 population) in 2023 was 134[8.2 million], a very small (0.2%) increase compared with 2022. Most of the people who develop TB disease each year are in 30 high TB burden countries, which account for 87% of the global total in 2023. Five countries accounted for 56% of the worldwide total: India (26%), Indonesia (10%), China (6.8%), the Philippines (6.8%) and Pakistan (6.3%). In 2023, 55% of people who developed TB were men, 33% were women and 12% were children and young adolescents. The global number of deaths caused by TB fell in 2023, reinforcing the decline that was achieved in 2022 after 2 years of increases the Covid-19 pandemic (2020 and 2021). TB caused an estimated 1.25 million deaths in 2023, including 1.09 million among HIV-negative people and 161,000 among people with HIV. The total was down from best estimates of 1.32 million in 2022, 1.42 million in 2021 and 1.40 million in 2020, and below the pre pandemic level of 1.34 million in 2019. Despite this progress, TB has returned to being the world's leading cause of death from a single infectious agent replacing Covid-19.

The treatment success rate for drug-susceptible TB remains high (at 88%) and has improved to 68% for MDR/ RR-TB. See below for end of TB Strategies

PRINCIPLES

1. Government stewardship and accountability, with monitoring and evaluation
2. Strong coalition with civil society organizations and communities
3. Protection and promotion of human rights, ethics and equity
4. Adaptation of the strategy and targets at country level, with global collaboration

PILLARS AND COMPONENTS

1. INTEGRATED, PATIENT-CENTRED CARE AND PREVENTION

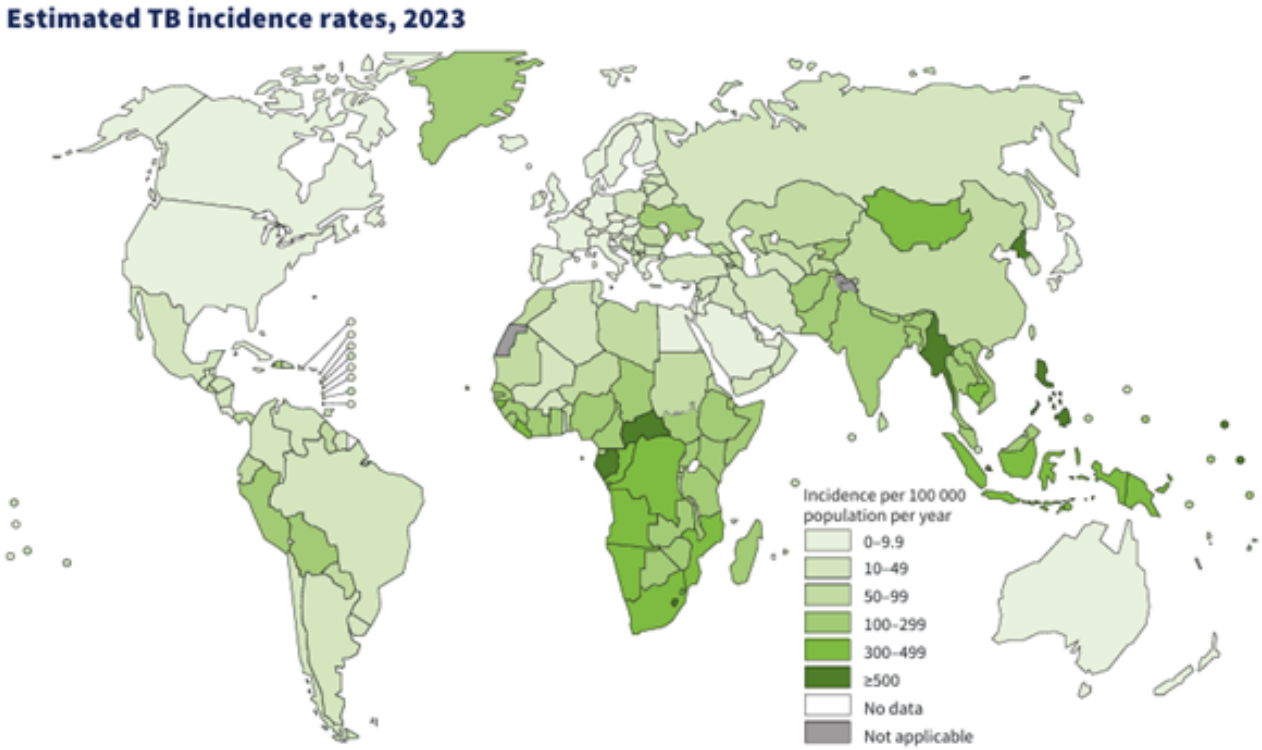
A. Early diagnosis of TB including universal drug-susceptibility testing, and systematic screening of contacts and high-risk groups
B. Treatment of all people with TB including drug-resistant TB, and patient support
C. Collaborative TB/HIV activities, and management of comorbidities
D. Preventive treatment of persons at high risk, and vaccination against TB

2. BOLD POLICIES AND SUPPORTIVE SYSTEMS

E. Political commitment with adequate resources for TB care and prevention
F. Engagement of communities, civil society organizations, and public and private care providers
G. Universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control
H. Social protection, poverty alleviation and actions on other determinants of TB

3. INTENSIFIED RESEARCH AND INNOVATION

I. Discovery, development and rapid uptake of new tools, interventions and strategies
J. Research to optimize implementation and impact, and promote innovations



Dr. Septimus's Annotations

TB replaced Covid-19 to become the top cause for infectious disease-related deaths in 2023. Last year about 8.2 million people were newly diagnosed, meaning they could access suitable treatment – the highest number recorded since WHO began global TB monitoring in 1995 – up from 7.5 million.

BOTTOM LINE

Tuberculosis replaced Covid-19 to become the top cause for infectious disease-related deaths in 2023. Accelerating progress towards ending TB requires that commitments made in 2023 are translated into action. More needs to be done.

19

Progress Toward Measles Elimination — Worldwide, 2000–2023.

Morbidity and Mortality Weekly Report November 14, 2024, 73(45);1036–1042

Worldwide, there were an estimated 10.3 million cases of measles in 2023, a 20% increase from 2022, according to new estimates from the WHO and the CDC. Measles is a vaccine preventable infection with 2 doses of measles vaccine; yet more than 22 million children missed their first dose of measles vaccine in 2023. Globally, an estimated 83% of children received their first dose of measles vaccine last year, while only 74% received the recommended second dose. Coverage with measles-containing vaccine (MCV) is lower, and measles incidence is higher, in low-income countries and countries experiencing fragile, and conflict-affected settings, which exacerbate inequities. During 2000–2023, an estimated 60.3 million measles deaths were averted by vaccination.

Dr. Septimus's Annotations

Inadequate immunization coverage globally is driving the surge in cases, noting that coverage of 95% or greater of 2 doses of measles vaccine is needed in each country and community to prevent outbreaks and protect populations from this highly contagious human virus. As a result of global gaps in vaccination coverage, 57 countries experienced large or disruptive measles outbreaks in 2023, affecting all regions except the Americas, and representing a nearly 60% increase from 36 countries in the previous year. Nearly half of all large or disruptive outbreaks occurred in the African region.

The new data show that an estimated 107,500 people, mostly children aged <5 years, died due to measles in 2023. Although this is an 8% decrease from the previous year, far too many children are still dying from this preventable disease.

As measles cases surge and outbreaks increase, the world's elimination goal, as laid out in Immunization Agenda 2030, is under threat. At the end of 2023 worldwide, 82 countries had achieved or maintained measles elimination.

In the US The CDC had recorded 58 cases of measles, as of March 14, 2024, the same as the whole of 2023. Most cases reported this year have been among children aged 12 months and older who had not received MMR vaccine. According to the CDC, coverage with measles vaccines among US children in kindergarten has decreased to 93.1% in the 2022–2023 school year from 95.2% in 2019–2020. In general, it requires 95% vaccine coverage to prevent outbreaks among populations.

BOTTOM LINE

Declines in measles vaccination rates globally have also increased the risk of measles outbreaks worldwide. Measles is one of the most contagious human viruses and is almost entirely preventable through vaccination. Progress toward eliminating measles will require improved surveillance and urgent and targeted improvements in coverage to reach all children with 2 MCV(measles-containing vaccine) doses.

20

Comparative Emergence of Maribavir and Ganciclovir Resistance in a Randomized Phase 3 Clinical Trial for Treatment of Cytomegalovirus Infection

The Journal of Infectious Diseases published online September 20, 2024
DOI: 10.1093/infdis/jiae469

Because of adverse effects of traditional CMV DNA polymerase inhibitor antiviral drugs such as ganciclovir and foscarnet, including myelotoxicity and nephrotoxicity, there has been a need for the development of alternative options with different viral drug targets and avoidance of these toxicities. Letermovir, a CMV terminase inhibitor, has been approved for prophylaxis, and maribavir, a viral UL97 kinase inhibitor, has been approved for treatment of refractory CMV infection with or without drug resistance. A concern about the newer CMV antiviral drugs is their lower genetic barrier to the development of drug resistance as observed in vitro. [Antimicrob Agents Chemother 2015; 59:6588–93] A phase 3 trial of maribavir for the treatment of refractory (with or without resistance) CMV infection revealed emergent maribavir resistance in 26% of treated patients. [J Infect Dis 2023; 229:413–21]

This phase 3 trial (AURORA, NCT02927067) involved 547 hematopoietic cell transplant (HCT) recipients with first-episode CMV infection (without end-organ disease), who received study drug after 1:1 randomization to maribavir at 400 mg twice daily, or valganciclovir at 900 mg twice daily, for a planned duration of 8 weeks with 12 weeks of follow-up. Serial plasma CMV DNA viral quantitation was performed using the COBAS AmpliPrep/TaqMan assay at a central laboratory. Viral clearance was defined as a reading of <137 IU/mL (lower limit of quantitation) in consecutive post-baseline samples, separated by 5 days.

The primary efficacy endpoint in the study was defined as clearance of plasma CMV DNA at the end of study week 8, with no alternative antiviral drug given up to that point. CMV therapy given prior to study entry was recorded. Genotypic assessment of drug resistance was performed by fluorescent dideoxy (Sanger) sequencing of nested polymerase chain amplification products of plasma DNA extracts. The entire coding sequences of CMV genes UL27, UL54, and UL97 were targeted for sequencing, using overlapping bidirectional sequencing primers.

An equal number (n=241) received valganciclovir or maribavir for at least 21 days (median 55-56 days). Among them, drug resistance mutations were detected in 24 (10%) maribavir recipients at 35-125 days (median 56) after starting therapy, including in 12 of 14 who experienced a viral load rebound while on therapy. Ganciclovir resistance mutations developed in 6 (2.5%) valganciclovir recipients at 66-110 days (median 90). One maribavir recipient developed a novel UL97 gene mutation (P-loop substitution G343A) that conferred strong maribavir and ganciclovir resistance in vitro. Viral clearance was confirmed in 17 (74%) of 23 patients with emergent maribavir resistance after re-treatment with an alternative CMV antiviral drug.

Dr. Septimus's Annotations

In this randomized treatment trial for first-episode asymptomatic CMV infection after HCT, emergent maribavir resistance was detected in 10% of those who received at least 3 weeks and a median of 8 weeks of maribavir therapy, significantly more often than the 2.5% who developed ganciclovir resistance after receiving a comparable duration of valganciclovir treatment. The overall incidence of maribavir resistance in this study was lower than the 26% reported in a previous phase 3 trial of treatment for refractory ± resistant CMV infection in transplant recipients. [J Infect Dis 2023; 229:413–21] A viral load rebound while on treatment after an initial response (encountered in this study with maribavir but not valganciclovir) suggests emerging drug resistance. The more frequent and earlier detection of maribavir drug resistance mutation (DRM) is consistent with in vitro data suggesting that resistance to the newer CMV antiviral drugs letermovir and maribavir emerges after fewer cell culture passages than for ganciclovir and foscarnet. Results of this trial, with limited prior antiviral exposure, comparable starting viral loads and treatment durations, are the best evidence for a clinically significant difference in the viral genetic barrier to drug resistance of newer antivirals in comparison with valganciclovir. Viral DNA clearance was observed in most cases of emergent maribavir resistance after alternative therapy, typically valganciclovir or ganciclovir, illustrating the absence of ganciclovir cross resistance of the most common maribavir drug resistance mutation [DRM]. Existing information indicates that maribavir and ganciclovir should not be used in combination. There were not enough serial virologic and genotypic data for individual patients that would assess longer-term outcomes of salvage therapy and the persistence of maribavir resistance mutations after treatment is discontinued.

BOTTOM LINE

This trial confirmed clinically significant drug resistance to be more common with maribavir than valganciclovir after 3–8 weeks of treatment for asymptomatic CMV infection at similar starting viral loads, consistent with a hypothesis of a lower viral genetic barrier to resistance developed from in vitro observations. This difference may account for the lower observed primary endpoint response rate with maribavir. In circumstances where maribavir is chosen due to fewer adverse effects, this study shows that emergent resistance can still be manageable by timely genotypic monitoring and switching to alternative therapy as necessary.

21

Mpox Cluster Caused by Tecovirimat-Resistant Monkeypox Virus — Five States, October 2023 February 2024

Morbidity and Mortality Weekly Report October 10, 2024; 43:903-905

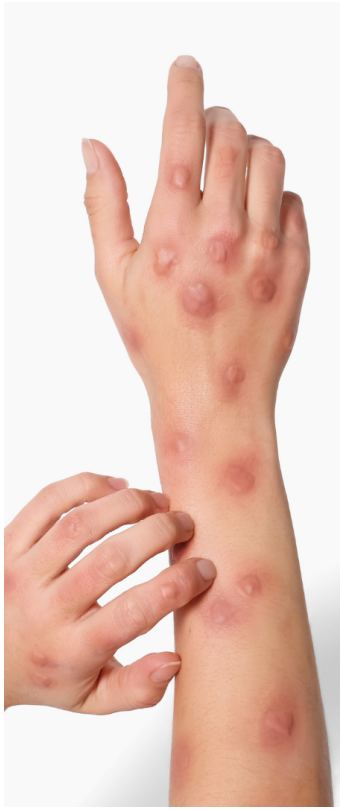
The antiviral drug tecovirimat has been used extensively to treat US mpox cases since the start of a global outbreak in 2022. Mutations in the mpox viral protein target (F13 or VP37) that occur during treatment can result in resistance to tecovirimat. [J Antimicrob Chemother 2015;70:1367–80] CDC and public health partners have conducted genetic

surveillance of monkeypox virus (MPXV) for F13 mutations through sequencing and monitoring of public databases. MPXV F13 mutations associated with resistance have been reported since 2022, typically among severely immunocompromised mpox patients who required prolonged courses of tecovirimat. Antimicrob Agents Chemother 2023;67: e0097223] Most patients with infections caused by MPXV with resistant mutations had a history of tecovirimat treatment; however, spread of tecovirimat resistant MPXV was reported in California during late 2022 to early 2023 among persons with no previous tecovirimat treatment. This report describes a second, unrelated cluster of tecovirimat-resistant MPXV among 18 persons with no previous history of tecovirimat treatment in multiple states.

Between 2023 and 2024, specimens from 18 patients in 5 states have yielded tecovirimat-resistant MPXV. Four patients had traveled to states in which this resistance mutation was recognized. None of the 18 had previously received tecovirimat. Isolates contained mutations in an MPXV gene that has been associated with resistance to the drug.

Dr. Septimus's Annotations

This is the second report of a tecovirimat-resistant MPXV variant spreading among persons in the US who had no documentation of previous tecovirimat treatment, and the first report of interstate spread. Because not all viruses from mpox cases are sequenced, these findings likely underestimate the prevalence of this newly recognized drug-resistant variant. Tecovirimat, a drug approved for treatment of smallpox based on animal studies, is being evaluated for efficacy in treating infection with mpox virus (MPXV) and has been used widely in the US since the worldwide mpox outbreak was recognized in 2022.



I am not surprised when drug resistance due to a viral mutation arises in patients who have received that drug — however, no such prior treatment had occurred in the present cases, emphasizing the transmissibility of this MPXV variant. The investigators suggest that lack of routine viral sequencing makes under-reporting of such resistance likely. While their recommendations regarding tecovirimat use such as adhering to indications may reduce the emergence of resistant mutants, prevention of viral transmission remains a priority with vaccination of high-risk individuals, and development of new drugs for managing mpox should be priorities.

BOTTOM LINE

Clusters of infection with a tecovirimat-resistant mpox variant have recently occurred in five states, mostly among persons who had not received tecovirimat. Prevention of viral transmission remains a priority including vaccination of high-risk individuals, and development of new drugs for managing mpox should be priorities.

22 Africa's mpox Outbreak Update

Last week African countries reported 2,532 new mpox cases, mostly in the Democratic Republic of the Congo (DRC) and Burundi, pushing the total since the first of the year to 50,840 cases according to officials from Africa Centers for Disease Control and Prevention (Africa CDC). The officials also reported 32 more deaths from the virus. Cases continue to rise in Uganda and the outbreak has spread to one more district of Central African Republic (CAR), Paoua, which is on the border with Chad.

One of the remaining challenges is immunization hasn't yet started for children, one of the hardest-hit groups, because of regulatory and supply issues. Currently, the Jynneos vaccine is recommended for adolescents and adults only. Kaseya said Africa CDC is still working with Japan on a plan to receive about 3 million doses of the LC16 vaccine, which the country used in the 1970s to vaccinate young children. Rwanda and the DRC, the two countries that have started vaccinating, have met or passed their vaccine targets. Nigeria's campaign was slated to begin on October 29, but due to logistical issues is now expected to launch on November 18. US has pledged 1 million vaccine doses and $500 million to support the outbreak response.

Dr. Septimus's Annotations

The UK Health Security Agency (HSA) recently announced two more clade 1b mpox cases, both of them contacts of the country's first imported case. The country reported its first clade 1b case on October 30th in a person in London who had recently traveled to countries in Africa where the virus is spreading. One further case of Clade Ib mpox has now been detected in a household contact of the first case, the UK Health Security Agency (UKSHA) has confirmed. This brings the total number of confirmed cases to 4. The United Kingdom was the fifth country outside of Africa to report an imported case of clade 1b mpox. The existing evidence suggests that mpox Clade Ib can be a more severe disease than Clade II. In the US the CDC is working to protect the public and prevent transmission. This includes securing vaccines and vaccinating high-risk people plus equipping healthcare professionals with the guidance and tools they need to respond to cases safely.

BOTTOM LINE

Mpox clade 1b cases continue to rise in Africa and are now spreading to other countries outside of Africa. Clade 1b mpox can be more severe than Clade II. Prevention of viral transmission remains a priority including vaccination of high-risk individuals.

23

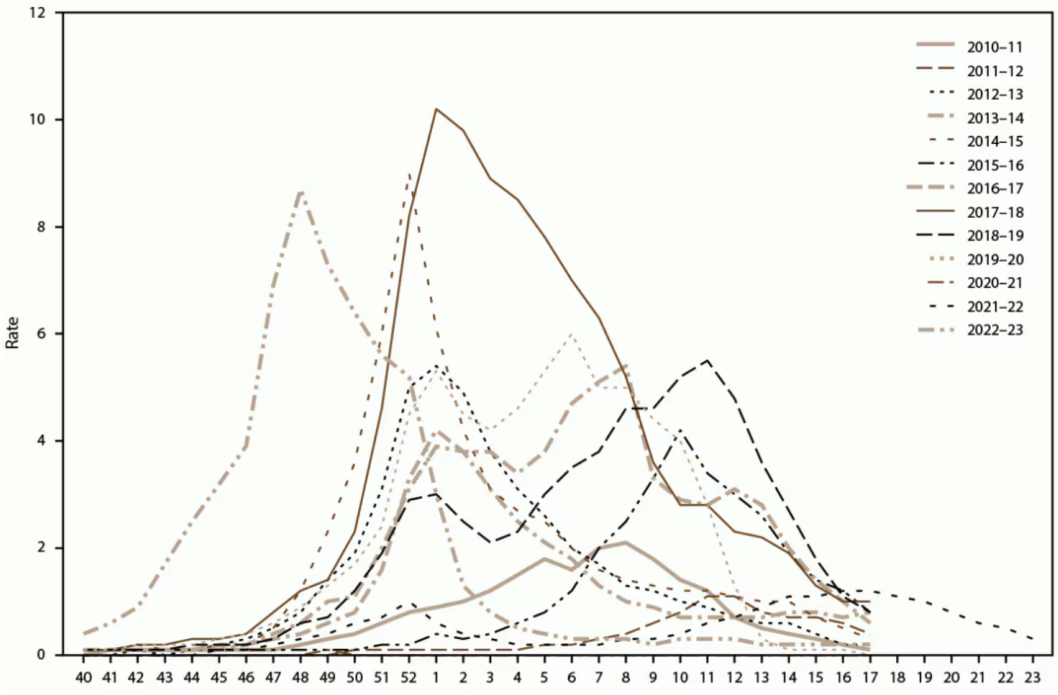
Laboratory-Confirmed Influenza US based Hospitalizations Among Children and Adults — Influenza Hospitalization Surveillance Network, United States, 2010–2023.

Morbidity and Mortality Weekly Report October 31, 2024

Since 2003, the Influenza Hospitalization Surveillance Network (FluSurv NET) has been conducting population-based surveillance for laboratory-confirmed influenza-associated hospitalizations in the US, including weekly rate estimations and descriptions of clinical characteristics and outcomes for hospitalized patients. However, a comprehensive summary of trends in hospitalization rates and clinical data collected from the surveillance platform has not been available. This report contains a comprehensive summary of data collected by FluSurv-NET from the 2010–11 through 2022–23 influenza seasons, including trends in cumulative rates, clinical characteristics, and outcomes for patients hospitalized with laboratory-confirmed influenza virus infections. A case of a laboratory-confirmed influenza associated hospitalization was defined as hospitalization of a person residing in the surveillance catchment area with a positive influenza laboratory result from a viral culture, direct or indirect fluorescent antibody staining, rapid antigen assay, or molecular assay (rapid or standard real-time reverse transcription–polymerase chain reaction (PCR] assays) within 14 days before or any time during hospitalization. Hospitalizations with admission dates of October 1–April 30 of each season are included; however, after discussion among CDC and participating sites, active surveillance was extended beyond April 30 to June 11 during the 2021–22 influenza season due to unusually late influenza activity.

During the 2010–11 to 2022–23 influenza seasons, laboratory-confirmed influenza-associated hospitalization

rates varied significantly across seasons. Before the Covid-19 pandemic, hospitalization rates per 100,000 population ranged from 8.7 (2011–12) to 102.9 (2017–18) and had consistent seasonality. After SARS-CoV-2 emerged, the hospitalization rate for 2020–21 was 0.8, and the rate did not return to recent prepandemic levels until 2022–23. Inconsistent seasonality also was observed during 2020–21 through 2022–23, with influenza activity being very low during 2020–21, extending later than usual during 2021–22, and occurring early during 2022–23. Molecular assays, particularly multiplex standard molecular assays, were the most common influenza test type in recent seasons, increasing from 12% during 2017–18 for both pediatric and adult cases to 43% and 55% during 2022–23 for pediatric and adult cases, respectively. During each season, adults aged ≥65 years consistently had the highest influenza-associated hospitalization rate across all age groups, followed in most seasons by children aged 0–4 years. Black or African American and American Indian or Alaska Native persons had the highest age-adjusted influenza-associated hospitalization rates across these seasons. Among patients hospitalized with influenza, the prevalence of at least one underlying medical condition increased with increasing age, ranging from 36.9% among children aged 0–4 years to 95.4% among adults aged ≥65 years. Consistently across each season, the most common underlying medical conditions among children and adolescents were asthma, neurologic disorders, and obesity. The most common underlying medical conditions among adults were hypertension, obesity, chronic metabolic disease, chronic lung disease, and cardiovascular disease. Although influenza antiviral use increased during 2010–11 through the 2017–18 influenza seasons, it decreased from 90.2% during 2018–19 to 79.1% during 2022–23, particularly among children and adolescents. Admission to the intensive care unit, need for invasive mechanical ventilation, and in-hospital death ranged from 14.1% to 22.3%, 4.9% to 11.1%, and 2.2% to 3.5% of patients hospitalized with influenza, respectively, during the reported surveillance period.



Dr. Septimus's Annotations

Influenza continues to cause severe morbidity and mortality, particularly in older adults, and disparities have persisted in racial and ethnic minority groups. Persons with underlying medical conditions represented a large proportion of patients hospitalized with influenza. Increased use of multiplex tests and other potential changes in facility-level influenza testing practices (e.g., influenza screening at all hospital admissions) could have implications for the detection of influenza

infections among hospitalized patients. Proportions of patients who received antiviral treatment decreased since the 2018–19 season, most notably for children and adolescents, and highlight missed opportunities to prevent influenza-associated complications among those at increased risk for influenza-associated complications. Antiviral treatment is recommended for all hospitalized patients with suspected or confirmed influenza regardless of duration of illness. [Clin Infect Dis 2019;68:e1–47] Earlier treatment initiation provides greater clinical benefit compared with late initiation, and treatment should not be delayed while laboratory results are pending.[Clin Infect Dis 2015;61:1807–14] The decline in antiviral treatment of hospitalized patients with influenza from 90% during the 2018–19 influenza season to 79% during the 2022–23 season represents a concerning trend, and highlights missed opportunities to prevent influenza-associated complications among those at increased risk for severe influenza complications.

Influenza testing was clinician-driven, likely leading to under ascertainment of influenza infection in seasons before the Covid-19 pandemic. In addition, FluSurv-NET has geographically diverse sites, but the network's catchment area covers only 8.8%–9.5% of the US population. Therefore, findings might not be generalizable to all persons hospitalized with influenza in the US.

BOTTOM LINE

Influenza continues to cause severe morbidity and mortality, particularly in older adults, and disparities have persisted in racial and ethnic minority groups. Persons with underlying medical conditions represented a large proportion of patients hospitalized with influenza. Continued influenza surveillance is critical to monitor progress in efforts to encourage antiviral treatment and improve clinical outcomes for persons hospitalized with influenza. In addition, efforts to increase access to preventive measures for influenza such as vaccination is essential.

24

Influenza and COVID-19 Vaccination Coverage Among Health Care Personnel — National Healthcare Safety Network, United States, 2023–24 Respiratory Virus Season.

Morbidity and Mortality Weekly Report October 31, 2024; 73:966-972

The National Healthcare Safety Network (NHSN) tracks vaccination among healthcare workers in hospitals, clinics, and nursing homes. From October 2023 to March 2024, NHSN defined up-to-date Covid-19 vaccination as receipt of a 2023-2024 Covid-19 vaccine, and up-to-date seasonal flu vaccine with that season's immunization.

Among approximately 8.8 million healthcare personnel (HCP) working in more than 4,000 acute care hospitals, flu vaccine coverage was 80.7%. Among approximately 2.1 million HCP working in 14,294 nursing homes, flu vaccine coverage was only 45.4%! [this is awful]

Covid-19 vaccine uptake was even lower. Among HCP working in acute care hospitals, only 15.3% were vaccinated. The percentage was even lower in nursing homes, at 10.5% overall. Uptake in Covid-19 vaccines decreased sharply from the previous year.

Dr. Septimus's Annotations

The Advisory Committee on Immunization Practices (ACIP) recommends annual influenza vaccination for HCP. In September 2023, ACIP also recommended receipt of a 2023–2024 Covid-19 vaccine for all persons aged ≥6 months. Although the Covid-19 public health emergency has ended, thousands of Covid-19–related hospitalizations and hundreds of Covid-19–associated deaths still occur weekly. Influenza vaccination among HCP has not returned to 2019 levels, and the number of Covid-19 vaccinations has continued to decline each season, underscoring the ongoing challenge of promoting vaccination among health care personnel during the post pandemic period.

This report includes data reported by facilities on behalf of HCP, which might have resulted in underestimates of vaccination acquired outside the health care facility. In addition, vaccination coverage could not be stratified by recent history of SARS-CoV-2 infection. CDC recommendations state that persons might consider delaying an updated vaccine by 3 months after experiencing SARS-CoV-2 infection. Therefore, some personnel might have declined vaccination against Covid-19 after a recent infection with SARS-CoV-2.

BOTTOM LINE

Respiratory viral diseases including influenza and Covid-19 pose risks to health care personnel and our patients in US health care settings, and vaccination of health care personnel is still the most effective strategy for maintaining a healthy workforce and improving health care system resiliency. The current findings highlight the need to further investigate barriers to vaccination among health care personnel and identify additional strategies to address these challenges.

25 ACIP votes to simplify meningococcal B vaccine recommendations

The CDC ACIP (Advisory Committee on Immunization Practices) voted unanimously to "harmonize" serogroup B meningococcal vaccine recommendations for healthy adolescents and young adults and children who have a higher risk for infection.

The ACIP voted to recommend a two-shot series for healthy adolescents and young adults aged 16 to 23 years given 6 months apart and a three-dose series for high-risk children aged 10 years or older given over the course of 6 months for MenB-4C, branded by GSK as Bexsero. These match the recommendations for MenB-FHbp, Pfizer's Trumenba vaccine. The vote followed the FDA's approval in August of new dosing schedules for MenB-4C, which are based on risk and shared clinical decision-making.

Dr. Septimus's *Annotations*

I think that it is important to harmonize and simplify to optimize uptake of vaccines. In addition to MenB vaccines, there are two other types of meningococcal vaccines: quadrivalent vaccines covering serogroups A, C, W and Y (MenACWY), and Pfizer's pentavalent vaccine, Penbraya, which covers all five (MenABCWY). MenABCWY was approved by the FDA for people aged 10 to 25 years and recommended by the CDC last year when MenACWY and MenB vaccines are indicated at the same time.

26 CDC Advisory Committee Votes to Lower Age Recommendation For Vaccines That Protect Against Pneumococcal Disease

The CDC ACIP (Advisory Committee on Immunization Practices) voted in favor of lowering the age recommendation for vaccines made by Pfizer Inc. and Merck & Co. that protect against pneumococcal disease. Members of the CDC's ACIP panel voted 14-to-1 to recommend all adults aged 50 and older get vaccinated to prevent the bacterial infections behind pneumonia and meningitis. The committee's recommendation was endorsed by CDC Director Mandy Cohen.

Lowering the age for pneumococcal vaccination gives more adults the opportunity to protect themselves from invasive pneumococcal disease at the age when risk of infection substantially increases.

27

FDA Approves RSV Vaccine for The Prevention of Lower Respiratory Tract Disease (LRTD) Caused By RSV In Individuals Aged 18 Through 59 Years

The FDA approved Abrysvo (Pfizer) RSV vaccine for the prevention of lower respiratory tract disease (LRTD) caused by RSV in individuals aged 18 through 59 years.

Dr. Septimus's Annotations

This approval marks the unadjuvanted, bivalent RSV prefusion F (RSVpreF) vaccine as the first and only RSV vaccine designated for adults younger than 50 that are at increased risk for LRTD triggered by RSV. This is a welcome decision.

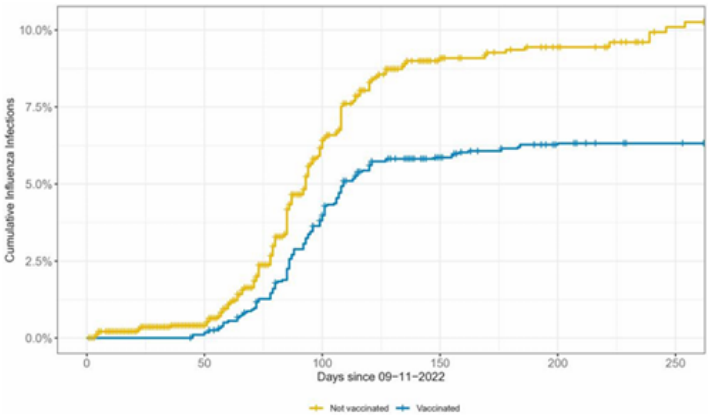
28

Influenza Vaccine Effectiveness Against Illness and Asymptomatic Infection in 2022–2023: A Prospective Cohort Study

Clinical Infectious Diseases published online October 24, 2024
DOI: 10.1093/cid/ciae491

In the HEROES-RECOVER cohort, adults at increased occupational risk of influenza exposure across 7 US sites provided weekly symptom reports and nasal swabs for PCR influenza testing. Laboratory-confirmed influenza virus infections were classified as symptomatic (≥1 symptom) or asymptomatic during the week of testing. Participants reported demographic information and vaccination through surveys; most sites verified vaccination through medical record and immunization registry review. Person-time was calculated as days from the site-specific influenza season start (September–October 2022) through date of infection, study withdrawal, or season end (May 2023). They compared influenza incidence among vaccinated versus unvaccinated participants overall, by symptom status, and by influenza A subtype. They estimated VE as (1 − adjusted hazard ratio) × 100%.

In total, 269 of 3785 (7.1%) participants had laboratory-confirmed influenza, including 263 (98%) influenza A virus infections and 201 (75%) symptomatic illnesses. Incidence of laboratory-confirmed influenza illness among vaccinated versus unvaccinated participants was 23.7 and 33.2 episodes per 100,000 person-days, respectively (VE: 38%; 95% CI: 15%–55%). The incidence of asymptomatic influenza virus infection was 8.0 versus 11.6 per 100,000 (VE: 13%; 95% CI: −47%, 49%).



Dr. Septimus's Annotations

During the 2022–2023 influenza season, influenza vaccination provided a significant reduction in the risk of any symptomatic influenza illness, but not asymptomatic infection, in this prospective occupational cohort. Overall rates of influenza virus infection and illness were low; fewer than 6% of vaccinated participants and 10% of

unvaccinated participants had laboratory-confirmed influenza virus infection during the 2022–2023 season. The cohort included highly vaccinated healthcare workers and less vaccinated first responders. The effectiveness of influenza vaccination against symptomatic infection during the 2022–2023 season in this cohort was similar to estimates from other observational studies using the test-negative study design. [J Infect Dis 2024; 230:141–51] Their findings are also consistent with studies from previous influenza seasons among highly exposed healthcare workers, which is important because influenza is a major cause of missed work, burden on healthcare and emergency response systems, and economic losses. [Vaccines (Basel) 2021; 9:1104] Of interest, they also found that influenza vaccination did not reduce the risk of asymptomatic infection. Although they controlled for occupational and site differences, there might be residual sources of unmeasured confounding. In addition, the HEROES-RECOVER cohort is more likely to be vaccinated (including a history of prior vaccination) and exposed to influenza virus than the general population.

BOTTOM LINE

Vaccination reduced incidence of symptomatic but not asymptomatic influenza virus infection, suggesting that influenza vaccination reduces progression from infection to illness.

29

CDC Recommends Second Dose of 2024-2025 COVID-19 Vaccine for People 65 Years and Older and for People Who are Moderately or Severely Immunocompromised.

October 23, 2024

CDC Advisory Committee on Immunization Practices' (ACIP) recommendation for people 65 years and older and those who are moderately or severely immunocompromised to receive a second dose of 2024-2025 Covid-19 vaccine six months after their first dose. These updated recommendations also allow for flexibility for additional doses (i.e., three or more) for those who are moderately or severely immunocompromised, in consultation with their healthcare provider (a strategy known as shared clinical decision making).

The recommendation acknowledges the increased risk of severe disease from Covid-19 in older adults and those who are immunocompromised, along with the currently available data on vaccine effectiveness and year-round circulation of Covid-19. The recommendation also provides clarity to healthcare providers on how many doses should be given per year to people who are moderately or severely immunocompromised and is meant to increase coverage of this second dose for that group.

Dr. Septimus's Annotations

Data continues to confirm the importance of vaccination to protect those most at risk for severe outcomes of Covid-19. Receiving recommended 2024-2025 Covid-19 vaccines can restore and enhance protection against the virus variants currently responsible for most infections and hospitalizations in the US. Covid-19 vaccination also may reduce the chance of long Covid. I am concerned about vaccine fatigue and uptake/acceptance of this new recommendation.

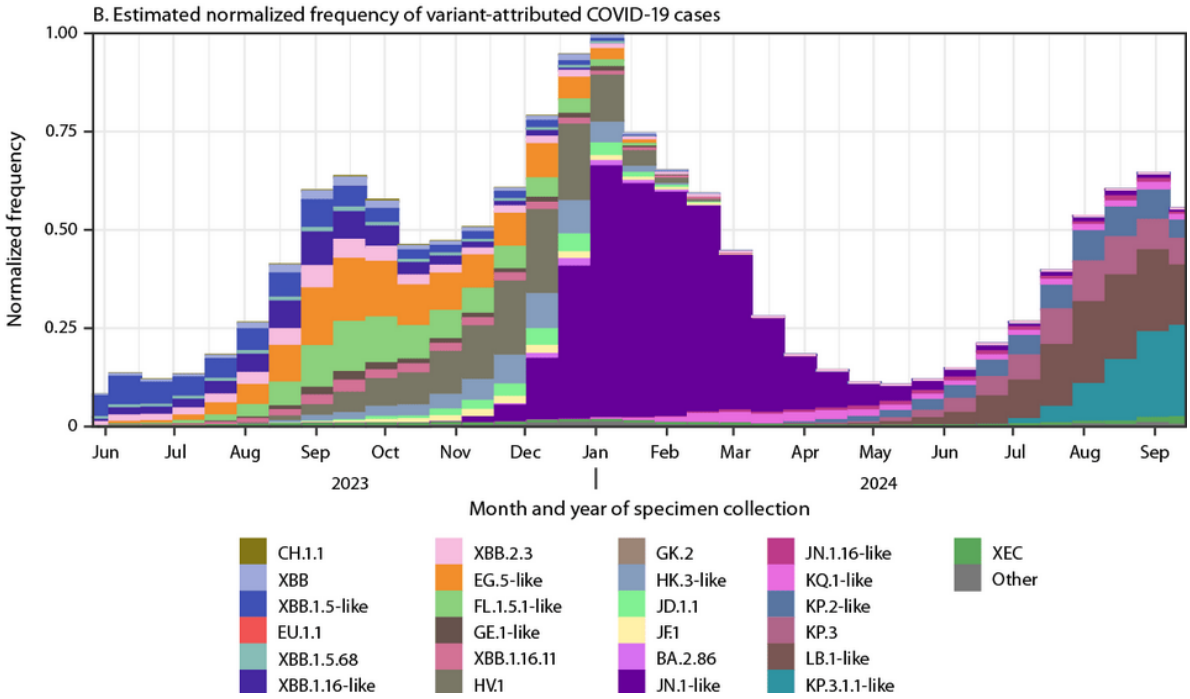
30

Genomic Surveillance for SARS-CoV-2 Variants: Circulation of Omicron XBB and JN.1 Lineages — United States, May 2023–September 2024.

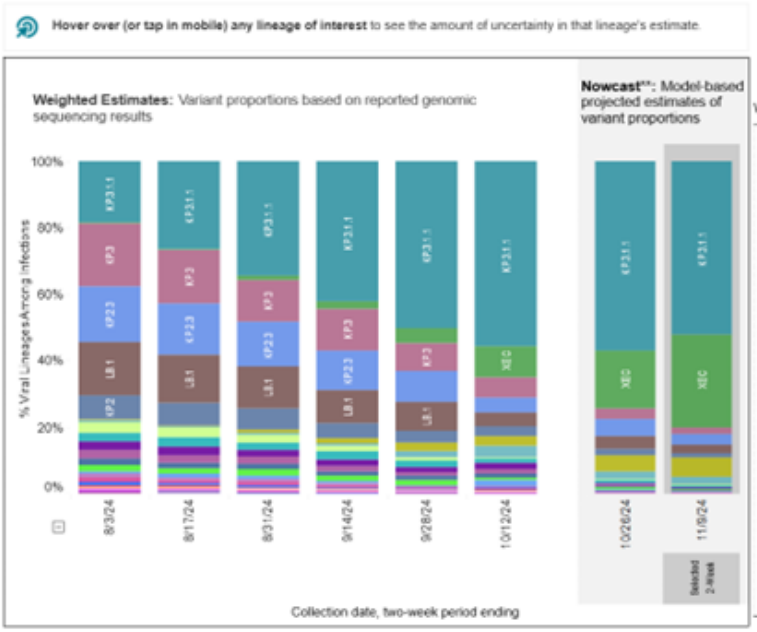
Morbidity and Mortality Weekly Report October 24, 2024; 73:938-945

This report summarizes US trends in variant proportion estimates during May 2023–September 2024, a period when SARS-CoV-2 lineages primarily comprised descendants of Omicron variants XBB and JN.1. During summer and fall 2023, multiple descendants of XBB with immune escape substitutions emerged and reached >10% prevalence, including EG.5-like

lineages by June 24, FL.1.5.1-like lineages by August 5, HV.1 lineage by September 30, and HK.3-like lineages by November 11. In winter 2023, the JN.1 variant emerged in the US and rapidly attained predominance nationwide, representing a substantial genetic shift from XBB lineages. Descendants of JN.1 subsequently circulated and reached >10% prevalence, including KQ.1-like and KP.2-like lineages by April 13, KP.3 and LB.1-like lineages by May 25, and KP.3.1.1 by July 20. Surges in Covid-19 cases occurred in winter 2024 during the shift to JN.1 predominance, as well as in summer 2023 and 2024 during circulation of multiple XBB and JN.1 descendants, respectively.



Weighted and Nowcast Estimates in United States for 2-Week Periods in 7/21/2024 – 11/9/2024



Nowcast Estimates in United States for 10/27/2024 – 11/9/2024

USA

WHO label	Lineage #	%Total	95%PI
Omicron	KP.3.1.1	52%	47–57%
	XEC	28%	21–36%
	MC.1	6%	3–10%
	KP.2.3	3%	3–4%
	LB.1	3%	2–4%
	LB.1.3.1	2%	1–7%
	KP.3	2%	1–2%
	KP.2	1%	1–2%
	KP.1.1.3	1%	0–1%
	JN.1.18	1%	0–1%
	LP.1	0%	0–1%
	JN.1.16.1	0%	NA
	KP.1.1	0%	NA
	JN.1	0%	NA
	KS.1	0%	NA
	KP.2.15	0%	NA
	JN.1.11.1	0%	NA
	LF.3.1	0%	NA
	KP.4.1	0%	NA

Dr. Septimus's Annotations

Genomic surveillance was critical for detecting the emergence of JN.1 and other variants in the US and demonstrated that SARS-CoV-2 continues to undergo large genetic shifts. However, surveillance data indicate that the consequences of these changes on rates of Covid-19 hospitalization and death have been reduced, likely because of widespread immunity to SARS-CoV-2. [Clin Infect Dis 2023; 77:547–57] Nonetheless, careful genomic monitoring remains important, as highlighted by evidence suggesting diminished 2023–2024 Covid-19 vaccine protection against JN.1 hospitalization. [Clin Infect Dis published online August 6, 2024. Data on variant proportions were used by the FDA to recommend inclusion of JN.1 lineages (preferentially KP.2) in updated 2024–2025 Covid-19 vaccines and should be used to guide composition of future vaccines just like influenza vaccines. KP.3.1.1 has remained the predominant variant for the last month. Covid-19 activity currently across the US remains low. However, given the unpredictability of SARS-CoV-2 evolution, continued monitoring for genetic changes and the impact of those changes on Covid-19 disease severity and medical countermeasure effectiveness remains essential to maintain preparedness.

BOTTOM LINE

The ongoing evolution of the Omicron variant highlights the importance of continued genomic surveillance to guide medical countermeasure development, including the selection of antigens for updated Covid-19 vaccines.

31

In Utero Exposure to Maternal COVID-19 and Offspring Neurodevelopment Through Age 24 Months.

JAMA Network Open 2024;7(10): e2439792.
DOI: 10.1001/jamanetworkopen.2024.39792

Covid-19 illness during pregnancy can affect offspring neurodevelopment. Early studies have yielded mixed results. This study was designed to assess whether in utero exposure to maternal Covid-19 is associated with abnormal neurodevelopmental scores among children ages 12, 18, and 24 months. Data were obtained from the ASPIRE (Assessing

the Safety of Pregnancy in the Coronavirus Pandemic) trial, a prospective cohort of pregnant individuals aged 18 years or older who were enrolled before 10 weeks' gestation and their children. Individuals were recruited online from May 14, 2020, to August 23, 2021, using the Society for Assisted Reproductive Technology and BabyCenter, an online media platform. Birth mothers completed the Ages & Stages Questionnaires, Third Edition, a validated screening tool for developmental delays, at 12-, 18-, and 24-months' post-partum. A score below the cutoff in any domain (communication, gross motor, fine motor, problem solving, and social skills) was considered an abnormal developmental screen (scores range from 0 to 60 in each domain, with higher scores indicating less risk for neurodevelopmental delay).

In this cohort study of 2003 pregnant individuals and their children, the adjusted prevalence of abnormal scores on the Ages & Stages Questionnaires, Third Edition of children through age 24 months did not differ between offspring exposed and unexposed to maternal SARS-CoV-2 infection in utero. Supplemental analyses did not identify differential risk based on trimester of infection, presence vs absence of fever, or breakthrough infection following vaccination vs primary infection.

Dr. Septimus's Annotations

In this prospective cohort study of pregnant individuals and offspring, in utero exposure to maternal SARS-CoV-2 infection was not associated with abnormal neurodevelopmental screening scores of children through age 24 months. Recently, concern regarding neurodevelopment following in utero exposure to maternal Covid-19 was raised by a 2022 study of 7772 infants from a Massachusetts health system. [JAMA Netw Open. 2022;5(6):e2215787] In that study using electronic health record ICD-10 codes, the investigators identified an increase of 1.9 in adjusted odds (95% CI, 1.0-3.4; P = .04) of neurodevelopmental disorder diagnoses in the first 12 months of life among exposed infants. A follow-up study of 18 335 children by the same group clarified that the increased risk was restricted to male children, and while a trend persisted at age 18 months, the association was no longer statistically significant. [JAMA Netw Open. 2023;6(3):e234415]

The strengths of this study include its prospective nature, large scale, geographic diversity, early gestational enrollment, granularity of data, surveillance screening for asymptomatic infection, and duration of childhood follow-up. Limitations includes its volunteer recruitment using partnerships with an online fertility organization and BabyCenter, which may restrict the distribution of baseline sociodemographic characteristics and hence generalizability to more vulnerable populations. They had imperfect retention and completion of study activities, which might also impose selection bias.

BOTTOM LINE

The results of this trial suggest that individuals infected with SARS-CoV-2 during pregnancy can be reassured that there is no association with abnormal neurodevelopmental scores in children through age 24 months.