ID WATCH
by Ed Septimus, MD

Editor's Choice

1

Impact of an enterprise-wide ambulatory antibiotic stewardship bundle on patient satisfaction surveys

Infection Control & Hospital Epidemiology published online September 16, 2024, 1-4
DOI: 10.1017/ice.2024.116

Ambulatory antimicrobial stewardship program (ASP) initiatives can reduce unnecessary antibiotic prescribing for tier 3 URI [diagnoses where antibiotics are never appropriate].However, a better understanding of the impact of these initiatives on patient satisfaction is needed.

The investigators conducted a quasi-experimental pre/post retrospective cohort study from 1/1/2019 to 12/31/22, with a 12-month washout during implementation from 7/1/2020 to 6/30/21. All enterprise adult and pediatric primary care ambulatory encounters with International Classification of Diseases, 10th Revision (ICD-10) diagnosis code(s) for tier 3 URIs

were included. [outpatient acute respiratory visits for which antibiotics are not needed, such as rhinitis, bronchitis, non-streptococcal pharyngitis, unspecified URIs, and asthma] Covid-19 encounters were excluded. The multifaceted ASP bundle was implemented in a stepwise fashion beginning 7/1/2020, consisting of standardized provider education, dissemination of symptomatic management strategies (i.e., viral prescription pad), development of a syndrome-based, prepopulated ambulatory order panel (clinical decision support tool), a patient-facing antimicrobial commitment poster, peer comparison reporting, and a provider-facing data dashboard. Regional ASP teams were responsible for rollout of Enterprise-developed tools, with timelines varying by region during the implementation phase. Following bundle implementation, pre- (1/1/2019–12/31/22) and post-implementation (7/1/2021–12/31/22) data for survey respondents were retrieved and compared retrospectively. Surveys were administered using a standard version of the Press Ganey outpatient medical practice survey as part of our standard patient experience surveying process and directly correlated with individual encounters. Patients were randomly solicited within one week of encounters for all primary care department specialties across the enterprise, excluding urgent care. Telemedicine surveys were administered electronically and solicited via e-mail. Surveys for in-person visits were either solicited via e-mail or mailed based on volume-based algorithms.

Questions:

1. Likelihood of you recommending our practice to others
2. Concern the care provider showed for your questions or worries
3. Explanations the care provider gave you about your problem or condition
4. Care provider's efforts to include you in decisions about your care
5. How well the staff worked together to care for you
6. Likelihood of your recommending this care provider to others

In this subset of primary care survey respondents, the tier 3 URI prescribing rate decreased from 28.3% to 14.1%, consistent with the decrease from 21.7% to 11.2% observed in the overall cohort as previously published. [Open Forum Infect Dis 2023;10:ofad585] Overall, no statistically significant changes in satisfaction were observed for any of the six survey questions or their associated means, when comparing pre- versus post-implementation. For the sensitivity analysis of impact of antibiotic prescribing on patient responses to survey question number 1 [likelihood of you recommending our practice to others], mean satisfaction was higher in antibiotic (n = 661) compared to non-antibiotic encounters (n = 2295) in the overall cohort (4.74 vs 4.64; P = 0.012). This trend was consistent in both the pre- and post-implementation cohorts, with higher mean satisfaction in antibiotic (n = 486) compared to non-antibiotic (n = 1129) encounters in the pre-implementation cohort (4.73 vs 4.64; P = 0.027), as well as in antibiotic (n = 175) compared to nonantibiotic (n = 1066) encounters in the post-implementation cohort (4.75 vs 4.64; P = 0.199).

Approximately 80–90% of antimicrobial prescribing occurs in ambulatory care settings, with up to 50% of antimicrobials prescribed being inappropriate and 30% entirely unnecessary. [Clin Infect Dis 2021;72:133–137] Upper respiratory infections (URIs) remain the most common indication for ambulatory antibiotic prescribing, though treatment is often not indicated. [Clin Infect Dis 2020;70:1781–1787] Patient expectations and physician assumptions regarding those expectations influence the decision to prescribe antibiotics. [Br J Gen Pract 2007;57:942–7] Moreover, multiple studies have demonstrated an association between antibiotic prescribing and higher patient satisfaction, though data are mixed. [Expert Rev Anti Infect Ther 2017;15:955–962]

Despite a 50% relative reduction in antibiotic prescribing, no differences were observed in patient satisfaction score responses when comparing the pre- and post-implementation cohorts; however, antibiotic prescribing was associated with statistically significantly higher mean satisfaction scores for question 1[likelihood of you recommending our practice to others] in the overall and pre-implementation cohorts, although the difference in mean score was small (i.e., ~0.1 points) and may not be meaningfully different.

They noted significantly more telehealth visits in the post-implementation cohort (22.5% vs. 3.8%; P < 0.001), consistent with changes in care following the Covid-19 pandemic. Previous studies have demonstrated higher

patient satisfaction with telehealth visits, which may have confounded patient satisfaction postimplementation. [J Eval Clin Pract 2022; 28:986–990] Second, given the known association between patient satisfaction and the patient–provider relationship, as well as the nearly infinite additional variables that can impact patient satisfaction scores, it was impossible to control for all possible confounders. Given their intervention was multifaceted including provider education, provision of a patient-directed viral prescription pad with over-the-counter symptomatic management recommendations, and routine peer comparison reporting, results may not be generalizable to stewardship efforts that utilize different interventions and/or interventions that focus less on providing tools for providers to provide patients with tangible value outside of antibiotic prescriptions.

BOTTOM LINE

Patient satisfaction did not diminish following implementation of a comprehensive, multimodal ambulatory antimicrobial stewardship bundle that resulted in a 50% relative reduction in unnecessary antibiotic prescribing for tier 3 URIs. [diagnoses where antibiotics are never appropriate] Efforts to reduce inappropriate antibiotic prescribing should not be concerned over reduced patient satisfaction, if providers are empowered with tools to educate patients and provide non-antibiotic value.

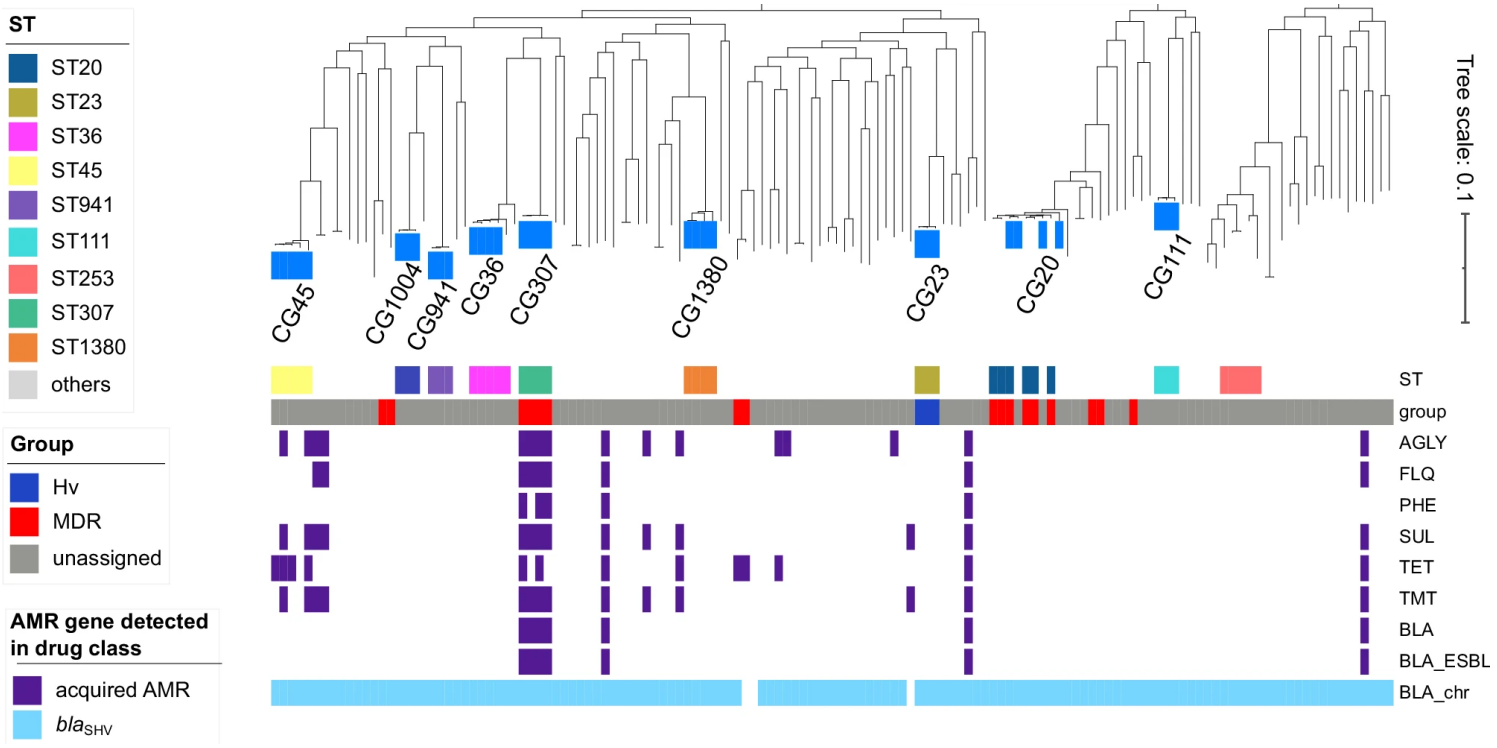
2

Clonal background and routes of plasmid transmission underlie antimicrobial resistance features of bloodstream Klebsiella pneumoniae.

Nature Communications published online August 14, 2024
DOI: 10.1038/s41467-024-51374-x

The investigators aimed to study the population structure of *K. pneumoniae* in bloodstream infections from a single medical center and the drivers that facilitate the dissemination of antimicrobial resistance (AMR).

Presence of multidrug resistant and hypervirulent clones.



Analysis of 136 short-read genome sequences complemented with 12 long-read sequences shows the population consisting of 94 sequence types (STs) and 99 clonal groups, including globally distributed multidrug resistant and hypervirulent clones. In vitro antimicrobial susceptibility testing and in silico identification of AMR determinants reveal high concordance (90.44–100%) for aminoglycosides, beta-lactams, carbapenems, cephalosporins, fluoroquinolones, and sulfonamides. IncF plasmids mediate the clonal (within the same lineage) and horizontal (between lineages) transmission of the extended-spectrum beta-lactamase gene blaCTX-M-15. Nearly identical plasmids are recovered from isolates over a span of two years indicating long term persistence. They found the genetic determinants for hypervirulence are carried on plasmids exhibiting genomic rearrangement, loss, and/or truncation.

Dr. Septimus's Annotations

Bloodstream infections caused by the opportunistic pathogen *K. pneumoniae* are associated with adverse health complications and high mortality rates. The burden of *K. pneumoniae* infections in hospitals is compounded by AMR, which greatly limits available treatment options and increases mortality rates especially for patients infected with invasive strains. [Infect. Dis. Ther. 2021; 10, 541–558] Some *K. pneumoniae* clones have become increasingly resistant to multiple antimicrobial agents and are designated as multidrug or extensively drug resistant. [BMC Infect. Dis. 2022; 22, 603]

K. pneumoniae comprises a phenotypically and genetically diverse assemblage of clones. It is broadly categorized into two pathotypes that exhibit distinct disease profiles. The so-called "classical" *K. pneumoniae* is a common cause of nosocomial infections and often harbor mobile plasmids encoding AMR genes. [Science 2024;27, 108875] Hypervirulent *K. pneumoniae* is a major cause of community acquired infections in healthy individuals, including liver abscess, pneumonia and meningitis, endophthalmitis, and infections of the central nervous system. [Clin. Microbiol Rev. 2019;32, e00001–e00019] Hypervirulent clones are often susceptible to most antimicrobial agents, but clones exhibiting both hypervirulence and multidrug resistance (referred to as convergent clones) have been described. [Nat. Commun.2023; 14, 7962]

BOTTOM LINE

The increasing burden caused by antimicrobial resistance (AMR) in bloodstream infections has life-threatening consequences because it can considerably increase the rates of treatment failure and death. Therefore, understanding the mechanisms of resistance dissemination remains a key strategy for effective management and control of AMR in invasive *K. pneumoniae*.

3

Global burden of bacterial antimicrobial resistance 1990–2021: a systematic analysis with forecasts to 2050.

The Lancet published online September 16, 2024
DOI: 10.1016/S0140-6736(24)01867-1

This study was conducted by the Global Research on Antimicrobial Resistance Project, is the first in-depth analysis of global health impacts of antimicrobial resistance. The study looked at 520 million data sets, including hospital discharge records, insurance claims and death certificates, from 204 countries to find deaths related to antimicrobial resistance between 1990 and 2021. The study analyzed results for 22 pathogens, 84 pathogen-drug combinations and 11 infectious syndromes. Using this statistical model, the researchers then estimate deaths between 2025 to 2050.

The study found more than one million people died each year from antibiotic-resistant infections between 1990 and 2021. The researchers estimated that 1.91 million people could die from infections in 2050, an increase of almost 70% per year compared to 2022.

Between 1990 and 2021, deaths among children under five declined by 50%, but deaths among those 70 and older increased by more than 80%. These trends are projected to continue with deaths among children to halve by 2050 globally and deaths among older people to more than double. The study predicted that 11.8 million deaths — about 30% of the total forecasted fatalities — would occur in South Asia.

In 1990, the number of deaths from MRSA was 57,200, compared to 130,000 deaths in 2021. Gram-negative bacteria also showed higher resistance to carbapenems compared to other types of antibiotics in the same time period (127,000 in 1990 to 216,000 in 2021.)

Researchers found improving access to healthcare and antibiotics could save 92 million lives between 2025 and 2050.

Dr. Septimus's Annotations

For the 84 pathogen-drug combinations studied, the analysis found that global mortality from AMR increased from 1990 to 2021, with drug-resistant infections directly responsible for more than 1 million deaths each year and a cumulative total of more than 36 million deaths. Only 2021 saw a slight decrease in AMR-related deaths, likely because physical distancing, along with other disease control measures put into place during the Covid-19 pandemic, led to a reduction in non-Covid respiratory tract infections. The biggest culprit behind AMR attributable deaths over the period was MRSA, which caused more than twice as many deaths in 2021 (130,000 attributable deaths) as in 1990 (57,200). Deaths caused by carbapenem-resistant gram-negative bacteria rose from 127,000 in 1990 to 216,000 in 2021. We also have a rapidly aging population; therefore, we have a greater number of elderly people that are more susceptible to infections.

Given the high variability of AMR burden by location and age, it is important that interventions combine infection prevention, vaccination, minimization of inappropriate antibiotic use in farming and humans, and research into new antibiotics to mitigate the number of AMR deaths that are forecasted for 2050.

BOTTOM LINE

The findings highlight the need for decisive actions — including expanded prevention and control measures, vaccinations, improved diagnostic and antimicrobial stewardship and new antibiotics — to protect people from the threat of antimicrobial resistance.

The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for Preventing Surgical Site Infection.

Diesease of the Colon & Rectum published on July 31, 2024
doi: 10.1097/DCR.0000000000003450

Highlights

1. Implementing a surgical site infection bundle for patients undergoing colorectal surgery can decrease the incidence of SSI. *Strength of recommendation: strong based on moderate quality evidence*

    - A 2017 meta-analysis including 17,557 patients documented a 40% risk reduction in SSI ($p < 0.001$) and that rates of superficial SSI and organ/space SSI were reduced by 44% ($p < 0.001$) and 34% ($p = 0.048$), respectively. [J [Gastrointest Surg. 2017;21:1915–1930] Bundles can include sterile closure trays (58.6% versus 33.1%; $p = 0.019$), mechanical bowel preparation (MBP) with oral antibiotics (55.4% versus 31.8%; $p = 0.015$[see #2], and pre-closure glove changes (56.9% versus 28.5%; $p = 0.002$) resulted in the greatest SSI risk reduction. Other bundle elements also incorporate intraoperative warming, supplemental oxygen intra- and postoperatively. restriction, and use of a surgical wound protector decreased the

overall SSI rate (24% versus 19%; p = 0.003) and superficial SSI rate (45% versus 36%; p = 0.004) as compared to bundles without those elements. [Arch Surg. 2011;146:263–269]

2. Oral antibiotics in combination with mechanical bowel preparation has been shown to decrease the incidence of surgical site infection after elective colorectal resection. Strength of recommendation: strong based on moderate-quality evidence

    - A meta-analysis of retrospective studies using NSQIP data (n = 40,446 in the largest cohort) demonstrated that a combined bowel prep is superior to either MBP alone or NBP (6.5% vs 11.6% vs 14.4%; p < 0.001). [Dis Colon Rectum. 2017; 60:729–737]

3. In circumstances where a mechanical bowel preparation is contraindicated or otherwise omitted, preoperative oral antibiotic preparation alone can reduce the incidence of SSI. Strength of recommendation: conditional based on moderate-quality evidence

4. Showering with chlorhexidine before colorectal surgery does not significantly impact SSI rates. Strength of recommendation: strong based on moderate-quality evidence

5. Smoking cessation before surgery may be recommended to reduce the risk of SSI. Strength of recommendation: conditional based on moderate-quality evidence

    - In a meta-analysis of 4 RCTs and 416 patients undergoing a variety of surgical procedures, smoking cessation significantly decreased the overall incidence of SSI (OR 0.40 95% CI: 0.20 – 0.83). [Arch Surg. 2012; 147:373–383]

6. On the day of colorectal surgery, patients should have their hair removed from the surgical site using a clipper or not removed at all. Shaving with a razor before surgery is discouraged. Strength of recommendation: strong based on moderate-quality evidence

7. Patients undergoing colorectal resection should have parenteral antibiotics administered within 60 minutes of incision. Dosing and redosing should be based on the pharmacokinetic profile of the antibiotic. Strength of recommendation: strong based on low-quality evidence.

8. Patients who report a penicillin allergy may be evaluated for having true hypersensitivity and high-risk reactions to penicillin. Delabeling a penicillin-allergic patient can facilitate the appropriate use of a preoperative prophylactic beta-lactam antibiotic and improve outcomes. Strength of recommendation: conditional based on low-quality evidence.

9. For most clean and clean-contaminated cases, prophylactic parenteral antibiotics should be limited to the initial 24 hours postoperatively. Strength of recommendation: strong based on moderate-quality evidence.

    - The duration of postoperative surgical antimicrobial prophylaxis (SAP) to prevent SSI has been extensively studied. A meta-analysis evaluating 34 studies (n = 5,123) demonstrated no difference in SSI comparing “short duration” of SAP (24 hours) versus “longer duration” (>24 hours) in patients undergoing colorectal surgery (RR 1.10, 95% CI: 0.93-1.29).[Cochrane Database Syst Rev. 2014;2014:CD001181] The same analysis evaluated 11 studies (n = 2,005) examining a single dose (SD) of SAP versus multiple doses and found no difference in the SSI rate (OR 1.21, 95% CI: 0.82 – 1.8). Most guidelines do not recommend post-op antibiotics.

10. Cleansing the surgical site with a chlorhexidine-alcohol based preparation is typically recommended for patients undergoing colorectal surgery. Strength of recommendation: strong based on moderate-quality evidence

11. Hyperglycemia on the day of surgery and in the immediate postoperative period may increase the risk of SSI following elective colorectal resection. Strength of recommendation: conditional based on moderate-quality evidence

    - In colorectal surgery patients specifically, hyperglycemia was associated with in-hospital mortality (3.1% versus 1.0%, p < 0.001), reoperative intervention (5.9% versus 4.3%, p < 0.001), and composite infections (14.8% versus 9.6%, p < 0.001) as compared to normoglycemia. [Ann Surg. 2013; 257:8–14]

12. Maintaining intraoperative normothermia may decrease the incidence of SSI in patients undergoing colorectal surgery. Strength of recommendation: conditional based on low quality evidence.

13. High-fractionated oxygen (FIO2) is not routinely recommended to prevent SSI. Strength of recommendation: conditional based on moderate quality evidence
14. Wound protectors can decrease the incidence of SSI after colorectal surgery. Strength of recommendation: strong based on high-quality evidence.
15. Minimally invasive colorectal surgery can decrease the incidence of SSI compared to open surgery. Strength of recommendation: strong based on high-quality evidence.
16. Topical antimicrobial agents applied to surgical incision are not recommended. Strength of recommendation: strong recommendation based on low-quality evidence.
17. Negative pressure wound therapy (NPWT) for primarily closed incisions may decrease the incidence of SSI. Strength of recommendation: conditional recommendation based on moderate-quality evidence
18. Advanced silver or antimicrobial dressings are not routinely recommended for clean or clean-contaminated wounds after colorectal surgery. Strength of recommendation: conditional recommendation based on moderate-quality evidence

Dr. Septimus's Annotations

Compared with other surgical sub-specialties, patients undergoing colorectal surgery are at the highest risk for developing an SSI with an estimated incidence of 5-30%. [Clin Colon Rectal Surg. 2019; 32:157–165] Patients undergoing emergency colorectal surgery with colon perforation have an SSI incidence as high as 80%. [Surg Infect (Larchmt). 2014; 15:256–261] An American College of Surgeons National Surgical Quality Improvement Program (NSQIP) study of nearly 500,000 patients reported that SSI was the most common cause of 30-day unplanned hospital readmissions. [JAMA. 2015; 313:483–495] This updated guideline should be reviewed, a gap analysis performed, and an action plan developed to optimize best practices to prevent SSIs in colon and rectal surgery.

BOTTOM LINE

Surgical site infection (SSI) prevention measures include institutional order sets that bundle multiple processes to help prevent SSI, preoperative optimization of high-risk patients, and perioperative interventions to reduce bacterial load and prevent contamination has been shown to decrease SSIs.

5

A Retrospective Assessment of Guideline Adherence and Treatment Outcomes from Clostridioides difficile Infection following the IDSA 2021 Clinical Guideline Update.

Open Forum Infectious Dieseases published online September 30, 2024
DOI: 10.1093/ofid/ofae524

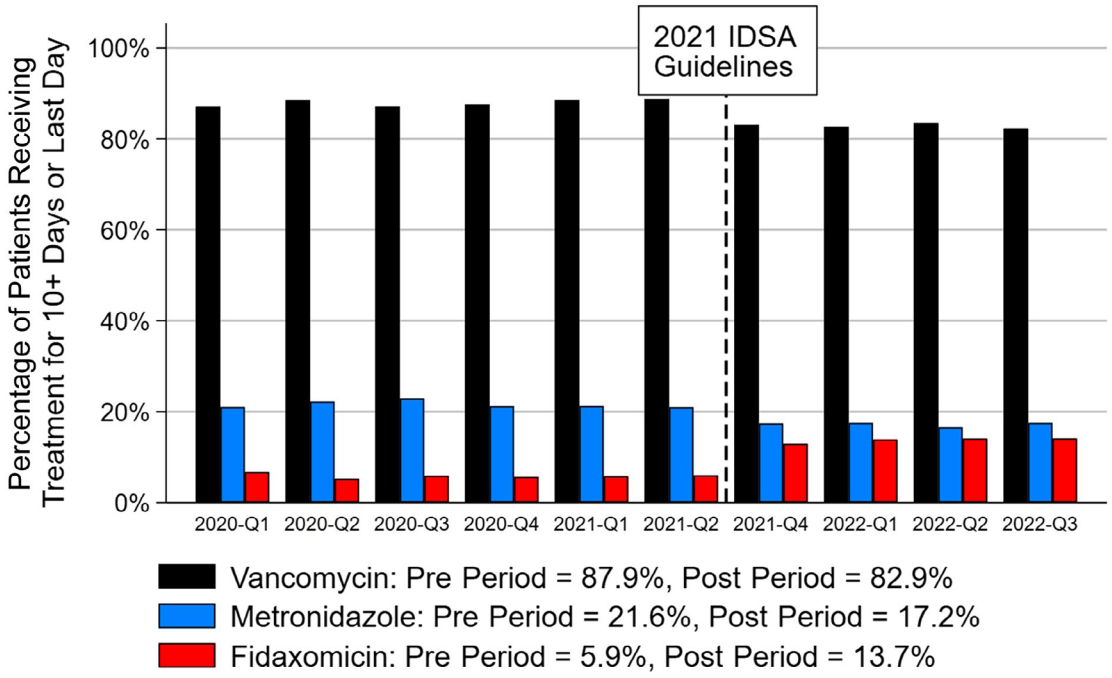
In 2021, the Infectious Diseases Society of America (IDSA) guidelines for treatment of C difficile infection (CDI) were updated. [Clin Infect Dis. 2021. 73(5): e1029-44] Using the PINC AI Healthcare database, investigators and Merck examined records on adults who received CDI treatment before and after 2021, when updated guidelines from the IDSA recommended fidaxomicin as the only first-line drug for CDI, with vancomycin as an alternative option. Prior to 2021 vancomycin and metronidazole had been the recommended first-line agents for CDI, Evidence on how CDI treatment patterns have changed since the 2021 guidelines has been limited. They examined treatment patterns of fidaxomicin, vancomycin, and metronidazole, as well as clinical and health care resource use outcomes of patients treated exclusively with fidaxomicin vs vancomycin, using nearest-neighbor propensity matching and hierarchical regression methods. As

a sensitivity analysis, they repeated the fidaxomicin vs vancomycin comparisons among patients with recurrent and nonrecurrent index infections.

A total of 45,049 patients from 779 US hospitals were included in the study, with 29,520 in the pre-period (January 2020 to June 2021) and 15,529 in the post-period (October 2021 to September 2022). From the pre-period to the post-period, fidaxomicin use increased from 5.9% to 13.7%, while vancomycin used declined from 87.9% to 82.9% and metronidazole from 21.6% to 17.2%.

In a secondary analysis that compared clinical and cost outcomes among patients treated exclusively with fidaxomicin versus vancomycin, fidaxomicin was associated with lower CDI recurrence (6.1% vs 10.2%) and higher sustained clinical response (91.7% vs 87.9%), while 90-day post-discharge costs were similar. They observed post-discharge costs associated with fidaxomicin were either lower than costs associated with vancomycin use or not significantly different.

The quarterly Clostridioides difficile infection treatment utilization pattern of vancomycin, metronidazole, and fidaxomicin pre– vs post–IDSA 2021 guideline update.



Dr. Septimus's Annotations

CDI affects approximately 460,000 patients in the US and is the most common healthcare associated infection in adults. CDI is also the number one cause of nosocomial diarrhea in the US. Recurrent infections are common with approximately 1 in 6 patients having a recurrent CDI infection within 8 weeks. [New Engl J Med. 2020. 382:1320 -30]

In the propensity matched results, they observed a more favorable sustained response (OR =1.48; 95% CI (1.11, 1.97)) and a lower CDI recurrence rate associated with fidaxomicin (OR = 0.61; 95% CI (0.44, 0.85)). Similarly, in a meta-analysis by Okumura et al, the observed sustained response was (OR = 1.61; 95% CI (1.27, 2.05) and the CDI recurrence rate was OR =0.50; 95% CI (0.37, 0.68). [J Infect Chemotherapy. 2020; 26:43- 50] In a more recent metanalysis, the CDI recurrence rate favoring fidaxomicin was relative risk = 0.59; 95% CI (0.47, 0.75). [J Infect Chemotherapy. 2022 Aug 11] They did not see

differences by treatment in the outcome of in-hospital mortality or discharged to hospice but in select populations (e.g., the Non-Recurrent CDI cohort) there were differences in in-hospital mortality only.

Fidaxomicin use has been limited, presumably since it is more expensive than vancomycin. While fidaxomicin use for CDI increased since the publication of the updated IDSA guidelines, it remained low relative to vancomycin and metronidazole use. These findings imply that a substantial number of patients could have received the benefits of fidaxomicin if clinicians had followed the ISDA 2021 guidelines.

It was beyond the study's scope to compare guideline adherence and treatment outcomes of fidaxomicin with vancomycin or metronidazole within select subgroups of patients such as those older than 65, immunocompromised patients, or patients requiring intensive care. The limited research on select subgroups such as those who are immunocompromised or have a high level of acuity suggests that the benefits of fidaxomicin remain.

BOTTOM LINE

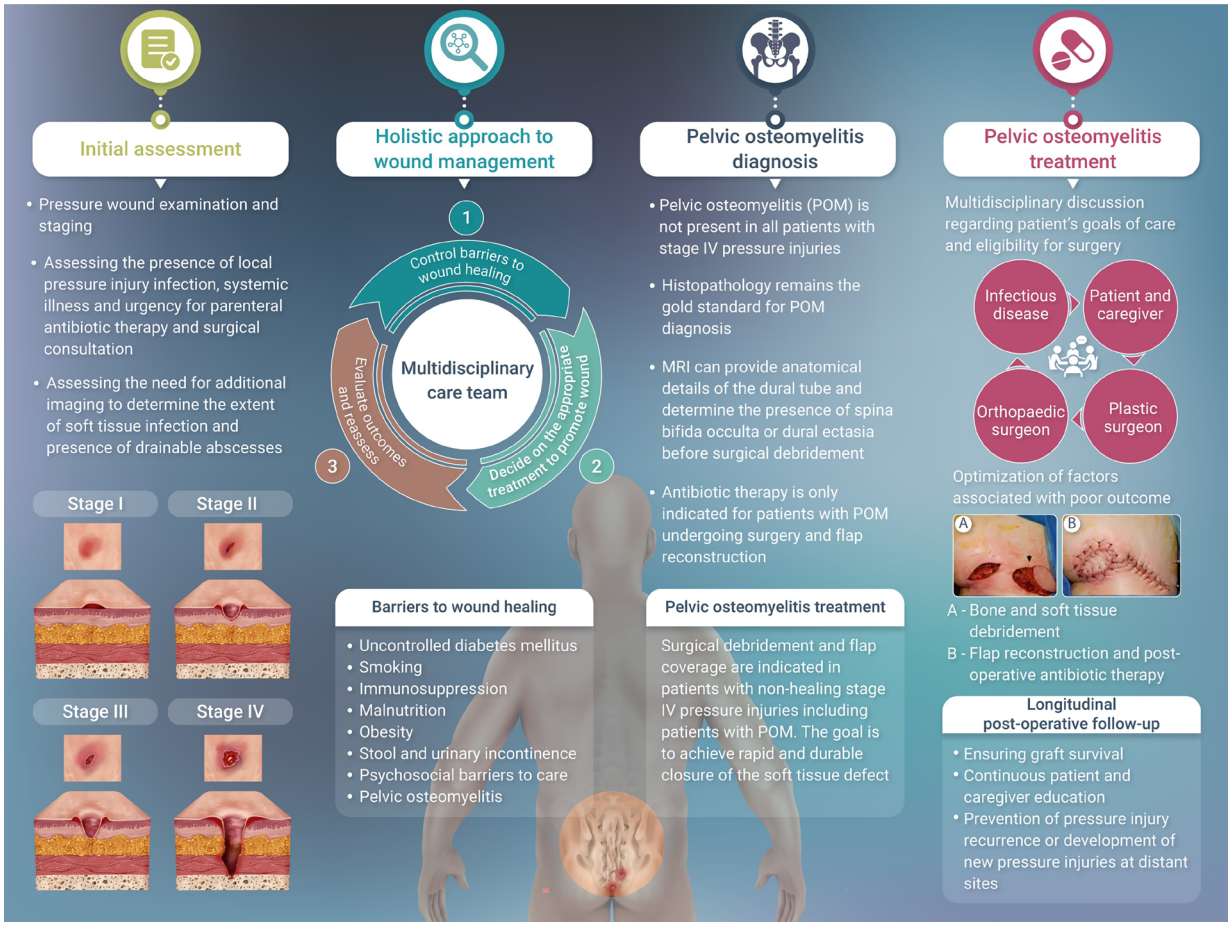
The investigators observed that most patients with CDI were not receiving fidaxomicin treatment in accordance with the updated IDSA guidelines published in 2021. While fidaxomicin use for CDI increased since the publication of the updated IDSA guidelines, it remained low relative to vancomycin and metronidazole use. Fidaxomicin was associated with lower CDI recurrence and higher sustained clinical response.

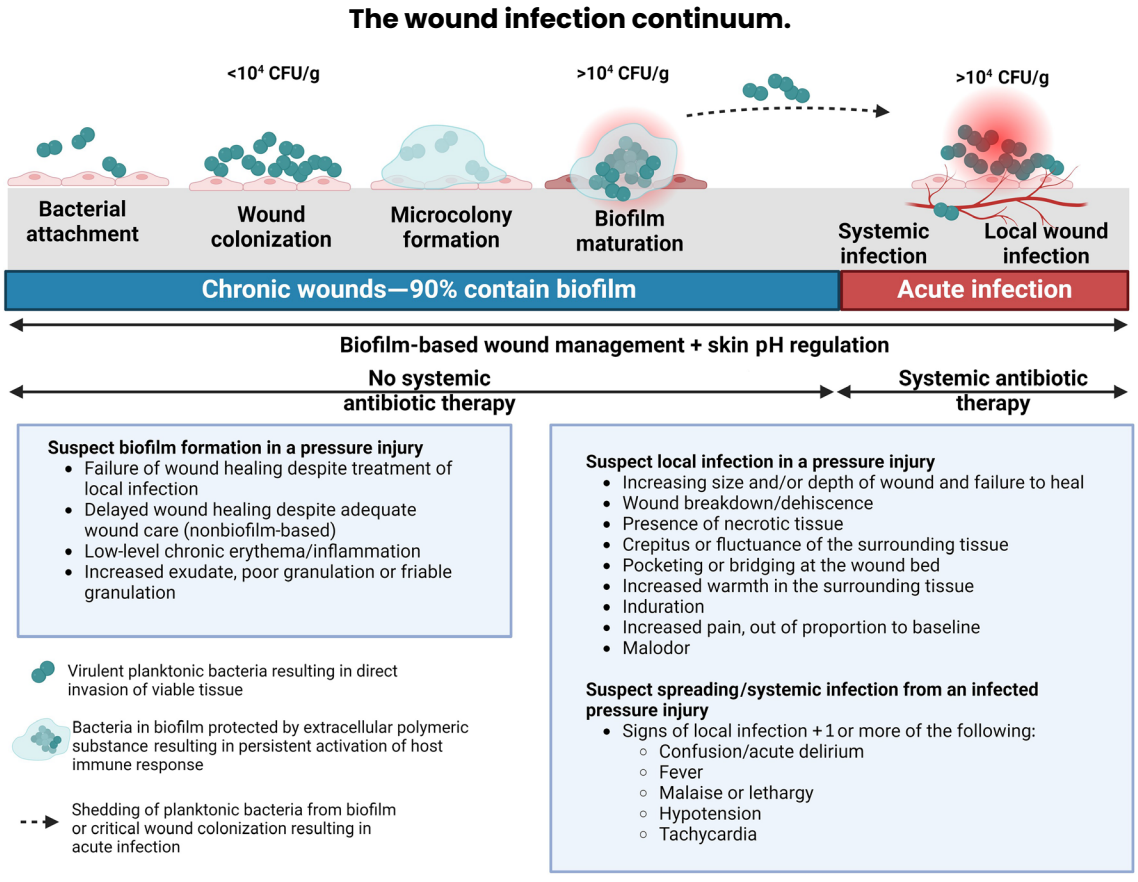
Evaluation and Management of Pelvic Osteomyelitis in Stage IV Pressure Injuries: A Multidisciplinary Collaborative Approach.

Clinical Infectious Disease published on September 15, 2024, Volume 79, Issue 3, Pages e11–e26
doi: 10.1093/cid/ciae394

A few highlights:

1. POM (pelvis osteomyelitis) is exclusively seen in stage IV pressure injuries and is characterized by full-thickness skin and tissue loss with exposure of bone, tendons, and/or muscle.
2. 80%–90% of chronic wounds are colonized by biofilm.
3. Wound cultures should be obtained only when pressure injury infection is suspected with the aim of guiding the selection of antibiotic therapy.
4. Given that microbial load is considered the most reliable indicator of tissue infection, quantitative cultures of viable wound tissue is considered the gold standard for identifying and differentiating pathogenic organisms from colonizers.
5. When debridement is warranted for an infected pressure injury, deep intraoperative tissue and/or abscess fluid is obtained for semiquantitative cultures.
6. Ideally, antibiotics should be withheld prior to bone sampling to increase the microbiological yield.
7. Osteomyelitis is not an inevitable occurrence in all individuals with stage IV pressure injuries and that exposed bone alone should not be used as an indicator of osteomyelitis.
8. Pressure-related changes such as fibrosis, reactive bone formation, and bone marrow edema were observed in all evaluated patients with stage IV pressure injuries, regardless of the presence of osteomyelitis, which is why MRI exhibits a sensitivity of 94%, but specificity may be as low as 22%.
9. Surgical debridement and flap coverage are indicated in patients with nonhealing stage IV pressure injuries; however, this is contingent on patient's eligibility for surgery.
10. Current evidence suggests that antibiotic therapy is recommended post-operatively for POM only for patients who undergo both debridement and flap reconstruction.
11. 6 weeks of antibiotics may not be universally necessary for all cases following adequate debridement. Some authors suggest that the treatment duration should be adjusted based on the extent of bone involvement according to the Cierny–Mader classification system, with 2-4 weeks being sufficient for cases of only cortical bone involvement following debridement.


Initial assessment
• Pressure wound examination and staging
• Assessing the presence of local pressure injury infection, systemic illness and urgency for parenteral antibiotic therapy and surgical consultation
• Assessing the need for additional imaging to determine the extent of soft tissue infection and presence of drainable abscesses
Stage I
Stage II
Stage III
Stage IV
Holistic approach to wound management
1
Control barriers to wound healing
Multidisciplinary care team
2
Decide on the appropriate treatment to promote wound
3
Evaluate outcomes and reassess
Barriers to wound healing
• Uncontrolled diabetes mellitus
• Smoking
• Immunosuppression
• Malnutrition
• Obesity
• Stool and urinary incontinence
• Psychosocial barriers to care
• Pelvic osteomyelitis
Pelvic osteomyelitis diagnosis
• Pelvic osteomyelitis (POM) is not present in all patients with stage IV pressure injuries
• Histopathology remains the gold standard for POM diagnosis
• MRI can provide anatomical details of the dural tube and determine the presence of spina bifida occulta or dural ectasia before surgical debridement
• Antibiotic therapy is only indicated for patients with POM undergoing surgery and flap reconstruction
Pelvic osteomyelitis treatment
Surgical debridement and flap coverage are indicated in patients with non-healing stage IV pressure injuries including patients with POM. The goal is to achieve rapid and durable closure of the soft tissue defect
Pelvic osteomyelitis treatment
Multidisciplinary discussion regarding patient's goals of care and eligibility for surgery
Infectious disease
Patient and caregiver
Orthopaedic surgeon
Plastic surgeon
Optimization of factors associated with poor outcome
A
B
A - Bone and soft tissue debridement
B - Flap reconstruction and post-operative antibiotic therapy
Longitudinal post-operative follow-up
• Ensuring graft survival
• Continuous patient and caregiver education
• Prevention of pressure injury recurrence or development of new pressure injuries at distant sites


The wound infection continuum.
<10⁴ CFU/g
>10⁴ CFU/g
>10⁴ CFU/g
Bacterial attachment
Wound colonization
Microcolony formation
Biofilm maturation
Systemic infection
Local wound infection
Chronic wounds—90% contain biofilm
Acute infection
Biofilm-based wound management + skin pH regulation
No systemic antibiotic therapy
Systemic antibiotic therapy
Suspect biofilm formation in a pressure injury
• Failure of wound healing despite treatment of local infection
• Delayed wound healing despite adequate wound care (nonbiofilm-based)
• Low-level chronic erythema/inflammation
• Increased exudate, poor granulation or friable granulation
Virulent planktonic bacteria resulting in direct invasion of viable tissue
Bacteria in biofilm protected by extracellular polymeric substance resulting in persistent activation of host immune response
Shedding of planktonic bacteria from biofilm or critical wound colonization resulting in acute infection
Suspect local infection in a pressure injury
• Increasing size and/or depth of wound and failure to heal
• Wound breakdown/dehiscence
• Presence of necrotic tissue
• Crepitus or fluctuance of the surrounding tissue
• Pocketing or bridging at the wound bed
• Increased warmth in the surrounding tissue
• Induration
• Increased pain, out of proportion to baseline
• Malodor
Suspect spreading/systemic infection from an infected pressure injury
• Signs of local infection +1 or more of the following:
◦ Confusion/acute delirium
◦ Fever
◦ Malaise or lethargy
◦ Hypotension
◦ Tachycardia

Dr. Septimus's Annotations

Managing stage IV sacral pressure injuries and POM requires multidisciplinary evaluation and patient engagement. There is a critical need for robust RCTs to answer key therapeutic questions. These include determining the optimal duration of antibiotics for patients who undergo bone debridement with flap reconstruction. In patients who are not candidates for flap reconstruction, the primary goal is to improve quality of life, manage symptoms, and treat acute infections with some local debridement. This includes stabilizing existing pressure injuries, preventing new ones, controlling pain, preventing local wound infections, using advanced absorbent dressings, and reducing the frequency of wound dressing changes. Pressure redistribution is crucial to prevent new injuries. Options for managing incontinence include intermittent catheterization, absorbent pads, indwelling catheters, external collection devices, toileting devices, fecal incontinence devices, and surgical diversion.

BOTTOM LINE

Managing pelvic osteomyelitis (POM) in the setting of stage IV pressure injuries requires multidisciplinary evaluation as well as patient engagement. There is limited high quality evidence data to guide best practices.

7

Effect of a bundle intervention on adherence to quality-of-care indicators and on clinical outcomes in patients with Staphylococcus aureus bacteraemia hospitalized in non-referral community hospitals.

Journal of Antimicrobial Chemotherapy published online August 30, 2024
DOI: 10.1093/jac/dkae298

Despite appropriate antimicrobial therapy, mortality associated with *Staphylococcus aureus* bacteremia (SAB) may be as high as 40%, varying substantially across hospitals. Nonetheless, clinicians' adherence to core quality-of-care indicators is thought to improve outcomes.

Investigators evaluated 90-day relapse and mortality among patients with SAB before (n=170) and after (n=103) implementation of a care bundle at six community hospitals in Spain. The bundle included:

- Blood cultures before and 48–72 hours after initiation of therapy
- Source control (e.g., catheter removal, abscess drainage)
- Sufficiently targeted therapy
- Echocardiography in patients with complicated SAB
- Adequate duration of therapy (10–14 days for uncomplicated SAB; 28 days for complicated SAB)

Characteristics of patients were comparable in both cohorts; overall, 16% of those with SAB had methicillin-resistant *S. aureus* (MRSA). Performing echocardiography was the only factor significantly associated with improved adherence to the bundle. In adjusted analysis, variables associated with 90-day failure (relapse or death) included Pitt bacteremia score >2, pneumonia, MRSA, and complicated SAB (the Pitt bacteremia score is an index of acute severity that ranges from 0 to 14 points and predicts risk for death in patients with bacteremia and candidemia [Int J Antimicrob Agents 1999; 11:7]). Use of the bundled intervention was not associated with clinical outcomes.

Dr. Septimus's Annotations

While the bundled clinical indicators evaluated here provide a solid framework for a diagnostic and therapeutic plan to manage SAB, they are insufficient to address the most complex 10%–20% of patients with SAB that drive relapse and mortality. Such patients require earlier identification, more-thorough risk stratification strategies, and perhaps more-intensive combination antimicrobial regimens than are typically deployed in a standard package. Distilling out a simple quality-of-care bundle across all SAB patients should be considered a starting point, rather than a goal, for improving outcomes. There was no mention if an infectious diseases consult was obtained. Literature has demonstrated that obtaining an infectious diseases consult improves outcomes and bundle compliance and is recommended as standard of care.

BOTTOM LINE

A bundle-of-care intervention for the management of S aureus bacteremia (SAB) at non-referral community hospitals increased adherence to quality indicators, but did not significantly reduce rates of 90-day mortality or relapse. Risk stratification strategies are needed.

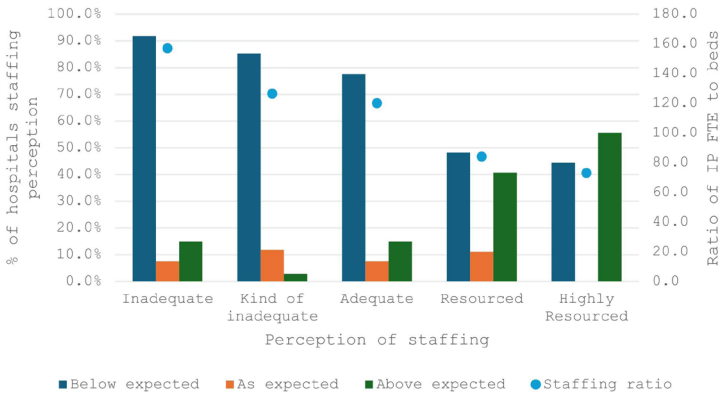
8

Closing the gap on infection prevention staffing recommendations: Results from the beta version of the APIC staffing calculator.

American Journal of Infection Control published online October 10, 2024
DOI: 10.1016/j.ajic.2024.09.004

An online survey-based calculator was created that incorporated factors intended to predict staffing needs and multiple investigative questions to allow for optimization of factors in the algorithm. Hospital characteristics, staffing ratios, staffing perception, and outcomes were analyzed to determine the optimal questions and benchmarks for future releases. The Association for Professionals in Infection Control and Epidemiology's (APIC) staffing calculator was developed through a collaborative member feedback process to create a predictive algorithm for facility-specific infection prevention staffing needs.

Perception of staffing by the current staffing ratio. IP FTE, infection prevention equivalent.



The median infection preventionist full-time equivalent to bed ratio was 121.0 beds for 390 participating hospitals. The calculator deemed 79.2% of respondent staffing as below expected. Significant association existed between higher standard infection ratio(SIR) ranges and staffing status for central line associated bloodstream infection (P = .02), catheter-associated urinary tract infections (P = .001), *C difficile* infections (P = .003), and colon surgical site infections (P = .0001).

Dr. Septimus's Annotations

There is little consensus on what constitutes an adequately staffed infection prevention department. Historically, the ratio of infection prevention employees to inpatient beds has been the most common measure utilized in acute

care hospital settings (usually expressed as infection prevention full-time equivalents or IP FTEs). [Am J Epidemiol. 1985; 121:182-205] Knighton et al conducted a comprehensive literature review highlighting significant variability in infection preventionist (IP) staffing in both traditional hospital settings and nonhospital settings. [Am J Infect Control. 2024; 52:91-106] The ratio of IPs to inpatient beds has increased over time in hospitals due to the growing complexity of the IP role. The SENIC Project, Haley et al evaluated US nosocomial infection prevention and control programs from 1970 to 1976 and recommended 1 infection control nurse per 250 beds. [Am J Epidemiol. 1985; 121:182-205] Recent analyses suggest a lower ratio, ranging from 1 IP per 100 beds [Am J Infect Control. 2002; 30:321-3333] to 1 IP per 69 beds. [Am J Infect Control. 2018; 46:487-491] As the role of the IP evolved from infection control nurses in the 1970s to infection preventionists in the 21st century, so did the responsibilities associated with the role. The expectations of the role were broadened to include expertise regarding construction in the health care setting, airflow impacts in critical and semi critical spaces, cleaning and disinfection of instruments, and state and federal regulations. [Infect Control Today. 2024; 28:26-27]

A key finding in this paper was the correlation between staffing levels and infection outcomes (CAUTI, CLABSI, C *difficile*, and colon SSI). Programs with below-expected staffing levels according to the calculator were more likely to have higher SIRs. This finding reinforces the value of well-staffed IP programs in maintaining lower SIRs, a correlation previously elusive in existing literature due to smaller study scales. The calculator adjusts staffing ratios based on specific facility characteristics, such as the presence of an ED, ICU, burn unit, stem cell transplant unit, inpatient rehabilitation unit (IRF), surveillance team, performing surgery, and CMI. The standard IP FTE to bed ratio is inadequate for today's complex health care environments, revealing that many facilities may overlook these critical factors. Stratifying very small and very large hospitals resulted in small sample sizes. The data entered into the calculator was self-reported from health care professionals that were APIC members and therefore the findings may not be generalizable to other hospitals that did not enter data into the calculator.

BOTTOM LINE

This novel approach allows facilities to staff their infection prevention program based on individual facility characteristics. Future versions of the calculator will be optimized based on the findings. Future research will clarify the impact of staffing on patient outcomes and staff retention.

9

Aztreonam–avibactam versus meropenem for the treatment of serious infections caused by Gram-negative bacteria (REVISIT): a descriptive, multinational, open-label, phase 3, randomised trial

The Lancet Infectious Diseases published online October 7, 2024
DOI: 10.1016/ S1473-3099(24)00499-7

This was a prospective, multinational, open-label study which enrolled adults who were hospitalized with complicated intra-abdominal infection (IAI) or healthcare-associated pneumonia-ventilator-associated pneumonia (HAP–VAP). Patients were randomly allocated via block randomization stratified by infection type in a 2:1 ratio to aztreonam–avibactam (with metronidazole for complicated intra-abdominal infection) or meropenem with or without colistin for 5–14 days for complicated intra-abdominal infection or 7–14 days for HAP–VAP. The primary endpoint was clinical cure at the test-of-cure visit (within 3 days before or after day 28) in the intention-to-treat (ITT) population. Secondary endpoints included 28-day mortality in the ITT population and safety in patients in the ITT population who received study drug.

422 patients were enrolled and randomly allocated (282 in the aztreonam–avibactam group and 140 in the meropenem group, forming the ITT analysis set), of whom ten patients (seven in the aztreonam–avibactam group and three in the meropenem group) were randomly allocated but did not receive study treatment. 271 (64%) of 422 patients had at least one Gram-negative pathogen from an adequate specimen identified at baseline. The most frequent baseline pathogens were *Enterobacterales* (252 [93%] of 271). Overall, 19 (24%) of 80 isolates tested for carbapenemases were carbapenemase-positive (serine, metallo-β- lactamase, or both). 193 (68·4%) of 282 patients in the aztreonam–avibactam group and 92 (65·7%) of 140 in the meropenem group had clinical cure at the test-of-cure visit (treatment difference 2·7% [95% CI −6·6 to

12·4]). For patients with complicated intra-abdominal infection, the adjudicated clinical cure rate was 76·4% (159 of 208) for the aztreonam–avibactam group and 74·0% (77 of 104) for the meropenem group. Cure rates in patients with HAP–VAP were 45·9% (34 of 74) for aztreonam–avibactam and 41·7% (15 of 36) for meropenem. 28-day all-cause mortality rates were 4% (12 of 282) for aztreonam–avibactam and 7% (ten of 140) for meropenem; in patients with complicated intraabdominal infection, mortality was 2% (four of 208) and 3% (three of 104) for aztreonam–avibactam and meropenem, respectively, and in patients with HAP–VAP, mortality was 11% (eight of 74) and 19% (seven of 36), respectively. Aztreonam–avibactam was generally well tolerated, but adverse drug events including relatively high rates of C difficile infection (8% in the aztreonam–avibactam group), hypersensitivity events (13% in the aztreonam– avibactam group, although none were reported to be anaphylaxis or angioedema), and mild-to-moderate liver-related adverse events (18%). Most patients were not critically ill, with approximately 60% of patients in both groups having an APACHE II score of 10 or under and a primary diagnosis of cIAI. In the microbiologically evaluable analysis set with metallo-β-lactamase-positive pathogens, clinical cure rates were 50·0% (two of four) and 0% (zero of one) in the aztreonam–avibactam and meropenem groups, respectively. [very small numbers]

Dr. Septimus's Annotations

Metallo-β-lactamase enzymes are responsible for β-lactam antibiotic hydrolysis and are increasing in prevalence worldwide. Despite the increase in antibiotic development over the past decade, a β-lactamase inhibitor that binds to metallo-β-lactamases is not commercially available. Treatment options for metallo-β-lactamases are restricted to non-β-lactam antibiotics, cefiderocol, or the combination of ceftazidime–avibactam and aztreonam. [Eur Respir Rev 2022; 31: 220068] Aztreonam is stable against metallo-β-lactamase-mediated hydrolysis, and avibactam inhibits most other clinically relevant β-lactamase enzymes, making this an attractive combination.

This study showed that aztreonam-avibactam had similar clinical cure rates as meropenem in 422 patients with either complicated intra-abdominal infection (76.4% vs 74.0%, respectively) or HAP-VAP (45.9% vs 41.7%) caused by gram-negative bacteria. The investigators also found that overall all-cause mortality rates at 28 days were relatively low, and similar between both treatment groups for each infection type (2% for aztreonam-avibactam vs 3% for meropenem in patients with complicated intra-abdominal infection and 11% vs 19% in patients with HAP-VAP). Anecdotal reports of positive outcomes for aztreonam in combination with ceftazidime–avibactam [Clin Infect Dis 2021; 72: 1871–78] supported an empirical dose recommendation by the Infectious Diseases Society of America (IDSA) for use of aztreonam plus ceftazidime–avibactam to treat serious infections caused by metallo-β-lactamase-producing Enterobacterales. [Clin Infect Dis 2023; published online July 18]

This was open-label rather than double-blind, and it was designed as a descriptive rather than a formal hypothesis-testing study. The number of patients with HAP–VAP was considerably lower than that of patients with complicated intra-abdominal infection, making it more difficult to draw conclusions regarding the HAP–VAP group. Relatively low numbers of ESBL-producing and carbapenemase-positive strains, and particularly low numbers of metallo-β-lactamase-producers were identified.

The phase 3 REVISIT study, alongside the phase 3 ASSEMBLE study, [34th European Society of Clinical Microbiology and Infectious Diseases (ECCMID); Barcelona, Spain: 2024] supported the recent European approval of aztreonam–avibactam for adults with complicated intra-abdominal infection, HAP–VAP, complicated urinary tract infections including pyelonephritis, and infections due to Gram-negative bacteria in adults with restricted treatment options.

The trial was conducted in a region where MBL-producing gram-negative pathogens are prevalent, however, few patients in the trial had infections caused by MBL-producing bacteria, highlighting the need for more data on the drug's efficacy against such pathogens. Therefore, due to the small number of patients with metallo-β-lactamases in the study limits the ability to draw conclusions about the utility of aztreonam-avibactam in eradicating these difficult-to-treat pathogens.

BOTTOM LINE

These phase 3 efficacy and safety data provide support for aztreonam-avibactam as a potential therapeutic option for complicated intra-abdominal infection or healthcare-associated pneumonia-ventilator-associated pneumonia (HAP-VAP) caused by Gram-negative bacteria, however, due to the small number of patients with metallo-β-lactamases in the study limits the ability to draw conclusions about the utility of aztreonam-avibactam in eradicating these difficult-to-treat pathogens.

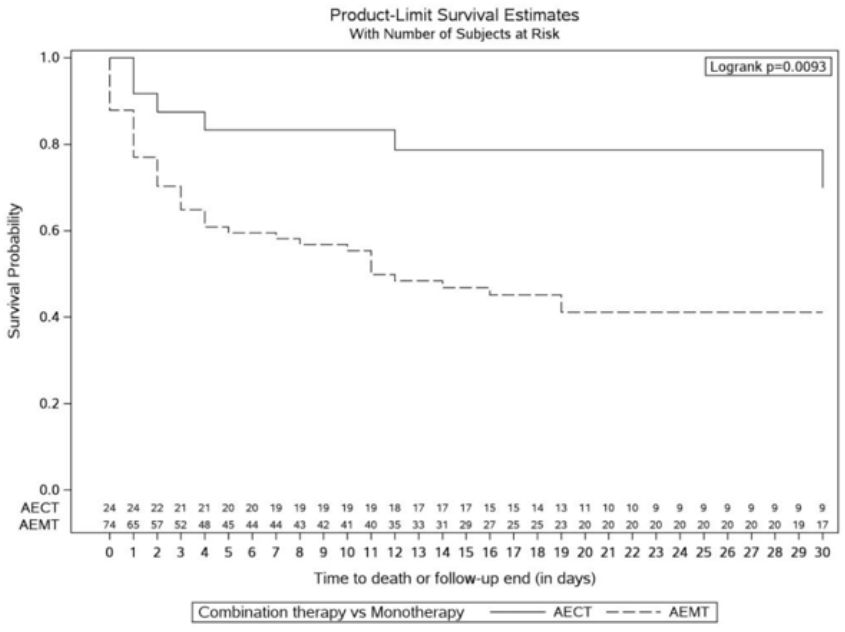
10

Impact of adequate empirical combination therapy on mortality in septic shock due to Pseudomonas aeruginosa bloodstream infections: a multicentre retrospective cohort study

Journal of Antimicrobial Chemotherapy published online September 3, 2024
DOI: 10.1093/jac/dkae296

This is a retrospective cohort study encompassing 14 hospitals comparing outcomes of P. aeruginosa septic shock in patients who had received adequate empirical combination therapy (AECT; 24 patients) or monotherapy (AEMT; 74 patients). Patients were classified into two groups based on the number of *in vitro* active empirical antibiotics: an AECT group that received simultaneously at least two active antibiotics with a different mechanism of action against the isolated pathogen and adequate empirical monotherapy group (AEMT) that received only one active *in vitro* antibiotic. If a patient received two antipseudomonal agents, but only one was adequate, empirical antibiotic therapy was considered also considered as AEMT. Definitive therapy was considered to be any treatment that continued or started on the day that the antimicrobial susceptibility tests were known by the physicians in charge of the patients. All definitive therapies were deemed adequate based on *in vitro* susceptibility testing. The primary endpoint was all-cause mortality within 30 days following the first positive blood culture for *P. aeruginosa*. Early adequate source control was defined as the removal of pre-existing infected hardware or drainage of an infected fluid collection thought to be the origin of the *P. aeruginosa* BSI, performed within 24 hours from the BSI onset.

The AECT group was significantly younger (median age, 60 vs. 70), had lower Charlson comorbidity scores (2 and 4), and were more likely to have multidrug-resistant *P. aeruginosa* than the AEMT group. No other significant differences were observed between groups in terms of underlying diseases, invasive procedures, source of BSI and early adequate source control of the infection.



Of the 98 patients who received adequate empirical antibiotic treatment for septic shock due to *P. aeruginosa* BSI, 24 underwent AECT and 74 were given AEMT. Among the 74 patients who received AEMT, only two (2.7%) were treated with two drugs simultaneously, but only one was *in vitro* active. Carbapenems (35/74; 47.3%) and piperacillin-tazobactam (29/74; 39.2%) were the most frequently used treatments in the AEMT group. Among the 24 patients treated with AECT, meropenem and aminoglycoside together with piperacillin-tazobactam and aminoglycoside (5/24; 20.8% each) were the most frequent antimicrobial combinations.

AECT was associated with a lower 30-day all-cause mortality (25%, six out of 24) compared to AEMT (56.8%, 42 out of 74; P= 0.007). Multivariate Cox regression analysis indicated AECT as the only factor significantly associated with improved survival (aHR 0.30; 95% CI 0.12–0.71; P =0.006). By contrast, the use of monotherapy or combination therapy in the definitive regimen did not influence mortality (aHR 0.73; 95% CI 0.25–2.14; P =0.568) meaning administration of combination antimicrobial therapy as the definitive regimen when susceptibility data were available did not significantly reduce mortality.

Dr. Septimus's Annotations

Recent guidelines for managing septic shock when *P. aeruginosa* is a known or suspected pathogen have recommended empirical combination therapy with at least two anti-pseudomonal antibiotics of different classes; however, the quality of the evidence supporting this recommendation is very low. [Clin Infect Dis, 2022 75: 187–212]

The key findings of this study can be summarized: (i) mortality rate in patients with septic shock due to *P. aeruginosa* BSI is surprisingly high; (ii) empirical combination therapy incorporating at least two in vitro active antibiotics significantly reduces the 30-day all-cause mortality risk compared to monotherapy and (iii) the administration of definitive adequate monotherapy or combination therapy yields similar outcomes, suggesting that once susceptibility is documented, switching to a single active *in vitro* drug is safe and feasible.

This retrospective cohort analysis reached a clinically useful conclusion that is probably true, although the median ages of the two groups differed significantly. Furthermore, I suspect that AECT might have been a marker of more-aggressive medical care delivered to younger patients, confounding the use of AECT toward lower mortality (and perhaps explaining why the AECT group was younger). For immunocompromised hosts with severe *P. aeruginosa* sepsis, combination therapy makes sense. Still, the decision is ideally addressed with a prospective clinical study.

BOTTOM LINE

In conclusion, this study supports the hypothesis that empiric combination therapy can decrease 30-day all-cause mortality in patients with septic shock caused by *P. aeruginosa* bloodstream infections (BSIs). However, there is still a need for well-designed randomized controlled trials to confirm the clinical benefit of empiric combination therapy in septic shock patients with *P. aeruginosa* BSI.

11

Incidence of serotonin syndrome in patients receiving tedizolid and concomitant serotonergic agents.

Antimicrobial Agents and Chemotherapy 2024, Vol. 68, No. 10
DOI: 10.1128/aac.00870-24

This was a retrospective study performed at two centers. This study included adult patients who received tedizolid for the treatment of an infection or for suppressive therapy between January 2015 and July 2023. Patients who received tedizolid more than once were included only for their first course with subsequent courses excluded. Patients were

considered on concomitant therapy with serotonergic agents if they received them during tedizolid therapy, within 2 weeks before the first tedizolid dose, or within 2 weeks after the last tedizolid dose. For patients receiving concomitant fluoxetine, up to a 5-week washout period was used. The Hunter Serotonin Toxicity Criteria, Sternbach's criteria [Am J Psychiatry 148:705– 713] and documented clinical diagnosis by the patient's treating clinicians in the electronic medical record were manually used by study investigators to identify the occurrence of serotonin syndrome. Tedizolid was dosed at 200 mg daily. The primary endpoint was the incidence of serotonin syndrome among patients who received tedizolid. Secondary endpoints were the adverse drug events resulting in unplanned tedizolid discontinuation as documented by the patient's treating clinicians in the electronic medical record.

479 unique patients received tedizolid while hospitalized, and 62% (297/479) of patients had received concomitant serotonergic agents. In patients receiving tedizolid for infection treatment (n = 463), the median (IQR) age was 61 (51–70), the median duration of therapy was 6 days (3–7), and 51.2% (237/463) of patients were female. While 19.9% (92/463) of the patients in the tedizolid treatment group previously received linezolid, 30.4% (28/92) discontinued linezolid due to an adverse event. Notably, 2.2% (2/92) of these patients developed serotonin syndrome on linezolid and later received tedizolid. Concomitant serotonergic agents were retained in both cases, but linezolid was discontinued. Of the two patients who developed serotonin syndrome on linezolid, neither patient developed serotonin syndrome on tedizolid. Among patients who received tedizolid for suppression (n = 16), the median age was 61 (44–68), the median duration of therapy was 119 days (30–336), and 43.8% (7/16) of patients were female. The most common serotonergic agent was sertraline (n = 63). Among the full cohort, 0.4% (2/479) of the patients required tedizolid discontinuation following clinical suspicion of possible serotonin syndrome. Six patients who received tedizolid for treatment (1.3%; 6/463) discontinued tedizolid due to adverse drug events: 0.4% (2/463) experienced thrombocytopenia, 0.7% (3/463) developed a skin reaction, and 0.2% (1/463) experienced severe nausea. Only 6.25% (1/16) of the patients who received tedizolid for suppression discontinued tedizolid due to an adverse drug event which was thrombocytopenia.

Dr. Septimus's Annotations

Oxazolidinone antimicrobials such as tedizolid and linezolid are often used as therapy for MRSA and VRE infections. Their inhibition of monoamine oxidase raises concerns about serotonin syndrome (altered mentation, rigidity, and myoclonus caused by build-up of high levels of serotonin) when they are coadministered with agents such as selective serotonin reuptake inhibitors. Given that up to 20% of American adults take antidepressant medications, we need a better understanding of this drug interaction. A list of serotonergic agents was compiled from the 2011 FDA safety announcement regarding serious adverse reactions when giving linezolid to patients taking certain psychiatric medications and other common agents studied in a pharmacovigilance study on serotonin.

"[Tedizolid and linezolid's] inhibition of monoamine oxidase raises concerns about serotonin syndrome... when they are coadministered with agents such as selective serotonin reuptake inhibitors."

This was a retrospective study of 479 hospitalized patients who were concomitantly receiving tedizolid and serotonergic agents. The primary endpoint was development of serotonin syndrome; secondary endpoints were other adverse events resulting in tedizolid discontinuation. The median duration of tedizolid therapy was only 6 days (for therapy) but 119 days (for suppression of chronic infection). In all, 2 patients (0.4%) required discontinuation of tedizolid for clinical suspicion of serotonin syndrome, although cyproheptadine antidote was not required for either patient. Also, only 3 of 479 patients (0.6%) in the combined cohort discontinued tedizolid due to thrombocytopenia.

This was an observational study; therefore, medication adherence upon discharge in the outpatient setting and criteria used for the diagnosis of serotonin syndrome relied on manual documentation in the electronic medical record. Second, this study lacks an active comparator

with linezolid or placebo. While a placebo group was not available, the incidence of patients experiencing symptoms of serotonin syndrome in the absence of an oxazolidinone antimicrobial has been reported to be 0.5%. My concern about this interaction is minimal in patients during hospital stays or very short outpatient courses (i.e., ≤1 week). However, this study suggests that tedizolid does carry a reduced risk for thrombocytopenia compared with linezolid. However, studies with linezolid also demonstrate a low risk for serotonin syndrome.

BOTTOM LINE

These results provide reassurance that the risk of serotonin syndrome is very low in patients receiving oxazolidinone antimicrobials such as tedizolid and linezolid with concomitant serotonergic agents such as sertraline.

Reaction Risk to Direct Penicillin Challenges A Systematic Review and Meta-Analysis

JAMA Internal Medicine published on September 16, 2024
doi: 10.1001/jamainternmed.2024.4606

The purpose of this review was to evaluate the frequency of reactions to direct penicillin challenges in individuals with penicillin allergy labels and to identify factors associated with such reactions. Three electronic databases were searched (MEDLINE, Web of Science, and Scopus) from inception to July 19, 2023, for primary studies assessing patients undergoing direct penicillin challenges. Articles were included regardless of publication year, language, status, or definition of allergy risk. The primary outcome was the frequency of reactions to direct penicillin challenges as calculated using random-effects bayesian meta-analysis of proportions. Secondary outcomes included risk factors for reactions and the frequency of severe reactions.

A total of 56 primary studies involving 9225 participants were included. Among participants, 438 experienced reactions to direct penicillin challenges without prior testing, corresponding to an overall meta-analytic frequency of 3.5% (95% credible interval [CrI], 2.5%-4.6%). Meta-regression analyses revealed that studies performed in North America had lower rates of reaction to direct challenges (odds ratio [OR], 0.36; 95% CrI, 0.20-0.61), while studies performed in children (OR, 3.37; 95% CrI, 1.98-5.98), in outpatients (OR, 2.19; 95% CrI, 1.08-4.75), and with a graded (OR, 3.24; 95% CrI, 1.50-7.06) or prolonged (OR, 5.45; 95% CrI, 2.38-13.28) challenge had higher rates of reaction. Only 5 severe reactions (3 anaphylaxis, 1 fever with rash, and 1 acute kidney injury) were reported, none of which were fatal.

A few points to consider. First, most studies excluded participants with severe index reactions, which may have resulted in an underestimation of the frequency of reaction to direct penicillin challenges in the general population. Second, the primary studies largely used different definitions of low risk, limiting the performance of subgroup analysis according to allergy risk group and highlighting the need to adopt more consistent international definitions of allergy risk.

Dr. Septimus's Annotations

In this systematic review of over 9000 patients, investigators found 438 experienced reactions (3.5%), with only 5 reactions classified as severe: 3 episodes of anaphylaxis, 1 delayed rash with fever, and 1 kidney injury. No fatalities were reported. These findings suggest that reactions to direct penicillin challenges in patients with penicillin allergy histories are infrequent, occurring at similar rates to challenges performed after negative results of allergy testing.

We have far more patients who should have their penicillin allergy delabeled than we have allergists to perform these challenges. Primary care clinicians and hospitalists can do this easily by giving one dose of amoxicillin (500 mg)

and watching the patient for 1 to 2 hours; intramuscular epinephrine and oral antihistamines should be available but are seldom needed. The PENFAST score is a good tool to help decide which patients can undergo direct oral challenge safely. [JAMA Intern Med 2023; 183:883] In general, if a patient has a history of severe immediate reaction (angioedema or anaphylaxis), a recent urticarial reaction (within 5 years), or any severe delayed reaction (e.g., Stevens–Johnson syndrome, serum sickness, drug reaction with eosinophilia, drug-induced cytopenia, organ injury), I would consult an allergist for evaluation.

BOTTOM LINE

This review found that reactions to direct penicillin challenges are infrequent, with rates comparable to indirect challenges after allergy testing. These findings suggest that direct challenges are safe for incorporation into penicillin allergy evaluation efforts across age groups and clinical settings.

13

Short Versus Long Antibiotic Duration in *Streptococcus pneumoniae* Bacteremia.

Open Forum Infectious Diseases September 2024, Volume 11, Issue 9, ofae478
DOI: 10.1093/ofid/ofae478

The investigators evaluated the effectiveness of short (5–10 days) versus long (11–16 days) antibiotic durations for S *pneumoniae* bacteremia. The study was a retrospective, single-center cohort study assessing hospitalized patients with S *pneumoniae*–positive blood cultures, who received active antibiotics within 48 hours of first positive blood culture collection and achieved clinical stability by day 10 of the first positive blood culture collection. Exclusion criteria included treatment duration 16 days, death before completion of 10 days of therapy, polymicrobial bloodstream infection, and invasive infection (endocarditis, meningitis, and lung abscess). Rates of clinical failure (composite of 30-day hospital readmission, bacteremia recurrence, and mortality) were compared between the groups.

Patients were identified for study inclusion via a query of the electronic medical record (EMR). Data captured during the EMR query included age, gender, hospital length of stay (LOS), intensive care unit (ICU) LOS, Charlson Comorbidity Index score, APACHE II score, Pitt bacteremia score, and central venous catheter placement. Additional demographic, clinical management, and laboratory data were collected via manual chart review, such as blood culture results with associated date, discharge disposition, start and stop dates of all inpatient and outpatient antibiotics, white blood cell count, serum creatinine level, and other applicable vital signs at the time of positive blood cultures and at day 10 of therapy.

A total of 162 patients were included, with 51 patients in the short- and 111 patients in the long-duration group. Pneumonia was the suspected source of bacteremia in 90.1% of patients. Rates of clinical failure were not significantly different between the 2 groups. Patients received a median antibiotic course of 7 days in the short group compared to 14 days in the long group; however, there was no significant difference observed in the median hospital length of stay, median intensive care unit length of stay, or rate of *C difficile* infection.

Dr. Septimus's Annotations

Current guidelines recommend a short course (5–7 days) of antibiotics for community-acquired pneumonia treatment; however, they do not specifically address duration of therapy for secondary BSI. [Am J Respir Crit Care Med 2019; 200: e45–67. In this study, there was no association between clinical failure and shorter duration of antibiotic therapy for S pneumoniae bacteremia. The shorter and longer antibiotic duration groups had similar rates of all-cause

hospital readmission, bacteremia recurrence, and all-cause mortality. There was also no significant difference between hospital LOS, ICU LOS, rate of C difficile occurrence, or central venous catheter placement in either group. Prescribing bias may have played a role in the duration of antibiotics received. They attempted to mitigate such disparities through utilization of IPTW but the potential for impact of unmeasured variables exists. They also counted both intravenous and oral antibiotic therapy equally in determining total duration.

BOTTOM LINE

In this study patients being treated with short versus long duration of antibiotics for uncomplicated S *pneumoniae* bacteremia, found no difference in overall clinical efficacy when evaluating all-cause hospital readmission, bacteremia recurrence, or all-cause mortality. Since this was single center retrospective analysis further research should be conducted to determine the appropriateness of shorter antibiotic durations for S *pneumoniae* bacteremia.

14

Adjunctive linezolid versus clindamycin for toxin inhibition in β-lactam-treated patients with invasive group A streptococcal infections in 195 US hospitals from 2016 to 2021: a retrospective cohort study with target trial emulation.

The Lancet Infectious Diseases published online October 10, 2024
DOI: 10.1016/ S1473-3099(24)00507-3

The investigators performed a retrospective emulated a target multicenter, non-blinded, non-inferiority trial to assess the efficacy of adjunctive linezolid compared with clindamycin in adult inpatients with invasive group A streptococcal (GAS) infection treated with a β-lactam using the PINC AI database between 2016 and 2021. Patients were eligible if they had a monomicrobial GAS culture and received adjunctive therapy within 3 days of culture either concurrently or after β-lactam initiation and completed at least 3 days of β-lactam therapy. The study only compared outcomes in patients who survived 3 days. Proven invasive GAS infection was defined as GAS isolated from a normally sterile site, such as blood, cerebrospinal fluid, pleural fluid, peritoneal fluid, pericardial fluid, bone, joint or synovial fluid, or internal body site (e.g., lymph node or brain), or GAS isolated from a wound culture and accompanied by NSTI or streptococcal toxic shock syndrome as defined by presence of a compatible ICD-10 code or vasopressor use. The primary outcome was adjusted risk ratio (aRR) of in-hospital mortality assessed by overlap-weighting using propensity scores. Secondary outcomes were length of stay among survivors and *C difficile* infection.

Of 1095 β-lactam-treated patients with GAS, 829 (76%) received clindamycin and 266 (24%) received linezolid. In the overlap weighted cohort, the receipt of linezolid was not associated with a statistically significant different aRR of in-hospital mortality compared with clindamycin (linezolid: 9·8% [26/266] vs clindamycin: 7·0% [58/829]; aRR: 0·92 [95% CI 0·42 to 1·43]; p=0·76). The risk difference was −0·005 (95% CI −0·05 to 0·04; p=0·81) and fell within the non-inferiority margin of 0·05. The primary analysis results were consistent across important subgroups and sensitivity analyses. Among survivors, median length of stay (adjusted ratio 0·96 [95% CI 0·16 to 0·08]; p=0·47) and C *difficile* infection risk (aRR 1·76 [95% CI 0·37 to 1·75]; p=0·29) were not statistically significantly different between the two groups.

Dr. Septimus's Annotations

Among 1095 β-lactam-treated patients with invasive GAS across 195 US centers, effectiveness of linezolid was non-inferior to clindamycin as an adjunctive antitoxin agent as gauged by mortality and important secondary outcomes. This is despite the linezolid cohort being older and having more comorbidities and increased severity of acute illness.

More cases of lower respiratory tract infection received linezolid. In-hospital mortality was, however, numerically higher among individuals receiving linezolid in the main analysis and a few key subgroups, including patients with bacteremia, patients with severe iGAS, and patients in the ICU, although in each case the difference was not statistically significant. Importantly, the vast majority of deaths from iGAS are known to occur in the first 48 h as this study only compared outcomes in patients who survived 3 days. The study's comparison of linezolid and clindamycin is restricted to the minority of iGAS deaths that occur late. This likely explains the low iGAS mortalities compared with those reported elsewhere.

Clindamycin was originally recommended as adjunctive therapy for treating invasive GAS infections based on in vitro and in vivo studies that showed the higher efficacy of clindamycin in high inoculum infections and decreased expression of streptococcal virulence factors and toxins. [Clin Infect Dis 2014; 59: 147–59] A meta-analysis of eight clinical studies with 1827 patients demonstrated a survival benefit of adjunctive clindamycin in invasive GAS infections (odds ratio 0·45 [95% CI 0·27–0·78]).[Clin Infect Dis 2023; 76: 346–50] Recently, linezolid has been used in clinical practice as an adjunctive agent in lieu of clindamycin. This is primarily due to similar toxin inhibiting properties, [Open Forum Infect Dis 2023; 10: ofad588] broad-spectrum activity which includes methicillin-resistant S aureus activity, concern for GAS clindamycin resistance, and C difficile infection risk with clindamycin.

BOTTOM LINE

The findings in this study indicate that linezolid is a non-inferior alternative to clindamycin as adjunctive therapy for invasive GAS infection. Given the variable clindamycin resistance among GAS isolates globally and the unclear potential of clindamycin to inhibit toxins from clindamycin-resistant strains, linezolid could be considered as acceptable first-line adjunctive therapy. However, this study only included patients who received at least 3 days of β-lactam therapy; therefore, additional studies are needed to confirm the effectiveness of linezolid early in the course of illness.

Development of an Electronic Clinical Surveillance Measure for Unnecessary Rapid Antibiotic Administration in Suspected Sepsis

Clinical Infectious Diseases published on October 3, 2024
doi: 10.1093/cid/ciae445

The investigators aimed to establish preliminary validity and usefulness of electronic health record (EHR) data–derived criteria for sepsis overtreatment surveillance (SEP-OS). They evaluated adults with potential sepsis (≥2 Systemic Inflammatory Response Syndrome criteria within 6 hours of arrival) presenting to the ED of 12 hospitals, excluding patients with shock. They defined SEP-OS as the proportion of patients receiving rapid IV antibiotics (≤3 hours) who did not ultimately meet the CDC Adult Sepsis Event (ASE) "true sepsis" definition. (see below) They evaluated the frequency and characteristics of patients meeting overtreatment criteria and outcomes associated with sepsis overtreatment.

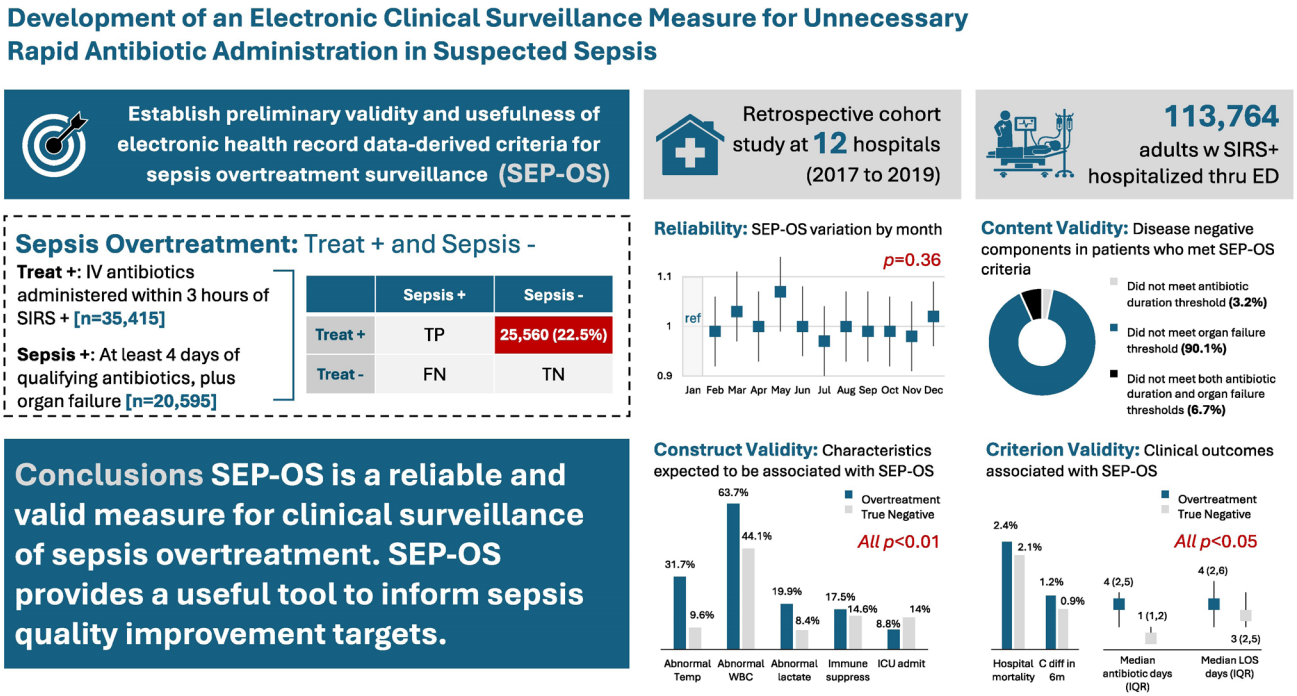
Adult Spesis Event (ASE)

A. Presumed Infection (presence of both 1 and 2):
   1. Blood culture obtained (irrespective of the result), AND
   2. At least 4 Qualifying Antimicrobial Days (QAD) – starting within the time period 2 calendar days before and after the collection date of a blood culture. AND B.

B. Organ Dysfunction (at least 1 of following criteria met within the time period 2 calendar days before and after the collection date of a blood culture.):
   1. Initiation of a new vasopressor infusion (norepinephrine, dopamine, epinephrine, phenylephrine, OR vasopressin). To count as a new vasopressor, that specific vasopressor cannot have been administered in the prior calendar day.
   2. Initiation of invasive mechanical ventilation (must be greater than 1 calendar day between mechanical ventilation episodes.
   3. Doubling of serum creatinine OR decrease by ≥50% of estimated glomerular filtration rate (eGFR) relative to baseline (see below), excluding patients with ICD-10 code for end-stage renal disease

4. Total bilirubin ≥ 2.0 mg/dL and increase by 100% from baseline.
5. Platelet count <100 cells/μL AND ≥ 50% decline from baseline.
6. Serum lactate ≥ 2.0 mmol/L

Of 113,764 eligible patients, the prevalence of sepsis overtreatment was 22.5%. The measure met prespecified criteria for reliability, content, construct, and criterion validity. Patients classified by the SEP-OS overtreatment criteria had higher median antibiotic days (4 days [IQR, 2–5] vs 1 day [1–2]; P < .01), longer median length of stay (4 days [2–6] vs 3 days [2–5]; P < .01), higher hospital mortality (2.4% vs 2.1%; P = .01), and higher frequency of C difficile infection(CDI) within 6 months of hospital discharge (P < .01) compared with "true negative" cases.



Taylor et al, 2024 | Clinical Infectious Diseases

Dr. Septimus's Annotations

Diagnostic uncertainty leads to high rates of both under- and overtreatment of sepsis, each of which can be harmful. [JAMA Intern Med 2017] Missed or delayed antibiotic initiation is associated with increased mortality, particularly for patients with severe disease. [N Engl J Med 2017; 376:2235–44] Conversely, overtreatment of sepsis (antibiotics in the absence of true disease) also yields harms. Overtreatment causes unintended consequences such as alteration of the microbiome, increasing antibiotic resistance, CDI, and can delay workup needed to address the true disease state. [Ann Intern Med 2021; 174:927–35] Overtreatment negatively affects antibiotic stewardship and is associated with increased healthcare costs. A multicenter study using administrative codes as a gold standard found that 42% of sepsis treatment pathway activations were false-positive, and this trend increased over time. [Ann Am Thorac Soc 2020; 17:520–2] Similarly, 35% of code sepsis activations were found to represent false-positive diagnoses against a chart review gold standard. [Jt Comm J Qual Patient Saf 2021; 47:157–64] Finally another study found that one-third of patients empirically treated with broad-spectrum antibiotics in the ED were ultimately diagnosed with noninfectious or viral conditions. [Am J Emerg Med 2020; 38:2570–3]

In this study the investigators used a robust dataset of 113,764 patients presenting to the ED with suspected infection and without shock. They developed surveillance criteria for overtreatment of sepsis (SEP-OS) calculated as the proportion of patients with antibiotics administered in 3 hours but not meeting modified ASE criteria out of all ED patients meeting SIRS criteria within 6 hours. This new measure represents an opportunity to integrate sepsis treatment and diagnostic stewardship efforts that have previously seemed to be at odds. [JAMA 2018; 320:1433–4]

Although the "perfect" definition of overtreatment does not exist, they evaluated SEP-OS on several domains of usefulness appropriate for a clinical surveillance definition. Definitions for each of the 6 metric domains are shown below.

SEP-OS does not capture sepsis overtreatment among patients who do not meet SIRS criteria, and evidence suggests that up to 1 in 8 ICU patients with infection and organ dysfunction are SIRS-negative.[N Engl J Med 2015; 372:1629-1638] Risk adjustment for SEP-OS, to account for differing prioritization of undertreatment versus overtreatment in patients with different risk profiles needs to be explored.

Sepsis Overtreatment Surveillance (SEP-OS) performance on domains of usefulness

Domain	Domain Definition	SEP-OS Performance Description
Measurement burden	Burden to implement surveillance testing	Low cost, EHR-based data collection
Timeliness	Criteria can be generated in a timely manner relative to the course of disease	Measure can be calculated in near real-time
Reliability		
Test-retest, interrater	Criteria yield reliable results when tests are repeated and interpreted	SEP-OS uses EHR-based clinical criteria and is based on pre-existing objective measurements (eg, ASE) to avoid test-retest and interrater reliability issues. Minimal changes in patients identified using different assessment methods.
Content validity	Criteria fit within current understanding/knowledge	SEP-OS definition incorporates harms of both antibiotic overuse and imposing wasteful urgency on treating non-severe disease.
Construct validity	Criteria measure what they purport to measure	SEP-OS is more frequent in patients with characteristics expected to lead to overtreatment.
Criterion validity (predictive)	Criteria associated with later outcomes believed to be strongly associated with the disease of interest	SEP-OS is associated with longer average days of antibiotics, longer hospital length of stay, and higher rates of *C difficile* infection at 6 months.

BOTTOM LINE

The investigators developed a reliable surveillance measure for sepsis overtreatment (SEP-OS) that demonstrates content, construct, and criterion validity and is predictive of downstream consequences of overtreatment. This new measure represents an opportunity to integrate sepsis treatment and antimicrobial/diagnostic stewardship.

16

Factors Associated With Poor Clinical and Microbiologic Outcomes in *Candida auris* Bloodstream Infection: A Multicenter Retrospective Cohort Study

Clinical Infectious Diseases published online August 13, 2024
DOI: 10.1093/cid/ciae411

The investigators assembled a multicenter retrospective cohort of patients with C. *auris* BSI from 2 geographics areas in the US. They collected data on demographic, clinical, and microbiologic characteristics to describe the cohort and constructed multivariate logistic regression models to understand risk factors for 2 clinical outcomes, all-cause mortality during facility admission, and blood culture clearance. Clinical data were collected retrospectively from electronic health records including information on demographics, medical comorbidities, presence of invasive medical devices, antifungal susceptibilities, antibiotic and antifungal administration history, documented infectious sources, severity of illness as defined by the Pitt bacteremia score, and clinical outcomes studies for use in severity of illness evaluations for non–C. *auris* Candida BSIs.

The cohort consisted of 187 patients with C. *auris* BSI (56.1% male, 55.6% age >65 years); 54.6% died by facility discharge and 66.9% (of 142 with available data) experienced blood culture clearance. Pitt bacteremia score at infection onset was associated with mortality

(odds ratio [95% confidence interval]: 1.19 [1.01–1.40] per 1-point increase). Hemodialysis was associated with a reduced odds of microbiologic clearance (0.15 [0.05–0.43]) and with mortality (3.08 [1.27–7.50]).

Dr. Septimus's Annotations

C auris has become a growing concern worldwide because of increases in incidence of colonization, reports of invasive infections, and multidrug resistance. *C auris* is now considered a high priority pathogen by the WHO and CDC. There has been an increase in reports of colonization and clinical cases globally, exacerbated by Covid-19 pandemic In the US, recent studies have suggested an increase in the rates of colonization, with clinical cases increasing concurrently. [Ann Intern Med 2023; 176:489–95] Of particular concern are invasive infections, primarily BSIs. Up to 25% of colonized patients in intensive care units may develop *C. auris* BSI. Infect Dis Ther 2022; 11:1149–60] Mortality as expected, was more common with had medical devices (urinary catheters, tracheostomies, CVCs as source of infection), prior bacteremia during hospitalization, prior colonization with carbapenem-resistant bacterial organisms, and longer lengths of facility admission. After multivariable adjustment, Pitt bacteremia score at the time of index culture (a marker of acute illness) and hemodialysis (a marker of chronic disease) were both associated with all-cause mortality during facility admission. Based on a time-to-event analysis, most patients with healthcare-associated *C. auris* BSI were hospitalized for more than 2 weeks. This highlights the importance of infection prevention including timely CVC removal and antimicrobial stewardship.

This study lacked available genomic data on specific isolates. A large portion of the cases come from a single site and the retrospective nature of this study limits the ability to determine causality.

BOTTOM LINE

C. *auris* colonization and infection continue to increase in prevalence across the US and the world. Targeted infection prevention (e.g., CVC appropriateness assessment, CVC access and maintenance best practices) among vulnerable populations, especially patients who are hemodialysis-dependent and have high Pitt bacteremia scores, may decrease healthcare-associated fungemia and reduce mortality.

Dexamethasone in adults with viral meningitis: an observational cohort study.

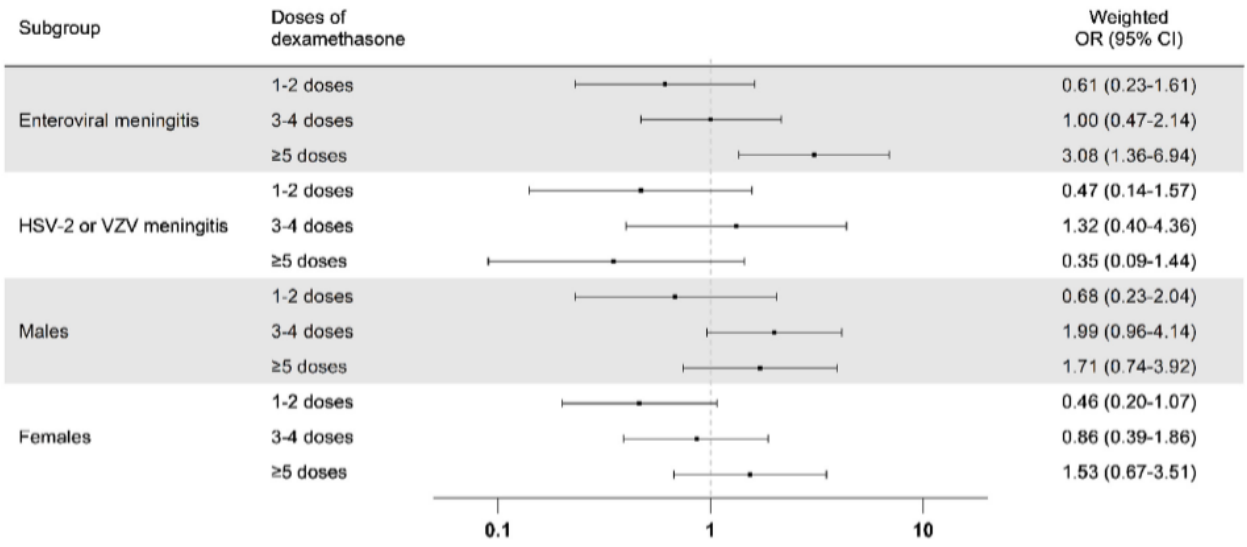
Clinical Microbial and Infection published on August 23, 2024
doi: 10.1016/j.cmi.2024.08.015

Adjunctive dexamethasone initiated before or with the first dose of antibiotic has proven beneficial in patients with community-acquired meningitis caused by *S pneumoniae* or *Hemophilus B*. When the causative pathogen is initially unknown, many patients receive dexamethasone until these two bacterial etiologies have been ruled out. But what about viral meningitis?

Investigators conducted a nationwide cohort study involving 1025 patients (median age, 33) hospitalized with viral meningitis to assess the outcomes associated with number of dexamethasone doses. Dose-dependent associations between dexamethasone (one dose = 10 mg) and an unfavorable outcome (Glasgow Outcome Scale score 1-4) at 30 days after discharge were assessed using weighted logistic regression.

Of 1025 included patients, 658 (64%) did not receive dexamethasone, 115 (11%) received 1-2 doses, 131 (13%) received 3-4 doses, and 121 (12%) received ≥5 doses. Among patients treated with dexamethasone, the median number of doses

was higher for those without an identified pathogen than for those with a microbiologically confirmed viral etiology (5 [interquartile range (IQR) 3-8] vs. 3 [IQR 2 -5]; p < 0.001). Using no doses of dexamethasone as a reference, the weighted OR for an unfavorable outcome were 0.55 (95% CI, 0.29-1.07) for 1-2 doses, 1.13 (95% CI, 0.67-1.89) for 3-4 doses, and 1.43 (95% CI, 0.77-2.64) for ≥5 doses. In the subgroup of enteroviral meningitis, the weighted OR was 3.08 (95% CI, 1.36-6.94) for ≥5 doses, but decreased to 2.35 (95% CI, 0.65-8.40) when the reference group was restricted to patients treated with antibiotics for suspected bacterial meningitis.



Dr. Septimus's Annotations

Treatment with dexamethasone adjunctive to antibiotics reduces mortality and sequelae in adults with pneumococcal meningitis and hearing loss in those with *Hemophilus influenzae type b* meningitis. [Cochrane Database Syst Rev 2015;2015:CD004405] The mechanisms leading to improved outcomes are not fully clarified, but reducing the inflammatory response may protect against increased intracranial pressure, edema, and cytokine-induced cell injury in the brain and hearing organs. [J Clin Invest 1980; 66:243e53] European and US guidelines for managing bacterial meningitis in adults recommend initiating dexamethasone concomitant with the first dose of antibiotics and as soon as possible if the diagnosis is suspected. [Clin Infect Dis 2004; 39:1267e84; Clin Microbiol Infect 2016;22(Suppl 3): S37e62] Patients without confirmed pathogen etiology received more dexamethasone than those with known etiology (5 vs. 3 doses). In all, 64% of patients received no dexamethasone, 11% received 1 or 2 doses, 13% received 3 or 4 doses, and 12% received ≥5 doses. Rates of unfavorable outcomes (Glasgow Outcome Scale score ≤4) at day 30 by dosage were 20%, 12%, 22%, and 26%, respectively. Median duration of hospitalization (3 days) did not differ between dexamethasone-treated and untreated patients. In enteroviral meningitis, ≥5 doses were associated with an increased risk of an unfavorable outcome. However, sensitivity analysis indicated that the association was affected by unmeasured or residual confounding by severity.

BOTTOM LINE

Administering dexamethasone for a central nervous system infection carries the dilemma that it benefits those with S pneumoniae and Hemophilus B but must be started before the microbiologic cause is confirmed. These results are reassuring in showing that such a practice apparently is not harmful in the setting of viral meningitis. However, dexamethasone should be discontinued as soon as bacterial etiology has been ruled out.

18

Nonantibiotic prophylaxis for urinary tract infections: a network meta-analysis of randomized controlled trials.

Infection published online August 2, 2024
DOI: 10.1007/s15010-024-02357-z

Two reviewers independently searched the Embase, PubMed, Web of Science, and Cochrane systematic review databases using search terms related to "urinary tract infection," "prevention," and corresponding interventions such as "cranberry," "vitamins," "vaccines," "probiotics," "D-mannose," "estrogen," and "immunostimulants," without language restrictions. Studies were considered eligible if they met the following criteria: the study population had a history of previous UTIs or had risk factors for UTIs, one or more nonantibiotic interventions for the prevention of UTIs were investigated, and the results included the incidence of urinary tract infections. The study design had to be a randomized controlled trial (RCT). Fifty randomized control trials (RCTs) were finally included in this network meta-analysis (NMA), encompassing 10,495 participants in total. Among the RCTs, 40 studies were double-blind or triple-blind in design, and 41 studies were conducted in adults. Interventions included placebo, cranberry, propolis plus cranberry, probiotics, vaccine, vitamin D, D-mannose, antibiotic, triple therapy (cranberry plus probiotics plus vitamin A), methenamine hippurate, estrogen, hyaluronic acid plus chondroitin sulphate, competitive inoculation and D-mannose plus estrogen. The participants in the 30 studies (60%) were all women and nearly 80% of the participants were female. 39 studies had a follow-up of 6 months or more.

The network meta-analysis results demonstrated that the incidence of UTI was significantly reduced by the following therapies vs placebo:

- D-mannose (RR, 0.34; 95% CI, 0.21-0.56);
- Triple therapy (RR, 0.27; 95% CI, 0.09-0.87);
- Vaccine (RR, 0.65; 95% CI, 0.52-0.82);
- Probiotics (RR, 0.69; 95% CI, 0.50-0.94); and
- Cranberry (RR, 0.72; 95% CI, 0.60-0.87).

Among adults, the following therapies demonstrated superiority vs placebo in the prevention of UTI:

- D-mannose (RR, 0.33; 95% CI, 0.20-0.53);
- Triple therapy (RR, 0.27; 95% CI, 0.09-0.85);
- Vaccine (RR, 0.66; 95% CI, 0.53-0.82); and
- Cranberry (RR, 0.72; 95% CI, 0.59-0.88).

Among nonadults, probiotics vs placebo were superior in preventing UTI (RR, 0.50; 95% CI, 0.28-0.89).

Compared with placebo, D-mannose (RR, 0.32; 95% CI, 0.19-0.52), vaccine (RR, 0.64; 95% CI, 0.47-0.85), and cranberry (RR, 0.67; 95% CI, 0.53-0.85) were more effective in preventing UTI in women.

In studies that considered long-term follow-up, vitamin D (RR, 0.46; 95% CI, 0.27-0.81), probiotics (RR, 0.48; 95% CI, 0.25-0.93), hyaluronic acid and chondroitin sulfate (RR, 0.51; 95% CI, 0.36-0.74), competitive inoculation (RR, 0.53; 95% CI, 0.33-0.86), and vaccine (RR, 0.69, 0.54-0.87) vs placebo were more effective in UTI prevention.

Within the intermediate follow-up group, D-mannose (RR, 0.23; 95% CI, 0.10-0.55) and triple therapy (RR, 0.26; 95% CI, 0.07-0.90) vs placebo were more effective in preventing UTI.

A total of 4173 patients reported adverse events (AEs) in 27 RCTs. There was no significant difference in the incidence of AEs across interventions vs placebo.

In Bayesian network meta-analysis, cranberry (RR, 0.72; 95% CI, 0.58-0.87), triple therapy (RR, 0.26; 0.07-0.79), D-mannose (RR, 0.34; 95% CI, 0.20-0.57), and vaccine (RR, 0.64; 95% CI, 0.50-0.82) were all linked to a significantly lower incidence of UTI.

Study limitations include the low number of RCTs providing data on D-mannose prophylaxis and triple therapy; potential bias; heterogeneity in the doses, frequencies, and baseline characteristics of interventions; and use of varying definitions of UTI across the included RCTs.

Dr. Septimus's Annotations

UTIs, one of the most widespread bacterial infections, affect approximately 150 million individuals globally each year and incur an estimated annual cost of $1.6 billion for evaluation and treatment in the US. Almost half of women

will encounter symptomatic acute bacterial cystitis during their lives, with nearly 50% experiencing recurring episodes between 6 months and 1 year after the initial infection. [Bmj 2013; 346: f3140] Over the last two decades, there has been a notable surge in drug resistance among urinary tract-causing organisms, leading to suboptimal antibiotic efficacy and impacting patients' quality of life. The overuse of antibiotics has contributed to the acceleration of antimicrobial resistance, which is a serious threat to global public health stimulating interest in nonantibiotic approaches to preventing UTIs. Guidelines have proposed various nonantibiotic interventions to prevent UTIs and provide different recommendation grades and opinions. [J Urol 2022;208: 536–541; Eur Urol 2020; 78: 645–646] This study aimed to compare the efficacy and safety of nonantibiotic interventions for UTI prevention through a network meta-analysis (NMA), which offered valuable insights for nonantibiotic interventions preventing UTIs. Based on current evidence more studies as needed.

BOTTOM LINE

This literature review suggests D-mannose, triple therapy (cranberry plus probiotics plus vitamin A), vaccine, probiotics, and cranberry may be potential nonantibiotic intervention choices for preventing UTIs. Considering the limited number of studies providing preventive measures and the study limitations, there is still a need for larger-scale, high-quality, and long-term follow-up randomized control trials to enhance future clinical decision-making.

19 Pertussis is at a decade-high level in US

October 17, 2024

Pertussis (whooping cough) is at its highest level in a decade for this time of year, per CDC. There have been 18,506 cases of pertussis reported so far. That's the most at this point in the year since 2014, when cases topped 21,800.

The increase is not unexpected — pertussis peaks every three to five years and the numbers indicate a return to levels before the Covid-19 pandemic, when pertussis and other contagious illnesses plummeted. Still, the tally has some state health officials concerned, including those in Wisconsin, where there have been about 1,000 cases so far this year, compared to a total of 51 last year.

Dr. Septimus's Annotations

Nationwide, CDC has reported that kindergarten vaccination rates dipped last year and vaccine exemptions are at an all-time high. CDC released state figures, showing that about 86% of kindergartners in Wisconsin got pertussis vaccine, compared to more than 92% nationally. Pertussis is usually seen mostly in infants and young children, who can develop serious complications. That's why the vaccine is recommended during pregnancy, to pass along protection to the newborn, and for those who spend a lot of time with infants. But public health workers say outbreaks this year are hitting older kids and teens. In Pennsylvania, most outbreaks have been in middle school, high school and college settings.

BOTTOM LINE

Pertussis can be prevented. We have safe and effective vaccines. We need to make sure all eligible persons are vaccinated.

20 Marburg virus disease (MVD) in Rwanda

As of October 17, 2024, Rwanda reports 62 cases of MVD and 15 deaths in country. [CFR 24%] Rwanda has a robust public health infrastructure and has controlled outbreak using case findings and antivirals [Remdesivir]/vaccine.

- CDC has a Level 2 travel advisory (practice enhanced precautions) currently for Rwanda. They should raise that to a Level 3 travel advisory (Reconsider Nonessential Travel) in the next 24 hours.
- CDC anticipates starting traveler screening for persons coming/returning to the US after time spent in Rwanda with a target start date of Oct 16, 2024. Daily traveler volume to the US from Rwanda averages around 120 travelers per day. The top seven receiving airports by traveler volume are: Dulles (18%), JFK (17%), O'Hare (15%), Atlanta (7%), LAX (6%), Boston (6%) and Newark (6%).
- Passengers will be routed through one of the 3 receiving airports (Dulles, JFK, and O'Hare) and will be screened at those ports of entry by federal partners (CDC/Homeland Security staff or contractors). It is expected that daily monitoring by state or local public health partners will NOT be recommended unless a traveler reports a high-risk exposure. High risk exposure definitions have not been finalized but are anticipated to include acting as a healthcare worker or other high-risk occupation, participation in funeral or burial rituals or services, or contact with non-human primates or bats.
- No confirmed cases of MVD related to this outbreak have been reported in the US

Background

- Marburg virus disease is a rare, severe viral hemorrhagic fever similar to Ebola. Both Marburg viruses are within the virus family Filoviridae, which also includes Ebola viruses. It is spread by certain types of bats in several countries in Africa and can be spread from person-to-person through direct contact with the body fluids of someone who is sick with MVD. Marburg is not spread through airborne transmission and people are not contagious before symptoms appear.
- Symptoms include fever, chills, headache, muscle aches, rash, chest pain, sore throat, nausea, vomiting, diarrhea, or unexplained bleeding or bruising (late stage of illness).
- There is no FDA approved treatment or vaccine for MVD.
- The only case of Marburg in the US occurred in 2008 in a US traveler who returned from Uganda. The patient was hospitalized and fully recovered.
- Last Marburg outbreaks were in 2023; two separate outbreaks occurred concurrently in Equatorial Guinea and Tanzania – daily traveler volume to the US from these two countries averaged around 150-200 travelers per day.

Recommendations for Clinicians

- Systematically assess patients with exposure risk and compatible symptoms for the possibility of viral hemorrhagic fevers including MVD through a triage and evaluation process including a travel history. Early identification of MVD or other viral hemorrhagic fevers is important for providing appropriate and prompt patient care and preventing the spread of infection.
- Include MVD in the differential diagnosis for an ill person who has been to an area with an active MVD outbreak in the past 21 days, AND who has compatible symptoms (e.g., fever, headache, muscle and joint pain, fatigue, loss of appetite, gastrointestinal symptoms, or unexplained bleeding), AND has reported epidemiologically compatible risk factors like any one or more of the below, within the 21 days before symptom onset:
  - Had direct contact with a symptomatic person with suspected or confirmed MVD, or with any objects contaminated by their body fluids.
  - Experienced a breach in infection prevention and control precautions that resulted in the potential for contact with body fluids of a patient with suspected or confirmed MVD.
  - Participated in any of the following activities while in an area with an active MVD outbreak:
    - Contact with someone who was sick or died or with any objects contaminated by their body fluids.
    - Attended or participated in funeral rituals, including preparing bodies for funeral or burial.
    - Visited or worked in a healthcare facility or laboratory.
    - Contact with cave-dwelling bats or non-human primates.
    - Worked or spent time in a mine or cave.

- Consider more common diagnoses such as malaria, Covid-19, influenza, or common causes of gastrointestinal and febrile illnesses in an ill patient with recent international travel, and evaluate and manage appropriately.
- Know that patients with a Marburg virus infection may present with concurrent infections (e.g., co-infection with malaria), and the possibility of a concurrent infection should be considered if a patient has a clinical and epidemiologic history compatible with MVD. Travel to or from Rwanda in the past 21 days should not be a reason to defer routine laboratory testing or other measures necessary for standard patient care.
- Isolate and manage patients with exposure risks and symptoms compatible with MVD in a healthcare facility until receiving a negative Marburg virus test result on a sample collected ≥ 72 hours after symptom onset. If a sample collected is <72 hours after symptom onset and is negative, the patient should remain in the healthcare facility and another test should be performed on a new sample taken ≥ 72 hours after initial symptom onset. Routine laboratory testing to monitor the patient's clinical status and diagnostic testing for other potential causes of the patient's illness should be pursued while Marburg virus testing is underway. Marburg virus diagnostic testing should not be delayed while awaiting results of other diagnostic testing.
  - Patients should be held in isolation at their presenting medical facility and cared for by personnel wearing appropriate PPE, pending test results.
  - If a patient tests positive, they would be transferred to a Regional Emerging Special Pathogens Treatment Center or a state-designated special pathogens treatment center. depending on the jurisdiction.
- Contact your state, territorial, local or Tribal (STLT) health department immediately if MVD is suspected and follow jurisdictional protocols for patient assessment. If a diagnosis of MVD is considered, health departments will work with CDC and the clinical team to coordinate care and testing for the patient and ensure appropriate precautions are taken to help prevent potential spread.
- Counsel patients with planned travel to an MVD outbreak-affected area on ways to prevent exposure during their travel. Prevention methods include:
  - Avoiding contact with blood and body fluids (or with materials possibly contaminated with blood and body fluids) of people who are sick.
  - Not participating in funeral or burial practices that involve touching the body of someone who died from suspected or confirmed MVD.
  - Avoiding contact with cave-dwelling fruit bats and non-human primates.
  - Refraining from entering areas known to be inhabited by cave-dwelling fruit bats, such as mines or caves.
- For this outbreak, travelers are additionally advised to avoid visiting healthcare facilities in the outbreak area for nonurgent medical care or for nonmedical reasons, and to avoid visiting traditional healers.

Recommendations for Infection Prevention and Control Measures in Hospitals

- Employ a combination of infection prevention and control measures to prevent transmission of MVD in hospitals. These infection prevention and control measures include, but are not limited to:
  - Isolating patients in a private room with a private bathroom or covered bedside toilet if MVD is suspected. Dedicated medical equipment (preferably disposable, when possible) should be used for the provision of patient care.
  - Following separate PPE guidance for managing clinically stable and clinically unstable patients.
  - Ensuring that healthcare workers caring for patients with VHFs have received comprehensive training and demonstrated competency in performing VHF-related infection control practices and procedures.
  - Following the infection prevention and control measures as recommended for VHFs including using recommended PPE and limiting the number of personnel who enter the room for clinical evaluation and management.
  - Having an onsite manager supervise personnel always providing care to these patients. A trained observer must also supervise each step of every PPE donning/doffing procedure to ensure established PPE protocols are completed correctly.

- Know that healthcare personnel can be exposed through contact with a patient's body fluids, contaminated medical supplies and equipment, or contaminated environmental surfaces. Splashes to unprotected mucous membranes (e.g., the eyes, nose, or mouth) are particularly hazardous.
- Minimize procedures that can increase environmental contamination with infectious material, involve handling of potentially contaminated needles or other sharps, or create aerosols.

BOTTOM LINE

Like Ebola we must be prepared to handle possible cases and alert our facilities to reinforce appropriate infection prevention policies for suspected cases.

21

Current Outbreaks Spectre (Special Pathogens Excellence in Clinical Treatment, Readiness, and Education)

October 14, 2024

Marburg Virus as of October 2024

- 58 confirmed cases, 13 resulting in death in Rwanda

Lassa Fever

- 9 confirmed cases and 1 confirmed death in Nigeria

Mpox

WHO conducted the latest global mpox rapid risk assessment in August 2024. Based on the available information, the risk was assessed as:

- In eastern Democratic Republic of the Congo and neighboring countries: high.
- In areas of the Democratic Republic of the Congo where mpox is endemic: high.
- In Nigeria and other countries of West, Central and East Africa where mpox is endemic: moderate.
- In all other countries in Africa and around the world: moderate.

In 2024, as of 06 October 2024, 16 countries have reported 7,535 confirmed cases, including 32 deaths. The three countries with the majority of the cases in 2024 are Democratic Republic of Congo, (n = 6 169), Burundi, (n = 987), and Nigeria, (n = 94).

Based on currently available information, the spread of mpox cases in the Democratic Republic of the Congo is attributed to two main outbreaks - spread of MPXV clade Ia in Equateur and other previously affected provinces of the country, and the spread of clade Ib MPXV in the provinces of North and South Kivu, as well as several clade Ib cases detected in Kinshasa.

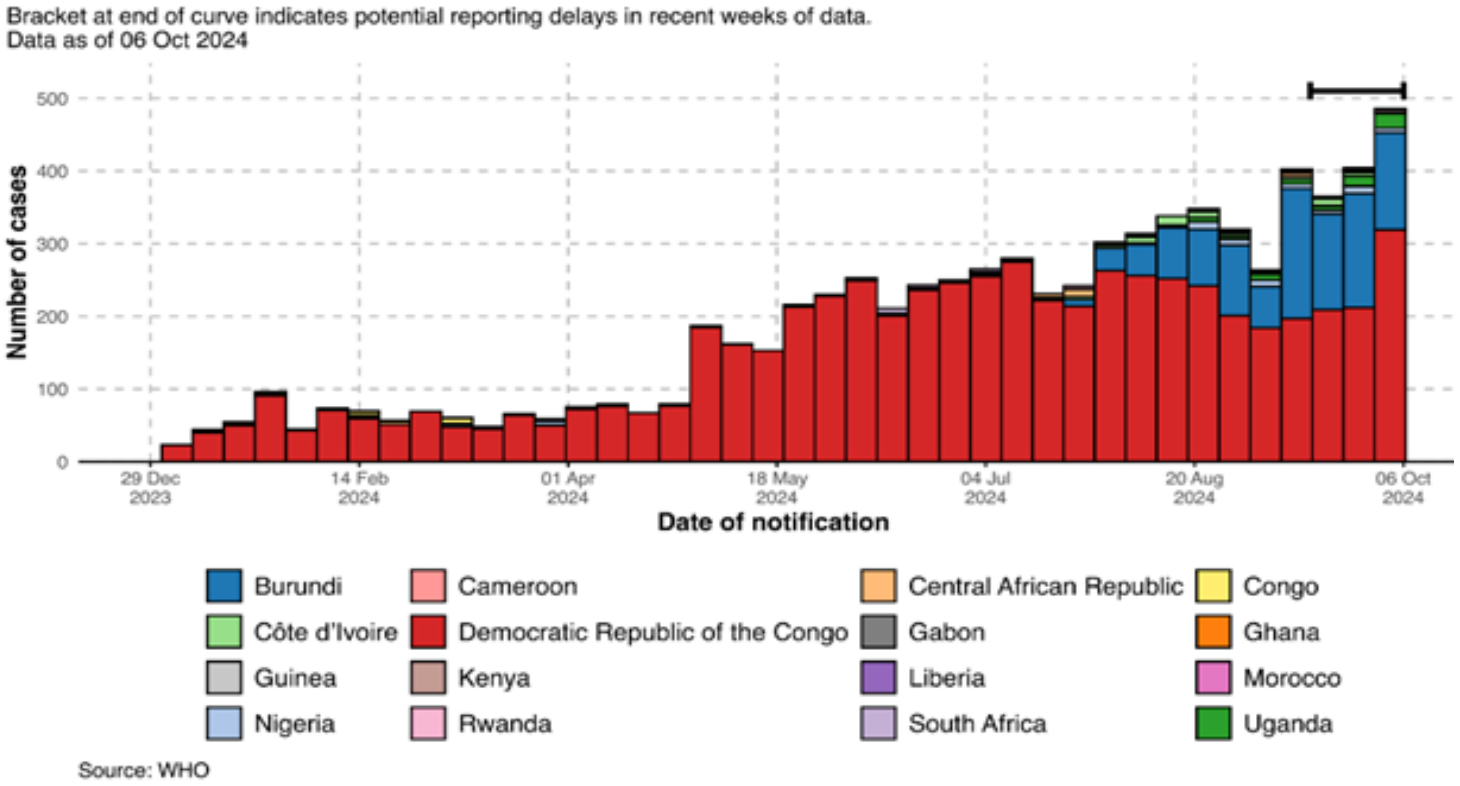
Asian Influenza H5N1 as of October 2024

- 1 confirmed case in Missouri
- 6 confirmed cases in California (4 more probable avian flu infections in dairy workers pending confirmation)

Crimean-Congo HF as of October 2024

- 3 confirmed cases in Duhok
- 1 confirmed case in India resulting in death
- 34 confirmed cases, 9 resulting in death in Pakistan

Data as updated weekly; from 01 January 2024 to 06 October 2024. Note that data shown here includes **laboratory confirmed cases only.** The most recent weeks presented in the epidemic curves should be interpreted with caution, as there are delays associated with reporting.



22 FDA approves nasal spray as first self-administered flu vaccine

The FDA in September approved the first ever influenza vaccine that does not have to be given by a health care professional. FluMist, an existing nasal spray vaccine, is now approved for self- or caregiver-administration in people aged 2 to 49 years, the FDA announced. People aged 18 years or older will have to complete an online questionnaire that will be reviewed by a pharmacist before the vaccine is shipped to their homes. The vaccine also will continue to be administered by health care professionals at offices and pharmacies.

Dr. Septimus's Annotations

Seasonal influenza vaccination is recommended for people aged 6 months or older. From 2010 to 2023, the CDC estimates that 9.3 million to 41 million people were infected with seasonal influenza annually, 100,000 to 710,000 people were hospitalized and 4,900 to 51,000 people died as a result of infection.

BOTTOM LINE

A self-administered influenza vaccine is an important advance that will, hopefully, increase vaccination rates against influenza.

23

Interim Effectiveness Estimates of 2024 Southern Hemisphere Influenza Vaccines in Preventing Influenza-Associated Hospitalization — REVELAC-i Network, Five South American Countries, March–July 2024

MMWR October 3, 2024

The investigators used a test-negative, case-control design to analyze data from a multinational surveillance network to generate estimates of interim vaccine effectiveness (VE) against hospitalization with flu-related severe acute respiratory illness (SARI).

Data were pooled from 30 hospitals in Argentina, 2,477 in Brazil, 13 in Chile, 5 in Paraguay, and 10 in Uruguay beginning 2 weeks after each country's flu vaccination campaign. Vaccination status was confirmed using national electronic vaccination records.

The study population was made up of 11,751 SARI patients from three Pan American Health Organization (PAHO) vaccination target groups: young children (58.3%), older children and people with underlying medical conditions (14.5%), and older adults (27.2%). Case-patients had SARI and tested positive for flu, while control patients had SARI and tested negative for flu and COVID-19.

All countries used World Health Organization (WHO)–recommended egg-based Southern Hemisphere formulations. Argentina, Brazil, Chile, and Uruguay used trivalent (three-strain) vaccines containing antigens from A/Victoria/4897/2022 (H1N1)pdm09–like virus, A/Thailand/8/2022 (H3N2)–like virus, and B/Austria/1359417/2021 (B/Victoria lineage)–like virus, while Paraguay used quadrivalent (four-strain) vaccines that also contained the B/Yamagata lineage–like virus. Vaccination coverage was only 21%.

The adjusted VE was 34.5% against hospitalization, 36.5% against the predominant A(H3N2) influenza strain, and 37.1% against the A(H1N1) pdm09 strain. VE was 58.7% among patients with chronic conditions, 39.0% among young children, and 31.2% among older adults.

Dr. Septimus's Annotations

The vaccine effectiveness estimated is within the confidence interval of prior H3N2 (34%–53%) and H1N1 (18%–56%) for the Southern Hemisphere. It is lower than what was observed in the US last season. The documented influenza vaccination coverage levels (21%) were below pre–Covid-19 norms. This finding is consistent with postpandemic declines in vaccination coverage across the Americas associated with vaccine misinformation, hesitancy, and disruptions in routine immunization services, prevalent during the Covid-19 pandemic. Small interim-estimate sample sizes precluded the estimation of VE against influenza B. 63% of patients were excluded because they did not receive PCR results in time for the interim analysis.

While flu vaccine effectiveness can vary from season to season, we know that influenza vaccination can offer significant protection for people who get vaccinated and is still the best protection against influenza. Importantly, influenza vaccination also can reduce severity of illness in people who get vaccinated but still get infected and ill. To enhance this year's modest influenza vaccine protection against hospitalization, providers should consider treating high-risk patients with suspected or confirmed influenza as soon as possible with antivirals.

BOTTOM LINE

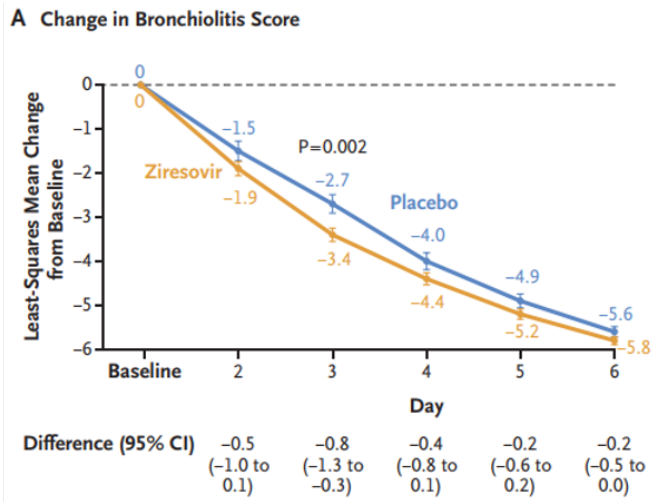
Vaccination is still one of the most effective interventions to prevent flu-related complications Annual influenza vaccination should be encouraged especially for the very young, persons with comorbidities, and older adults.

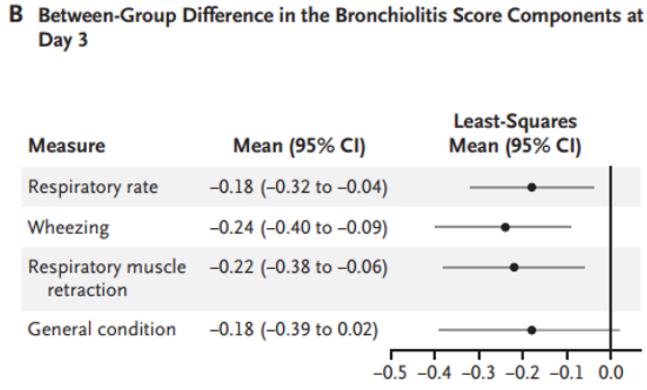
Ziresovir in Hospitalized Infants with Respiratory Syncytial Virus Infection.

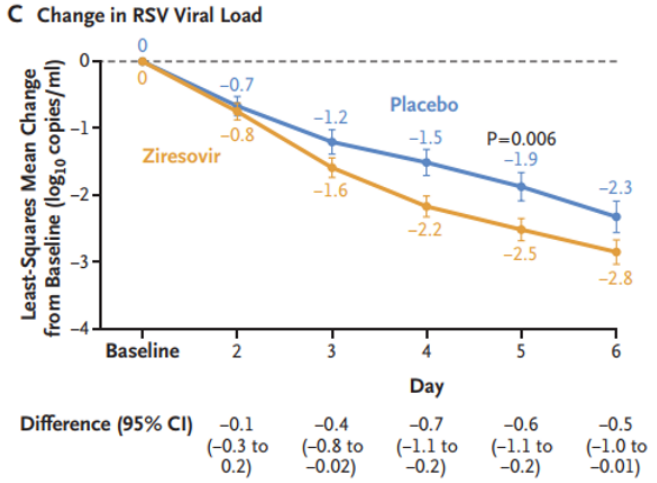
The New England Journal of Medicine published September 25, 2024, VOL. 391 NO. 12, 1096-1107
doi: 10.1056/NEJMoa2313551

This is a phase 3, multicenter, double-blind, randomized, placebo-controlled trial conducted in China. They enrolled participants 1 to 24 months of age who were hospitalized with RSV infection. Participants were randomly assigned, in a 2:1 ratio, to receive ziresovir (at a dose of 10 to 40 mg, according to body weight) or placebo, administered twice daily, for 5 days. Nirsevimab is a new prophylactic RSV antibody. Clinical virologic assessments, including RSV F gene sequencing, determination of viral load, and detection of coinfection with other respiratory viruses were performed. The primary end point was the change from baseline to day 3 (defined as 48 hours after the first administration) in the Wang bronchiolitis clinical score (total scores range from 0 to 12, with higher scores indicating greater severity of signs and symptoms). The intention-to-treat population included all the participants with RSV-confirmed infection who received at least one dose of ziresovir or placebo; the safety population included all the participants who received at least one dose of ziresovir or placebo.

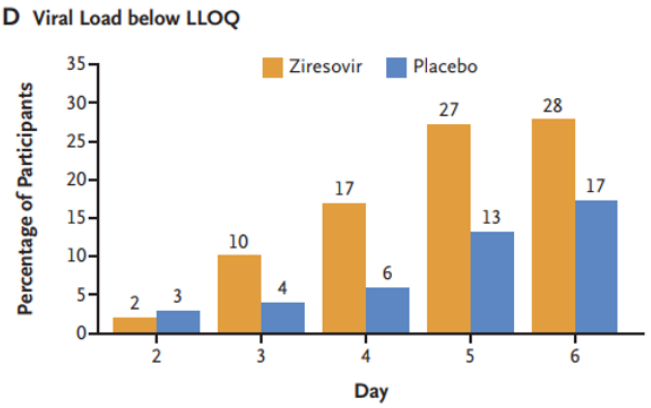
The intention-to-treat population included 244 participants, and the safety population included 302. The least-squares mean change from baseline to day 3 in the Wang bronchiolitis clinical score was -3.4 points (95% confidence interval [CI], -3.7 to -3.1) in the ziresovir group, as compared with -2.7 points (95% CI, -3.1 to -2.2) in the placebo group, for a difference of -0.8 points (95% CI, -1.3 to -0.3), or 30%, in favor of ziresovir (P=0.002). The reduction in the RSV viral load at day 5 was greater in the ziresovir group than in the placebo group (-2.5 vs. -1.9 log10 copies per milliliter; difference, -0.6 log10 copies per milliliter [95% CI, -1.1 to -0.2]). Improvements were observed in prespecified subgroups, including in participants with a baseline bronchiolitis score of at least 8 and in those 6 months of age or younger. The incidence of adverse events related to the drug or placebo was 16% with ziresovir and 13% with placebo. The most common adverse events that were assessed by the investigator as being related to the drug or placebo were diarrhea (in 4% and 2% of the participants, respectively), an elevated liver-enzyme level (in 3% and 3%, respectively), and rash (in 2% and 1%). Resistance-associated mutations were identified in 15 participants (9%) in the ziresovir group.







Dr. Septimus's Annotations



RSV infections are estimated to cause 3.6 million hospitalizations annually and 97,200 to 124,900 deaths among children 5 years of age or younger worldwide, primarily in developing countries. [Lancet 2022; 399:2047-64] Although RSV vaccines have been approved for use in adults 60 years of age or older and in pregnant persons, none are currently approved for use in children. Nirsevimab, a new prophylactic RSV antibody, decreased the incidence of medically attended RSV-associated lower respiratory tract infections through 150 days by 74.5%, but how nirsevimab may change the epidemiologic features of RSV in children is unknown. [N Engl J Med 2022; 386:837-46]

Ziresovir (AK0529) is a potent, selective, orally administered RSV F protein inhibitor. A recent phase 2 trial involving 72 participants 1 to 24 months of age showed that treatment with ziresovir was associated with greater reductions in the RSV viral load and in scores representing signs and symptoms than placebo, with no evident safety concerns. [Influenza Other Respir Viruses 2023;17(7): e13176]

In this phase-3 study, treatment with ziresovir was associated with significantly greater clinical improvement and a greater decrease in the viral load than placebo. The finding that 14 participants (9%) in the ziresovir group had a resistance mutation arise during the treatment period is similar to results in the previous phase 2 trial, in which a resistance mutation was identified in 1 of 11 participants treated with ziresovir at a dose of 2 mg per kilogram twice daily for 5 days. No resistance associated mutations were identified in the lower dose groups of that trial, which suggests that the incidence of resistance mutations may be dose dependent. The main limitation of this trial is the use of the Wang bronchiolitis clinical score, a clinical tool that has not been fully validated in studies of RSV infection.

BOTTOM LINE

In this trial ziresovir treatment (a new prophylactic RSV antibody) in infants and young children who were hospitalized with RSV infection resulted in a significantly greater resolution of signs and symptoms associated with RSV infection as well as greater decrease in the viral load than placebo. These initial findings warrant further evaluation in an international, phase 3 trial of ziresovir treatment for RSV infection.

25

Integrase strand transfer inhibitor (INSTI) related changes in BMI and risk of diabetes: a prospective study from the RESPOND cohort consortium.

Clinical Infectious Diseases published online August 9, 2024
DOI: doi.org/10.1093/cid/ciae406

This study explored the relationship between INSTI/non-INSTI regimens, body mass index (BMI) changes, and DM risk. This study was conducted within the RESPOND consortium, a prospective, multicohort collaboration, including data from 19 well-established observational cohorts and over 30,000 people with HIV in Europe and Australia. RESPOND participants were included if they had CD4, HIV RNA, and ≥ 2 BMI measurements during follow up. Those with prior DM were excluded. DM was defined as a random blood glucose ≥ 11.1 mmol/L, HbA1c ≥ 6.5%/48 mmol/mol, use of antidiabetic medication, or site reported clinical diagnosis. Poisson regression assessed the association between natural log (ln) of time-updated BMI, current INSTI/non-INSTI, and their interactions, on DM risk.

Among 20,865 people with HIV included, most were male (74%) and White (73%). Baseline median age was 45 years (IQR 37–52), with a median BMI of 24 kg/m2 (IQR 22–26). There were 785 DM diagnoses with a crude rate of 0.73 (95%CI 0·68–0.78)/100 PYFU. Ln(BMI) was strongly associated with DM (adjusted incidence rate ratio (aIRR) 16.54 per log increase, 95%CI 11.33–24.13; p<0.001). Current INSTI use associated with increased DM risk (IRR 1·58, 95%CI 1.37–1.82; p<0.001) in univariate analyses, only partially attenuated when adjusted for variables including ln(BMI) (aIRR 1.48, 95%CI 1.29–1.71; p<0.001). There was no interaction between BMI, INSTI and non-INSTI use, and DM (p=0.130). This study also found similar non-HIV related predictors of onset DM, namely male sex, Black/Other race, older age, high BP, increasing BMI as found in the general population. They also found lower CD4 cell counts, and injecting drug use, associated with DM risk. They found little evidence of a difference in DM risk between current TAF and TDF users.

Dr. Septimus's Annotations

INSTIs are now recommended by the WHO as the preferred first- and second-line anti-retroviral therapy (ART) for treating HIV.[2018:79. https://www.who.int/publications/i/item/WHO-CDS-HIV-18.51] Currently, five approved INSTIs are available for people with HIV: raltegravir (RAL), cobicistat boosted elvitegravir (EVG/c), dolutegravir (DTG) and bictegravir (BIC), and cabotegravir (CAB) for those virologically suppressed. With high efficacy for viral suppression, easy use, better tolerability, higher resistance barrier in DTG and BIC, and relatively low cost, most countries have now adopted DTG-containing regimens as the preferred first-line therapy. Despite a good short-term safety profile and high tolerability, INSTIs have been linked to weight gain and treatment-emergent obesity, increasing the risk of weight-related comorbidities such as incident diabetes mellitus (DM).[J Antimicrob Chemother. 2018; 73:2177-2185] This weight gain has been observed with DTG, RAL, and BIC. [Clin Infect Dis. 2020;71:593-600] Additionally, switching from tenofovir disoproxil fumarate (TDF) to tenofovir alafenamide (TAF) has been linked to higher weight gain compared to continuous use of TDF, [Ann Intern Med. 2021;174:758-767] but this study found little evidence of a difference in DM risk between current TAF and TDF users. Higher body mass index (BMI) is known to increase the risk of DM. Sci Rep. 2021; 11:3016] This relationship between time-updated BMI and DM risk provided an opportunity to explore whether BMI increases seen with INSTI use translate into increased DM risk.

"...this study found little evidence of a difference in [diabetes mellitus] risk between current [tenofovir alafenamide] and [tenofovir disoproxil fumarate] users."

During the 4.8 years median follow-up our study found 785 incident DM diagnoses with a crude rate of 0.73 (CI 0.68–0.78) /100 PYFU. As expected, the BMI was strongly associated with DM, and the association between current INSTI use and DM risk was only partially attenuated when adjusted for BMI and other variables. This study found those on INSTI regimens were more likely to develop DM compared to those on non-INSTI regimens. Other possible factors influencing BMI, such as co-medication of corticosteroids, psychiatric drugs, known to increase appetite, exercise, and diet, were not collected in RESPOND.

BOTTOM LINE

In this study the current use of INSTIs (Integrase strand transfer inhibitor) was associated with an increased DM risk compared with PIs (proteus inhibitors) and NNRTIs (non-nucleotide reverse transcriptase inhibitor) which partially reduced when adjusted for BMI changes and other variables.

26

The Effect of Semaglutide on Mortality and COVID-19–Related Deaths.

Journal of the American College of Cardiology published online August 30, 2024
DOI: 10.1016/j.jacc.2024.08.007

This study sought to assess the effect of semaglutide [ozempic, wegovy] 2.4 mg on all-cause death, CV death, and non-CV death, including subcategories of death and death from Covid-19. The SELECT (Semaglutide Effects on Cardiovascular Outcomes in Patients With Overweight or Obesity) trial randomized 17,604 participants ≥45 years of age with a body mass index ≥27 kg/m2 with established CV disease but without diabetes to once-weekly subcutaneous semaglutide 2.4 mg or placebo; the mean trial duration was 3.3 years. Adjudicated causes of all deaths, Covid-19 cases, and associated deaths were captured prospectively.

Of 833 deaths, 485 (58%) were CV deaths, and 348 (42%) were non-CV deaths. Participants assigned to semaglutide vs placebo had lower rates of all-cause death (HR: 0.81; 95% CI: 0.71-0.93), CV death (HR: 0.85; 95% CI: 0.71-1.01), and non-CV death (HR: 0.77; 95% CI: 0.62-0.95). The most common causes of CV death with semaglutide vs placebo were sudden cardiac death (98 vs 109; HR: 0.89; 95% CI: 0.68-1.17) and undetermined death (77 vs 90; HR: 0.85; 95% CI: 0.63-1.15). Infection was the most common cause of non-CV death and occurred at a lower rate in the semaglutide vs the placebo group (62 vs 87; HR: 0.71; 95% CI: 0.51-0.98). Semaglutide did not reduce incident Covid-19; however, among participants who developed Covid-19, fewer participants treated with semaglutide had Covid-19–related serious adverse events (232 vs 277; P = 0.04) or died of Covid-19 (43 vs 65; HR: 0.66; 95% CI: 0.44-0.96). High rates of infectious deaths occurred during the Covid-19 pandemic, with less infectious death in the semaglutide arm, and resulted in fewer participants in the placebo group being at risk for CV death.

Dr. Septimus's Annotations

Covid-19 patients with overweight and obesity are at increased risk of death from multiple causes, including cardiovascular (CV) death, with few therapies proven to reduce the risk. Semaglutide injection 2.4 mg is an injectable prescription medicine used with a reduced calorie diet and increased physical activity. In the SELECT (Semaglutide Effects on Cardiovascular Outcomes in Patients With Overweight or Obesity) trial, compared to placebo, once-weekly subcutaneous semaglutide 2.4 mg reduced the primary endpoint of CV death, nonfatal myocardial infarction (MI), or nonfatal stroke in 17,604 patients who had pre-existing CV disease and overweight or obesity but without diabetes. In addition, there was a 19% lower rate of all-cause death in patients assigned to semaglutide vs placebo. The relative reductions are reflected in the above-noted outcomes, but absolute differences are all 1 percentage point or less.

BOTTOM LINE

This trial demonstrated reductions of 33% and 19% in Covid-19–related death and overall mortality, respectively. The extent to which these outcomes are related to weight loss, or secondary actions of a drug that are different from the primary purpose of semaglutide independent of weight loss, remains unclear.

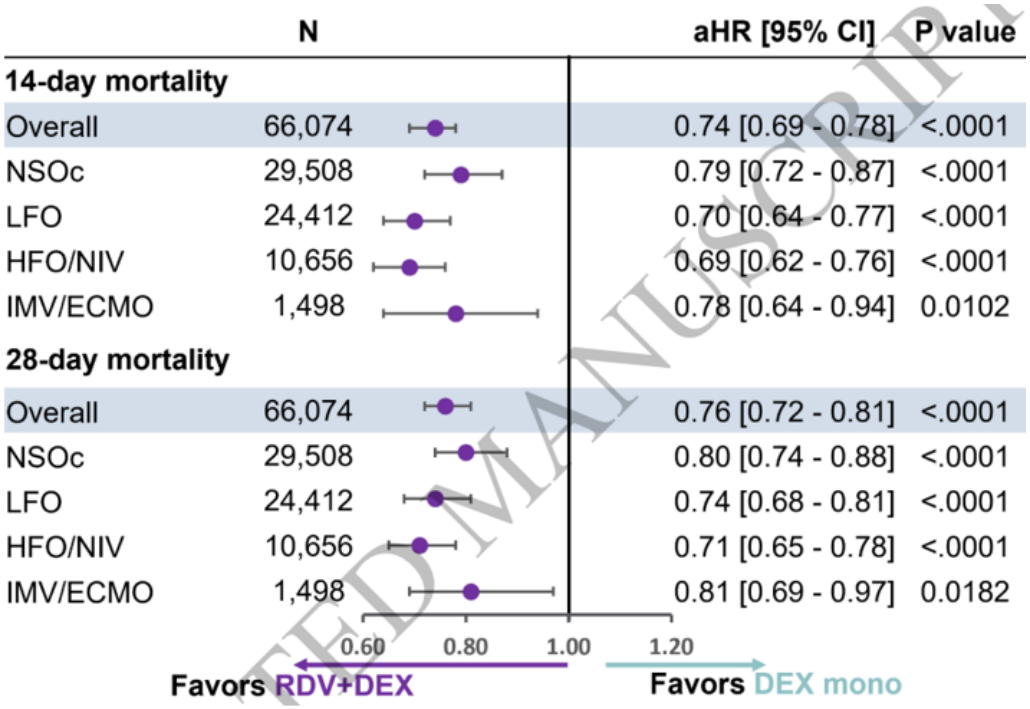
Lower mortality risk associated with remdesivir + dexamethasone versus dexamethasone alone for the treatment of patients hospitalized for COVID-19.

Clinical Infectious Diseases published online September 20, 2024
doi: 10.1093/cid/ciae477

This was a large, retrospective, multicenter US hospital database was used to identify hospitalized adult patients, with a primary discharge diagnosis of Covid-19 also flagged as present on admission treated with remdesivir+dexamethasone

or dexamethasone alone from December 2021 to April 2023. Patients were matched 1:1 using propensity score matching and stratified by baseline oxygen requirements. Cox proportional hazards model was used to assess time to 14- and 28-day in-hospital all-cause mortality.

A total of 33,037 patients were matched, with most patients ≥65 years old (72%), White (78%), and non-Hispanic (84%). Remdesivir+dexamethasone was associated with lower mortality risk versus dexamethasone alone across all baseline oxygen requirements at 14 days (no supplemental oxygen charges: adjusted hazard ratio [95% CI]: 0.79 [0.72-0.87], low flow oxygen: 0.70 [0.64-0.77], high flow oxygen/non-invasive ventilation: 0.69 [0.62-0.76], invasive mechanical ventilation/extracorporeal membrane oxygen (IMV/ECMO): 0.78 [0.64-0.94]), with similar results at 28 days. Among those who did receive oxygen, 37% received low-flow, 17% high-flow, and 3% either invasive mechanical ventilation or extracorporeal membrane oxygenation.



Dr. Septimus's Annotations

Current clinical guidelines for treatment of Covid-19 in hospitalized patients include recommendations for use of remdesivir and/or dexamethasone and generally recommend dexamethasone without an antiviral only for patients on invasive mechanical ventilation/extracorporeal membrane oxygen (IMV/ECMO). Remdesivir+dexamethasone is recommended for most patients on supplemental LFO (typically ≤10-15 L/min) or high flow oxygen/noninvasive mechanical ventilation (HFO/NIV) (typically >10-15 L/min). [https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/]

This study updated our understanding and clinical use of the drugs in a post-vaccine era. Most data on the efficacy of remdesivir and dexamethasone came from randomized control trails (RCTs) early in the pandemic, before vaccination, boosters, and widespread natural immunity. To assess these drugs in the post-Covid-emergency era, observational studies must be used.

Both the observational and RCT level evidence shows that if you have Covid-19 pneumonia with a requirement for oxygen, you should receive dexamethasone, remdesivir, and potentially an IL-6 or JAK inhibitor. For patients who are hospitalized but do not require supplemental oxygen therapy, it is probable that remdesivir still shortens the duration of illness, and it may reduce mortality, but the benefit is almost certainly less striking than in the initial non-immune population in the RCTs. All patients in this study were hospitalized when the Omicron variant was the most dominant strain in the US.

BOTTOM LINE

Remdesivir+dexamethasone was associated with a significant reduction in 14- and 28-day mortality compared to dexamethasone alone in patients hospitalized for Covid-19 across all levels of baseline respiratory support, including IMV/ECMO in the Omicron era.

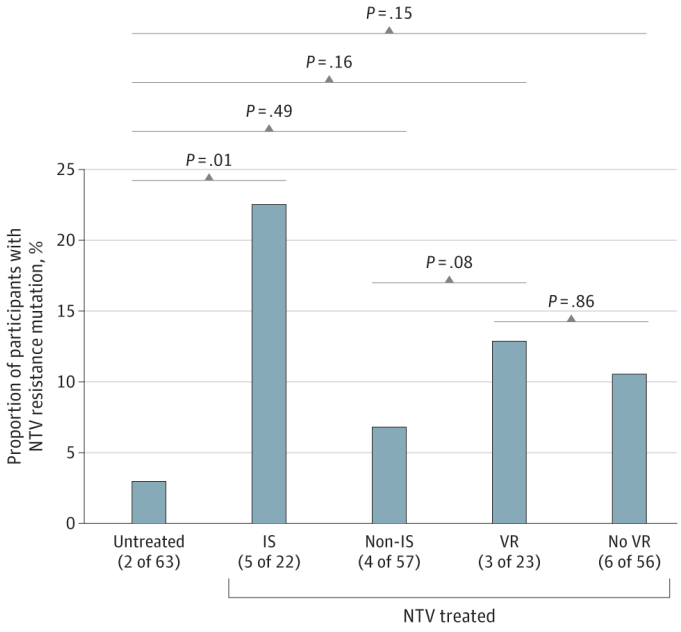
28

Emerging SARS-CoV-2 Resistance After Antiviral Treatment

JAMA Network Open 2024;7(9):e2435431
DOI: 10.1001/jamanetworkopen.2024.35431

This cohort study enrolled outpatient adults with acute Covid-19 infection from May 2021 to October 2023. Participants were divided into those who received antiviral therapy (nirmatrelvir or remdesivir) and those who did not. The primary outcome was emergent SARS-CoV-2 antiviral resistance, defined as the detection of antiviral resistance mutations, which were not present at baseline and emerged during or after completion of a participant's treatment. Next-generation sequencing was used to detect low frequency mutations down to 1% of the total viral population.

Prevalence of Emergent Nirmatrelvir Resistance Mutations in Untreated and Nirmatrelvir-Treated Individuals



Overall, 156 participants (114 female [73.1%]; median [IQR] age, 56 [38-69] years) were included. Compared with 63 untreated individuals, the 79 who received nirmatrelvir were older and more commonly immunosuppressed. After sequencing viral RNA from participants' anterior nasal swabs, nirmatrelvir resistance mutations were detected in 9 individuals who received nirmatrelvir (11.4%) compared with 2 of those who did not (3.2%) (P = .09). Among the individuals treated with nirmatrelvir, those who were immunosuppressed had the highest frequency of resistance emergence (5 of 22 [22.7%]), significantly greater than untreated individuals (2 of 63 [3.1%]) (P = .01). Similar rates of nirmatrelvir resistance were found in those who had virologic rebound (3 of 23 [13.0%]) vs those who did not (6 of 56 [10.7%]) (P = .86). Most of these mutations (10 of 11 [90.9%]) were detected at low frequencies (<20% of viral population) and reverted to the wild type at subsequent time points. Emerging remdesivir resistance mutations were only detected in immunosuppressed individuals (2 of 14 [14.3%]) but were similarly low frequency and transient.

Dr. Septimus's Annotations

Nirmatrelvir and remdesivir are SARS-CoV-2 antivirals recommended for use in mild to moderate COVID-19 to reduce risk of progression to severe disease and hospitalization in high-risk individuals. [N Engl J Med. 2022; 386:1397-1408] Nirmatrelvir, the active component of nirmatrelvir-ritonavir, inhibits the main protease (Mpro) of SARS-CoV-2 and blocks the cleavage of the viral polyprotein precursors. Remdesivir, a prodrug of the adenine nucleoside analogue, GS-441524, inhibits the RNA-dependent RNA polymerase (RdRp) of SARS-CoV-2 and blocks viral RNA synthesis. The risk of treatment-emergent drug resistance after SARS-CoV-2 antiviral therapy remains unclear. An additional concern is the possibility of an association between posttreatment virologic rebound and emergence of antiviral resistance. While virologic rebound has been observed in a subset of patients following nirmatrelvir treatment, consensus sequencing in these studies did not identify nirmatrelvir resistance mutations during rebound. [Clin Infect Dis. 2023;76(3): e526-e529]

In this cohort study with 156 participants, nirmatrelvir resistance mutations were detected more often in individuals who were treated with nirmatrelvir, especially those who were immunosuppressed, compared with untreated individuals. However, all mutations were present at relatively low frequencies, appeared transiently, and were unlikely contributors to instances of virologic rebound. They were unable to evaluate the phenotypic effects of these low frequency resistance mutations on viral fitness.

BOTTOM LINE

In this cohort study of 156 participants, treatment-emergent nirmatrelvir resistance mutations were detected, especially in individuals who were immunosuppressed. These mutations were generally present at low frequencies and were transient in nature. However, until a new antiviral with similar efficacy emerges, managing nirmatrelvir resistance, especially in vulnerable populations, requires heightened medical vigilance.

29

Health outcomes 3 months and 6 months after molnupiravir treatment for COVID-19 for people at higher risk in the community (PANORAMIC): a randomised controlled trial.

Lancet Infectious Diseases published Online September 9, 2024
DOI: 10.1016/ S1473-3099(24)00431-6

Several large observational studies have suggested that using molnupiravir to treat patients with acute Covid-19 lowers the prevalence of persistent symptoms (i.e., long Covid-19). In the open-label PANORAMIC randomized trial, researchers enrolled 26,000 people (largely vaccinated against Covid-19; age, ≥50 or <50 with major risk factors) who tested positive for SARS-CoV-2 between December 2021 and March 2022; patients were randomized to molnupiravir plus regular care or regular care alone. Adherence to medications and follow-up were both excellent. Molnupiravir can substantially shorten the time to recovery in patients with acute Covid-19. [Lancet 2023; 401:281]

The investigators now report outcomes at 3 and 6 months. Patients randomized to molnupiravir had significantly fewer persistent symptoms, less-severe persistent symptoms, superior health-related quality of life (using a validated instrument), and less use of healthcare. However, absolute differences in all these measures were relatively small.

Dr. Septimus's Annotations

Previous research has shown that people with long Covid are more likely to harbor residual reservoirs of viral nucleic acid and antigens and to have ongoing immune responses that might be the cause of persisting symptoms. Antiviral

treatment during acute Covid-19 likely reduces those reservoirs and the resulting symptoms. However, molnupiravir is used much less frequently these days than nirmatrelvir-ritonavir (Paxlovid), because molnupiravir is less efficacious for acute disease. It seems likely that nirmatrelvir-ritonavir would provide similar or superior protection against long Covid: This hypothesis is being tested in ongoing trials.

BOTTOM LINE

In a vaccinated population, people treated with molnupiravir for acute Covid-19 felt better, experienced fewer and less severe Covid-19 associated symptoms, accessed health care less often, and took less time off work at 6 months. However, the absolute differences in this open-label design are small with high numbers needed to treat.

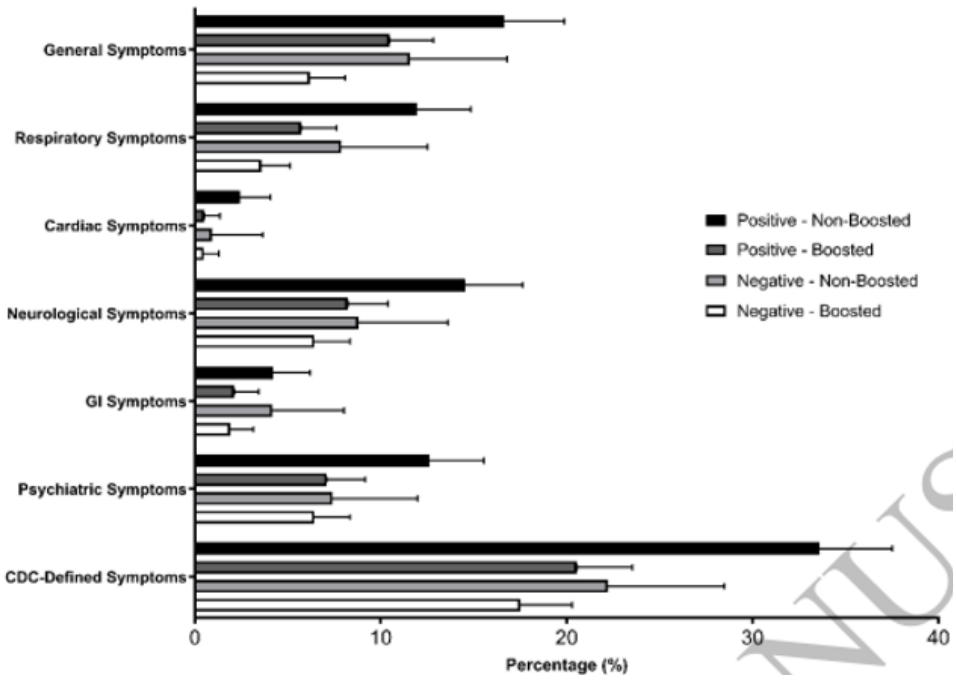
30

Symptoms 6 Weeks After COVID-19 are Reduced Among US Healthcare Personnel Receiving Additional Vaccine Doses during the Omicron Period, December 2021–April 2022.

Open Forum Infectious Diseases published online September 25, 2024
DOI: 10.1093/ofid/ofae545

The objective of this study was to measure the association between receipt of an original monovalent mRNA Covid-19 additional vaccine dose prior to infection and the prevalence of 6-week symptoms among HCP with Covid-19. This was a case-control analysis of HCP in an ongoing multicenter Covid-19 vaccine effectiveness study. The investigators enrolled participants at the time of Covid-19–like symptoms between December 19, 2021, and April 27, 2022, which corresponded to the early Omicron-predominant period after original monovalent SARS-CoV-2 additional vaccination doses became available. The outcome was self-reported symptoms completed 6 weeks after the onset of symptoms. Individuals with prior SARS-CoV-2-positive nasal, nasopharyngeal, or oral tests were not eligible for participation. All participants reported Covid-19-like symptoms within 14 days of a qualifying test and were stratified into those with a positive antigen or PCR test result for SARS-CoV-2 or those with a negative SARS-CoV-2 test result by PCR. Participants with a negative antigen test only were not eligible because of the low sensitivity of the antigen test. They defined Covid-19-like symptoms to be the presence of abdominal pain, bruised toes or feet, changes in ability to taste or smell, chest pain or tightness, chills, cough, diarrhea, fatigue, fever, headache, loss of appetite, myalgia, nausea or vomiting, rhinorrhea, rigors, sever respiratory illness including pneumonia, shortness of breath or difficulty breathing, sinus or nasal congestions, and sore throat.

Frequency of symptoms at 6 weeks by SARS-CoV-2 infection and monovalent vaccine status.



They enrolled 2,478 participants, of which 1,422 (57%) had Covid-19. The prevalence of symptoms at 6 weeks was 26% (n=373) in those with Covid-19 and 18% (n=195) in those without Covid-19. Fatigue (11%) and difficulty sleeping (7%) were most strongly associated with Covid-19. A

total of 1,643 (66%) of participants had received a subsequent vaccine dose (after the primary series). Participants with Covid-19 who had received a subsequent vaccination had lower odds of symptoms at 6 weeks (adjusted odds ratio [aOR] 0.55, 95% confidence interval [95% CI] 0.43–0.70).

Dr. Septimus's Annotations

Prolonged symptoms are most prevalent in those with more severe Covid-19, though they may occur with mild disease. [Nat Med. 2021; 27:601-15] Initial Covid-19 vaccination has been associated with a lower risk of prolonged symptoms in individuals with subsequent Covid-19. [BMJ Open. 2023;13(2):e063141], but the role of vaccine doses after the primary series is less clear until this study. In this study, they found that symptoms were common among HCP 6 weeks after Covid-19 infection with about a quarter of HCP reporting symptoms, and symptoms were approximately 13% less prevalent in those who had received an additional vaccine dose during the Omicron variant-predominant period of the pandemic. They also found a higher proportion of SARS-CoV-2 negative controls received an additional vaccine dose compared to the SARS-CoV-2 positive cases. The investigators hypothesized Covid-19 vaccination might lead to fewer 6-week symptoms among persons with symptomatic infection because of its effect in attenuating the severity of acute illness. Immunologic protection against severe disease is generally greater than that against milder infections, and receipt of an additional vaccine dose has been previously associated with attenuated case severity. [Lancet Infect Dis. 2023; 23:556- 67] Consistent with this observation, they found that receipt of an additional vaccine dose was associated with 23 percentage point lower prevalence of fever or cough at the time of enrollment, and severity of baseline symptoms was generally correlated with symptoms after 6 weeks. Multiple meta-analyses have also demonstrated that Covid-19 vaccination reduces the likelihood of developing long Covid with more vaccines doses often provide greater protection. [Vaccine. 2023; 41:1783-90]

The investigators relied on self-reported symptoms, which introduces the potential for recall bias since people knew their SARS-CoV-2 status. Since the study's assessment of symptoms was conducted within a relatively short timeframe, the longer-term effect of additional vaccinations remains uncertain.

BOTTOM LINE

The investigators found that healthcare professionals who received an additional dose of Covid-19 vaccine had a lower prevalence of symptoms after 6 weeks than those who did not. Their findings add to evidence of the benefit of Covid-19 vaccines, not only in preventing infection and severe illness, but also in improving recovery from Covid-19.