ID WATCH

by Ed Septimus, MD

Editor's Choice

LOOK FOR THE YELLOW BANNER

American Society for Microbiology evidence-based laboratory medicine practice guidelines to reduce blood culture contamination rates: a systematic review and meta-analysis

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Interpretation of blood culture (BC) results is often complicated by detecting contamination rather than true infection. False positives due to blood culture contamination (BCC) vary from 1% to as high as >10% of all BC results. False-positive BC results may result in patients undergoing unnecessary antimicrobial treatments, increased healthcare costs, and delay in detecting the true cause of infection or other non-infectious illness. The authors performed a systematic review of the literature between 2017 and 2022 using numerous databases. Of the 11,319 unique records identified, 311 articles were sought for full-text review, of which 177 were reviewed; 126 of the full-text articles were excluded based on pre-defined inclusion and exclusion criteria. Data were extracted from a total of 49 articles included in the final analysis. They used Grading of Recommendations, Assessment, Development and Evaluations to assess strength of evidence.

Executive Summary

1. ***Key action statement:***
Institutions (facilities) that draw BCs should consider incorporating chlorhexidine (with or without alcohol) into the protocol for skin antisepsis prior to drawing peripheral BCs in adult or pediatric populations.

   Evidence quality:
   II

   Recommendation strength:
   Moderate

   Benefits:
   Use of chlorhexidine skin antisepsis reduces BCC by an average of 57% which, in turn, may lead to more appropriate therapy for bloodstream infection. [PLoS One 2012; 7: e44277]

   Risk, harm, and cost:
   use of chlorhexidine may be harmful in patients with sensitivity to chlorhexidine.

   Benefit–harm assessment:
   preponderance of benefit. Exclusions: patients with sensitivity to chlorhexidine.

2. ***Key action statement:***
Institutions (facilities) that draw BCs should consider implementing a diversion device as part of the procedure for drawing peripheral BCs.

   Evidence quality:
   II

   Recommendation strength:
   Moderate

   Benefits:
   Diversion devices reduce BCC by an average of 64% and may lead to more appropriate therapy for bloodstream infections. [J Clin Microbiol 2010; 48:4501–4503]

   Risk, harm, and cost:
   There is a potential to contribute to iatrogenic anemia in patients with prolonged hospital stays with frequent phlebotomy to obtain BCs if large amounts of blood are discarded. Diversion tubes must be labeled with patient information as with any other specimen tube to avoid unlabeled or mislabeled tubes being processed for other lab studies. The cost of using a non-commercial diversion tube should keep additional costs to a minimum.

   Benefit–harm assessment:
   Preponderance of benefit.

3. ***Key action statement:***
Clinical laboratory and institutional leadership should endorse having a specially trained team of phlebotomists (laboratory, nursing, and other medical professionals) perform peripheral venipunctures for obtaining BCs.

   Evidence quality:
   II, [I believe this should have been graded quality I]

   Recommendation strength:
   Moderate

   Benefits:
   Blood cultures obtained by peripheral venipuncture and drawn by trained phlebotomists result in an average 41% decrease in BCC rates; less harm to patients (i.e., multiple sticks and bruising) when performed by trained phlebotomists and other medical professionals trained in blood-drawing techniques. [Eur J Clin Microbiol Infect Dis 2019; 38:325–330]

   Risk, harm, and cost:
   There is a significant cost to maintaining a trained phlebotomy team, but costs may be offset by fewer false-positive BC results.

   Benefit–harm assessment:
   Preponderance of benefit.

4. ***Key action statement:***
Institutions (facilities) should consider a standardized procedure for using sterile technique for drawing BCs by peripheral venipuncture.

   Evidence quality:
   II

   Recommendation strength:
   moderate

   Benefits:
   using a standardized sterile technique by all providers for obtaining BCs reduces BCC rates

by an average of 56% and may lead to more appropriate therapy for bloodstream infections. Fewer false-positive BCs may reduce patient harm with inappropriate antimicrobial therapy and subsequent adverse events. [Ann Intern Med 2011; 154:145–151]

Risk, harm, and cost:
Implementing a standard method for sterile collection of BCs may increase costs but may be offset by fewer false-positive BCs.

Benefit–harm assessment:
Preponderance of benefit.

5. ***Key action statement:***
Clinical laboratories are responsible for mandating procedures for obtaining BCs and should work with institutional leaders to develop strong education programs (which include skills training and/or feedback and "continuous" monitoring) that may be integrated into larger quality management/quality assurance initiatives [quality management–quality improvement (QMQI)] for teams who draw BCs (laboratory phlebotomists, nurses, residents, and attendings).

Evidence quality:
I

Recommendation strength:
Strong

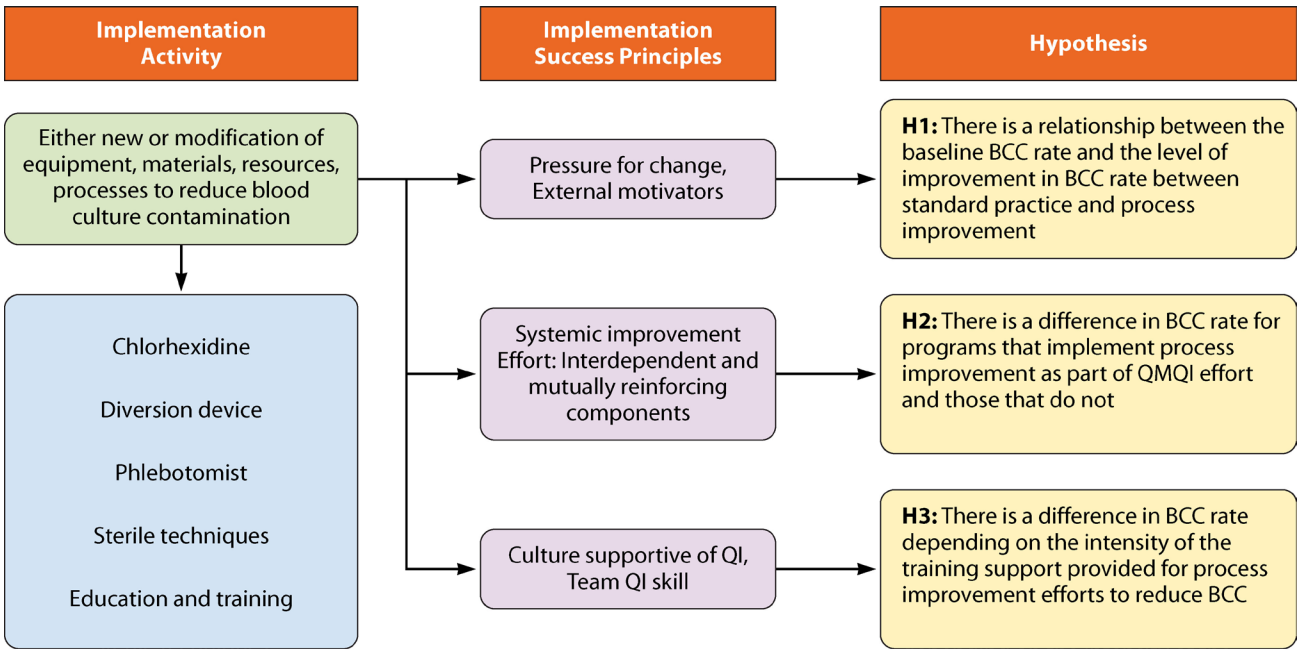
Benefits:
Integrating intensive training programs into larger QMQI efforts to reduce BCC rates is demonstrated to bring about an average 56% reduction in BCC rates compared to only a 15% reduction when neither intensive training nor QMQI improvement efforts are used (P = 0.032). [Infect Dis Ther 2020; 9:389–401]

Analyses demonstrate that even using only one of these process improvement modalities (intensive training or integrating BCC reduction techniques into a larger QMQI effort) results in a 57% reduction in BCC rates.

Risk, harm, and cost:
The costs of implementing education programs or integrating BCC reduction techniques into a larger QMQI effort may be offset by reducing BCC rates and the adverse effects associated with false-positive BCs. Additionally, there is no known risk for a multicomponent approach to process improvement.

Benefit–harm assessment:
Preponderance of benefit.

Conceptual framework for blood culture contamination analyse.



Dr. Septimus's Annotations

Controlling and lowering BCC rates is important to minimize the inappropriate use of antimicrobial agents, adverse events associated with antimicrobial use, unnecessary removal of lines, additional laboratory testing, increased length of stay, improper diagnosis, and controlling healthcare costs.[J Clin Microbiol 2022; 60:e0100521] Medical institutions frequently use ≤3% BCC rates as a quality indicator determined by expert opinions and BCC rate surveys rather than evidence-based practice, but lower rates may be achievable.[Am J Infect Control 2018; 46:571–576] The current review found approximately three-fourths of the outcomes from the studies included in their meta-analysis resulted in BCC rates of <2%, and approximately one-third resulted in <1% BCC rates. Although the BCC rate of ≤3% has been used for many years as a benchmark for BC quality, a recent survey suggested that a majority of survey respondents achieved contaminations well below 3% and supports the goal of developing new lower BCC rate benchmarks, and others promote a BCC of ≤1% as achievable. [Clin Microbiol Rev 2019; 33:00009–00019]

BOTTOM LINE

There are several interventions that resulted in significant reduction in blood culture contamination (BCC) rates: chlorhexidine as a disinfectant for skin preparation, using a diversion device prior to drawing BCs, using sterile technique practices, using a phlebotomy team to obtain BCs, and education/training programs. This evidence-based systematic review and meta-analysis supports several interventions to effectively reduce BCC by approximately 40%–60%. The new benchmark for BCC should be ≤1.

2

Use of Multiplex Molecular Panels to Diagnose Urinary Tract Infection in Older Adults

JAMA Network Open published online November 26, 2024
DOI: 10.1001/jamanetworkopen.2024.46842

Multiplex molecular syndromic panels for diagnosis of urinary tract infection (UTI) lack clinical data supporting their use in routine clinical care. Most existing rapid multiplex molecular panels, such as those for bloodstream, respiratory tract, and central nervous system infections, have been subjected to rigorous scientific testing and standardized regulatory approval through the FDA. The investigators assessed the number and rate of paid claims for UTI multiplex tests from CMS data. The study included more than 36 million older community-dwelling adults and nursing home residents with Medicare Part A and Part B benefits. Over the study period, researchers identified 1,679,328 claims for UTI multiplex testing. The median age of beneficiaries with claims was 77, and 66% of claims were from female beneficiaries.

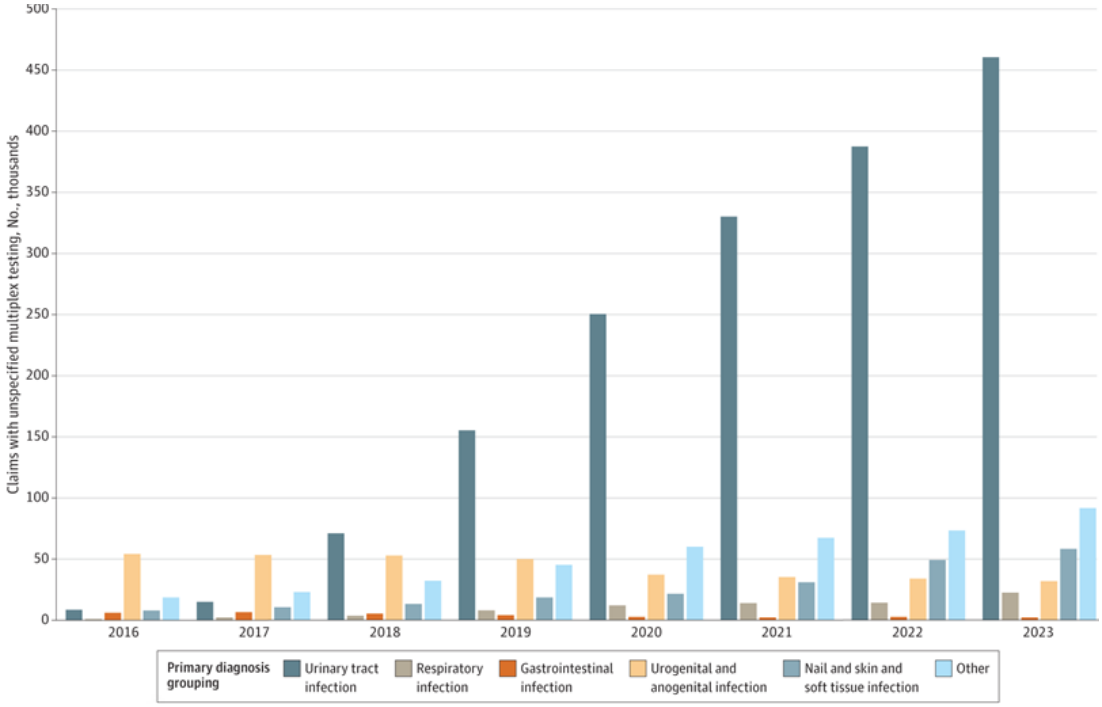
From 2016 to 2023, the observed rate of UTI multiplex testing increased from 2.4 to 148.1 claims per 10,000 fee-for-service beneficiaries annually. The rate of urine cultures (1,116.2 claims/10,000 fee-for-service beneficiaries annually) did not increase over the same period.

The increase in UTI multiplex testing was most pronounced among beneficiaries residing in nursing homes, rising from 1% in 2016 to 12% in 2020. In addition to laboratories or pathologists, urology was the most common clinician specialty conducting this testing. The study also found that the cost of UTI multiplex testing was 70 times higher than urine cultures, with a median cost per claim of $585 in 2023, compared with $8 for a urine culture.

Dr. Septimus's Annotations

This study highlights several important issues regarding the use of urine multiplex molecular tests. First, the widespread use of these unregulated tests likely causes significant clinical harm to patients through misdiagnosis of UTI and unnecessary antibiotics. There are currently

Annual Number of Carrier Claims With Procedure Codes Indicating Unspecified Multiplex Tests Stratified by Primary Infection Diagnosis, 2016-2023



no standards or best practices for urine molecular tests, including for sample collection, bacterial targets, polymerase chain reaction or sequencing protocols used, antimicrobial resistance gene testing, and reporting of results. Furthermore, multiplex molecular tests detect more organisms than urine culture, but many of those are not considered clinically significant pathogens. One prior study found that among 22 asymptomatic and healthy adults, 21 (95%) had a positive urine molecular test. [Rev Urol. 2017;19(4):213-220] Inappropriate treatment of misdiagnosed UTI in patients with asymptomatic bacteriuria (ASB) is already a signifiicant problem, particularly among nursing home residents. Most research on urine molecular tests compared with urine culture comes from small studies with high risk of bias, many with vendor sponsorship or funding by private companies that develop and sell molecular diagnostic tests.[Eur Urol Open Sci. 2022;44:113-124] These companies emphasize the benefit of molecular tests from increased detection of organisms, especially among culture-negative urine samples most represent asymptomatic bacteriuria (ASB). Another important finding from this study was that claims for urine multiplex molecular tests were 70 times more expensive than those for urine culture. There is high potential for urine molecular tests to increase antibiotic overuse, causing increased antimicrobial resistance, adverse effects, and health care costs. Additional data are necessary to clarify what thresholds of bacteria in molecular tests correlate with UTI, identify associations with antimicrobial susceptibility tests, and quantify the impact of urine molecular tests on antibiotic use and resistance.

Dr. Septimus's Annotations

The rise in multiplex molecular tests for diagnosis of UTIs is particularly concerning because these tests are not FDA approved and lack scientific evidence of clinical benefit. The dramatic rise in Medicare claims for these tests suggests the need for FDA oversight and for rigorous clinical trials. We urgently need studies evaluating clinical utility of these tests in various patient populations and care settings.

3 Antimicrobial resistance in the EU/EEA (EARS-Net) Annual Epidemiological Report for 2023

In 2024, all European Union/European Economic Area (EU/EEA) countries reported data for 2023 to the European Antimicrobial Resistance Surveillance Network (EARS-Net). Antimicrobial resistance (AMR) can be expressed as the estimated total incidence of bloodstream infections with antimicrobial-resistant bacteria (infections per 100,000 population).

- In 2023, the estimated total EU incidence of methicillin-resistant S *aureus* (MRSA) bloodstream infections was 4.64 per 100 000 population (country range 0–15.5). This was 17.6% lower than in 2019 (baseline year) and 0.15 per 100 000 population lower than the 2030 target of 4.79 per 100 000 population. For the EU overall, a statistically significant decreasing trend was detected between 2019 (baseline year) and 2023.
- The estimated total EU incidence of third-generation cephalosporin-resistant *E coli* bloodstream infections was 10.35 per 100 000 population (country range 0–19.56) in 2023. This was 3.6% lower than in 2019 (baseline year) and 0.68 per 100 000 population higher than the 2030 target of 9.67 per 100,000 population. For the EU overall, there was no statistically significant trend detected between 2019 (baseline year) and 2023.
- The estimated total EU incidence of carbapenem-resistant *K pneumoniae* bloodstream infections was 3.97 per 100,000 population (country range 0.00–21.44) in 2023. This was 57.5% higher than in 2019 (baseline year) and 1.58 per 100 000 population higher than the 2030 target of 2.39 per 100,000 population. For the EU overall, a statistically significant increasing trend was detected between 2019 (baseline year) and 2023.
- In summary, while the EU target for the incidence of MRSA bloodstream infections had already been reached by 2023, the EU incidence of third-generation cephalosporin-resistant *E coli* bloodstream infections only showed a small decrease compared to 2019 (baseline year) and the EU incidence of carbapenem-resistant *K. pneumoniae* bloodstream infections showed an increase by over 50% compared to 2019 (baseline year), which counteracts the target of a 5% reduction by 2030.
- Data from EARS-Net show that, as in previous years, AMR levels remained high in the EU/EEA in 2023. Increases in the estimated EU incidences of bloodstream infections with resistant bacteria were observed not only for two of the above-mentioned AMR-pathogen combinations with an EU target, but also for many other bacteria and antimicrobial groups under surveillance, such as antimicrobial-resistant *K. pneumoniae* (other than carbapenem-resistant), vancomycin-resistant *Enterococcus faecium* and piperacillin-tazobactam-, ceftazidime-, and carbapenem-resistant *P aeruginosa*.
- The European Surveillance of Antimicrobial Consumption Network (ESAC-Net) report, meanwhile, shows that antibiotic consumption in 2023 rose by 1% from 2019, despite sharp declines in community antibiotic use in the first 2 years of the Covid-19 pandemic. The EU population-weighted mean total consumptions of antibiotics for systemic use in 2023 was 20.1 defined daily doses (DDD) per 1,000 inhabitants per day—4.1 DDD/1,000 inhabitants per day higher than the 2023 target, which calls for a 20% reduction in systemic antibiotic use.

Dr. Septimus's Annotations

Estimates based on EARS-Net data from 2020 indicate that each year more than 35,000 people die in the EU/EEA as a direct consequence of antimicrobial-resistant infections. The overall poor progress towards the EU targets on

AMR and, more particularly, the continued increase in the incidence of carbapenem-resistant K. *pneumoniae* bloodstream infections, highlights the urgent need for intensified public health action against AMR. The plan should include key elements, such as enhanced surveillance and strengthened infection prevention in hospitals and other healthcare settings, plus integration with diagnostic and antimicrobial stewardship programs. Healthcare-associated infections accounted for 70% of the AMR-related health burden in Europe. Unless the plan is strengthened and executed the consequence will be an increased number of infections with antibiotic-resistant bacteria that will be more difficult to treat, leading to increasing challenges for patients and AMR-related deaths.

"In October 2024, ID Watch reported new data in the US showing that six bacterial antimicrobial-resistant hospital-onset infections increased by a combined 20% during the Covid-19 pandemic compared to the pre-pandemic period..."

In October 2024, ID Watch reported new data in the US showing that six bacterial antimicrobial-resistant hospital-onset infections increased by a combined 20% during the Covid-19 pandemic compared to the pre-pandemic period, peaking in 2021, and remaining above pre-pandemic levels in 2022. In 2022, rates for all but one of these pathogens (MRSA) remained above pre-pandemic levels. In addition, the number of reported clinical cases of C. *auris* increased nearly five-fold from 2019 to 2022. See below

AR Threats

	Threat	Change in Rates or Number of Infections***			
		2020 vs. 2019	2021 vs. 2020	2022 vs. 2021	2022 vs. 2019
URGENT*	Hospital-onset CRE	▲ Increase	▲ Increase	— Stable	▲ Increase
URGENT*	Hospital-onset Carbapenem-resistant *Acinetobacter*	— Stable	— Stable	— Stable	▲ Increase**
URGENT*	Clinical Cases of *C. auris*	▲ Increase	▲ Increase	▲ Increase	▲ Increase
SERIOUS*	Hospital-onset MRSA	▲ Increase	— Stable	▼ Decrease	— Stable
SERIOUS*	Hospital-onset VRE	▲ Increase	▲ Increase	— Stable	▲ Increase
SERIOUS*	Hospital-onset ESBL-producing Enterobacterales	▲ Increase	— Stable	— Stable	▲ Increase
SERIOUS*	Hospital-onset MDR *Pseudomonas aeruginosa*	▲ Increase	▲ Increase	— Stable	▲ Increase

BOTTOM LINE

New data released today by the European Centre for Disease Prevention and Control (ECDC) indicate that the European Union (EU) is not on track to meet targets for reducing antimicrobial resistance (AMR) and antibiotic consumption. See next review

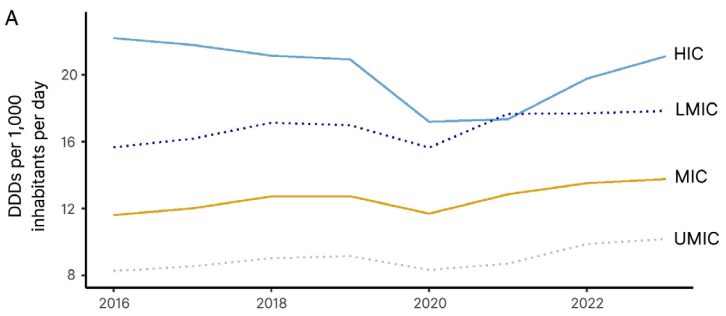
4 Global trends in antibiotic consumption during 2016–2023 and future projections through 2030.

Proceedings of the National Academy of Sciences 2024; 121 (49) e2411919121
DOI: 10.1073/pnas.2411919121

The authors used antibiotic sales data from IQVIA MIDAS and conducted an analysis of trends in antibiotic consumption, focusing on the differences in consumption associated with World Bank income classification throughout the study period 2016–2023. Additionally, they quantify the impact of the Covid-19 pandemic on antibiotic use, where despite several studies finding low rates of bacterial coinfection, antibiotics were continually prescribed to Covid-19 patients at high rates.

They found that estimated antibiotic consumption in reported countries increased 16.3% from 29.5 to 34.3 billion defined daily doses (DDDs) from 2016 to 2023, reflecting a 10.6% increase in the consumption rate from 13.7 to 15.2 DDDs per 1,000 inhabitants per day. Increases were most pronounced in upper-middle- and lower-middle-income countries. While the Covid-19 pandemic significantly reduced consumption globally, this was most pronounced in high-income countries, and in these countries, reductions in antibiotic use in 2020 were sharper, and lasted longer, than in other countries. By 2030, they project that, without reductions in rapidly developing nations, such as investments to improve infrastructure, particularly water and sanitation, along with improved access to vaccination, global antibiotic consumption will increase by 52.3% from an estimated 49.3 billion in 2023 to 75.1 billion DDDs.

Yearly antibiotic consumption rate, measured in DDDs per 1,000 inhabitants per day, by country income classification.



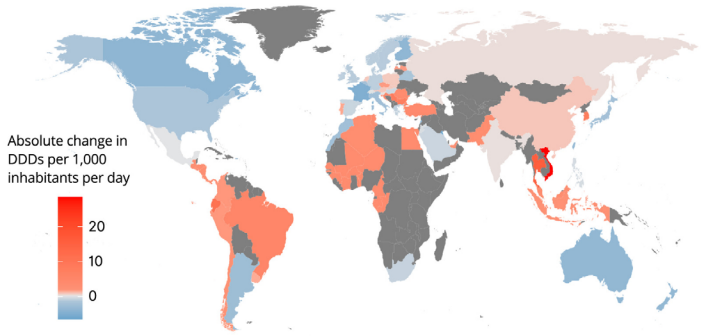
LMIC = lower-middle-income countries
MIC = middle-income countries
UMIC = upper-middle-income countries
HIC = high-income countries
DDD = Defined daily dose

Dr. Septimus's Annotations

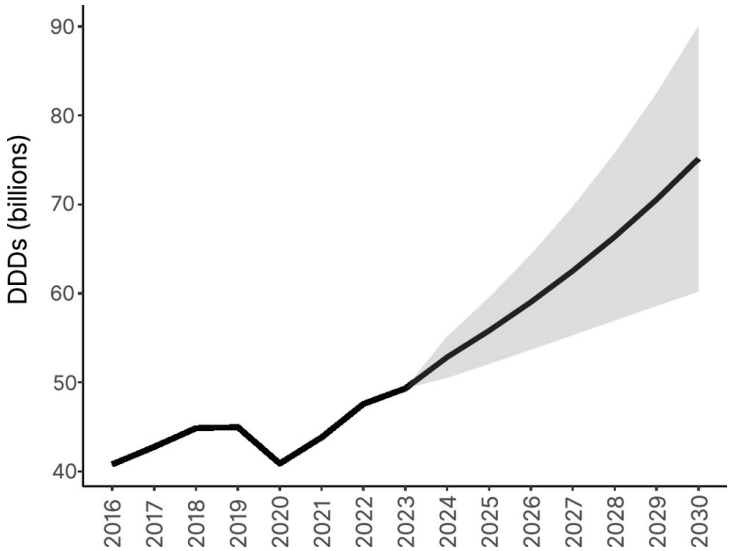
This new analysis of pharmaceutical sales data from 67 countries indicates that antibiotic consumption has risen by more than 20% globally since 2016 but would likely have been much higher had the Covid-19 pandemic not occurred. The Covid -19 pandemic temporarily disrupted antibiotic use, but global consumption has rebounded quickly and continues to rise at an alarming rate. From 2016 through 2019, antibiotic consumption increased in the 28 lower-middle– and upper-middle–incomes countries (LMICs and UMICs) by 9.8% and decreased in the 39 high income countries (HICs) by 5.8%. However, HICs experienced a 'delayed rebound' in antibiotic consumption following the pandemic, with a very small (0.8%) increase in consumption in 2021 followed by larger increases in 2022 and 2023. While antibiotic consumption rates rose in 2023 in HICs, they had not quite returned to prepandemic levels by the end of 2023, but the trend is disturbing. Broad-spectrum penicillins (BSPs), cephalosporins, macrolides, fluoroquinolones, and tetracyclines remained the classes with the highest consumption rates.

Several factors drive the rapid increase in antibiotic consumption in developing settings, including environmental, political, socioeconomic, and cultural factors [JAC Antimicrob. Resist 2023. 5, dlad062], though economic growth is likely the most important factor in lower-income settings. Improvements in sanitation and hygiene measures, including the widespread

Absolute change in antibiotic consumption rate between 2016 and 2023 by country in DDDs per 1,000 inhabitants per day.



Estimated total global antibiotic consumption in DDD (billions).



implementation of water treatment facilities, sewer systems, and personal hygiene practices, played a pivotal role in significantly reducing the burden of infectious diseases and increasing life expectancies in HICs in the early 1900s. Many growing economies are facing rapid urbanization and population growth associated with higher population density and promotion of infectious disease spread, which access to sanitation and clean water could improve. [Global Health Epidemiol. Genom. 2017. 2, e4] In addition, increasing use of vaccines and point-of-care diagnostics could substantially decrease unnecessary antibiotic use. Such a reduction can occur directly, through vaccination against bacterial infections, such as pneumococcal and Hemophilus conjugate vaccines, and indirectly, by diminishing the prevalence of viral illnesses that are frequently and inappropriately treated with antibiotics. Several recent studies have highlighted how vaccines (against bacterial pathogens and viruses) can help curb AMR and avert antibiotic prescriptions and highlight the potential and importance of robust immunization programs and proper diagnostics as an AMR mitigation strategy. [Proc. Natl. Acad. Sci. U.S.A. 1 2022.19, e2112410119; PLoS Med. 2023. 20, e1004239] Focus on prevention does not diminish the need to reduce the misuse and overuse of antibiotics globally. Cooperation regarding antibiotic stewardship and access, which has been major a focus of the 2024 United Nations General Assembly (UNGA) High-level Meeting on AMR, is crucial for the success of a global framework.

Data provided were estimated sales in kilograms, which may not accurately reflect actual consumption. The data utilized were aggregated sales data, which limits the ability to draw conclusions on overuse or misuse due to the absence of indications for prescribing. Lastly, data only included human consumption; a more comprehensive One Health approach that includes surveillance of animal antibiotic consumption and agricultural use is needed to combat overuse and detect concerning AMR trends.

BOTTOM LINE

The findings in this report show that while the Covid-19 pandemic had a major impact on antibiotic use across all income levels, the overarching trend of increasing global antibiotic consumption is alarming. Antimicrobial and diagnostic stewardship should be strengthened. In addition, greater emphasis is needed globally on preventing transmission of infections to reduce the need for antibiotics including improving infrastructure and access to clean water, sanitation, and hygiene which are also important pillar in the fight against AMR.

5 Global report on infection prevention and control 2024

A new report from the World Health Organization (WHO) provides an updated analysis of the harm caused to both patients and healthcare workers worldwide by the avoidable infections that result from gaps in infection prevention and control (IPC).

Among the findings of the report, which was published in December, is that healthcare-associated infections (HAIs) are an issue in hospitals around the world, and not only during epidemics and pandemics. In European countries, an estimated 4.8 million HAIs occur every year in patients admitted to acute-care hospitals. Globally, nearly 1 in 4 (23.6%) cases of sepsis are healthcare related.

> **"...[H]ealthcare-associated infections are an issue in hospitals around the world, and not only during epidemics and pandemics."**

But most studies show the problem is particularly acute in low- and middle-income countries (LMICs). For example, WHO analysis of published data shows an average of 7 out of every 100 patients in acute-care hospitals in high-income countries (HICs) will acquire at least one HAI during their hospital stay. In LMICs, the figure is twice that (15%). Similarly, the incidence of HAIs in intensive care units is 30% overall but 2 to 20 times higher in LMICs than HICs.

Heightening the problem is the fact that HAIs are frequently caused by antimicrobial-resistant pathogens, making them harder to treat and more likely to lead to complications, longer hospital stays, increased costs, and higher mortality. The global number of HAIs resistant to antibiotics is estimated to be 136 million annually, with 119 million occurring in middle-income countries, according to the report. Mortality among patients infected with resistant HAIs is two to three times higher compared with those infected by susceptible pathogens.

Dr. Septimus's Annotations

The emerging pattern is that HAIs continue to be one of the most frequent adverse events with the highest burden in low- and middle-income countries. The key to reducing the burden and mitigating the harm of HAIs is implementing effective IPC interventions that are based on common sense, evidence-based interventions. These interventions require trained and dedicated staff, infrastructure, and financial resources. But as the report shows, progress on implementing IPC at all levels of the health system has been slow in all countries, regardless of income level. According to the WHO's 2023-24 Tracking AMR Country Self-assessment Survey, only 39% of countries had IPC programs fully implemented nationwide. Nine percent of countries had not developed any IPC program or plan.

Global surveys carried out by the WHO in 2019 and 2023-24 show that the level of implementation of IPC core components—which include guidelines, education and training, surveillance, and monitoring, audit, and feedback—range from "inadequate" to "advanced," with LMICs as expected scoring significantly lower than HICs. On average, low-resource countries scored at a "basic" level of implementation for most IPC core components, with limited implementation of IPC guidelines, HAI surveillance, training, and monitoring. Furthermore, IPC programs in LMICs are often unable to function properly and sustainably because they lack an enabling environment, the surveys found.

Many healthcare facilities in LMICs often lack access to clean water. A 2024 report by the WHO and UNICEF Joint Monitoring Programme for Water Supply, Sanitation and Hygiene (WASH) estimated that in 2022, 1.7 billion people worldwide were using a healthcare facility that lacked basic water services and 697 million were using facilities with unimproved toilets or no toilets.

The report also notes that improvements achieved during the Covid-19 pandemic may have been recently lost, with some countries reallocating resources and funds from IPC and WASH to other areas.

On a more positive note, the report points to recent commitments WHO member states have made to prioritizing IPC at the global and national level. These include the adoption of a resolution focusing on IPC as a critical priority across the healthcare continuum at the 75th World Health Assembly, followed by the approval of a WHO-developed global action plan and monitoring framework for IPC in 2023. That plan was subsequently adopted by all countries at the 77th World Health Assembly.

The WHO action plan consists of eight core targets at the global level and four core targets at the national level. Targets at the global level include increasing the proportion of countries with an approved national action plan and monitoring framework on IPC, a dedicated budget allocated to the national IPC action plan, legislation and regulations to address IPC, and basic WASH services in all healthcare facilities. At the national level, targets include increasing the number of healthcare facilities that meet the WHO's minimum IPC requirements, have dedicated funding for WASH services, provide IPC training to all frontline clinical and cleaning staff, and have an HAI and related AMR surveillance system.

The WHO says it will support all countries in efforts to boost IPC, and that additional action and investment by international donors and nongovernmental organizations will make a huge difference, particularly in countries with limited resources and expertise.

BOTTOM LINE

The emerging picture is that healthcare-associated infections (HAIs) continue to be among the most frequent adverse events in health service delivery, with the highest burden in low- and middle-income countries. Strong infection prevention and control (IPC) is essential for strong health systems and quality care, in emergencies and as part of every country's journey towards safer health care.

Epidemiology and Outcomes of Antibiotic De-escalation in Patients with Suspected Sepsis in US Hospitals

Clinical Infectious Diseases published online December 6, 2024
DOI: 10.1093/cid/ciae591

The investigators retrospectively analyzed all adults admitted to 236 US hospitals between 2017-2021 with suspected sepsis [adult sepsis event] (defined by a blood culture draw, lactate measurement, and intravenous antibiotic administration) who were initially treated with ≥2 days of anti-MRSA and anti-pseudomonal antibiotics but had no resistant organisms requiring these agents identified through hospital day 4. Resistant organisms were defined as (a) gram positives resistant to beta-lactams (e.g. MRSA) or vancomycin-resistant enterococcus, and/or (b) gram-negatives resistant to ceftriaxone, as determined per each hospital's antimicrobial susceptibility testing, or assumed if the species had intrinsic resistance (e.g. Pseudomonas aeruginosa) or high risk for inducible AmpC resistance. De-escalation was defined as stopping anti-MRSA and anti-pseudomonal antibiotics or switching to narrower antibiotics by day 4. They created a propensity score for de-escalation using 82 hospital, demographic, and clinical variables, matched de-escalated to non-de-escalated patients, and then assessed associations between de-escalation and outcomes. Outcomes were hospital-onset acute kidney injury (AKI) (defined as an increase in initial creatinine level by ≥0.5 mg/dL during hospitalization), Clostridioides difficile infection (CDI) (ICD-10 CDI discharge code [A04.7] without a present-on-admission indicator, or C.difficile positive test [toxin or PCR assay] after day 4), admission to ICU after day 4, and in-hospital mortality.

Among 124,577 eligible patients, antibiotics were de-escalated in 36,806 (29.5%) including narrowing in 27,177 (21.8%) and cessation in 9,629 (7.7%). De-escalation rates varied widely between hospitals. De-escalation was associated with lower adjusted risks for acute kidney injury (OR 0.80, 95% CI: 0.76–0.84), ICU admission after day 4 (OR 0.59, 95% CI: 0.52–0.66), and in-hospital mortality (OR 0.92, 95% CI: 0.86-0.996).

Clinical predictors of de-escalation included positive cultures for non-resistant pathogens, present-on-admission infections, and less severe illness, especially on hospital day 3-4. Conversely, positive MRSA nasal swabs were associated with a lower likelihood of de-escalation. [The positive predictive value of a positive nasal MRSA screen is only ~50%].

Dr. Septimus's Annotations

The Surviving Sepsis Campaign guidelines recommend early antibiotics targeting all likely pathogens for adults with suspected sepsis, followed by daily assessments for potential antibiotic de-escalation-start broad and narrow later. [Intensive Care Med. 2021; 47:1181-1247] Real world experience demonstrate clinicians often start empiric anti-MRSA and anti-pseudomonal therapy then may reassess after 48-72 hours based on patients' clinical course and microbiologic results, but in general are slow to de-escalate if at all. A meta-analysis on empiric antibiotic de-escalation in 1,873 patients with sepsis reported a mean de-escalation rate of 39.5% in the 9 studies included. [Heart Lung J Crit Care. 2016; 45:454-459] Other estimates of antibiotic de-escalation rates have ranged from 10-70% in various studies focused on different hospital settings or specific conditions, including community-acquired pneumonia and culture-negative suspected serious infections. [Intensive Care Med. 2020; 46:1404-1417; Clin Infect Dis. 2021; 72:1314-1322] In addition, the impact of antibiotic de-escalation on patient outcomes is limited.

This study analyzed a large cohort of US hospitals to evaluate the frequency and variations in antibiotic de-escalation rates for patients initially treated with broad-spectrum antibiotics for suspected sepsis who subsequently did not grow a resistant pathogen and evaluate associations between de-escalation and clinical outcomes using detailed individual and hospital-level data to adjust for potential confounders. After propensity-

matching, de-escalation was associated with lower odds of hospital-onset AKI, ICU admission, in-hospital mortality, and a trend towards lower CDI. This study substantially supports the evidence in favor of de-escalation.

This study has several limitations. First antibiotics may have been administered before cultures were drawn in some patients. Second, some resistant pathogens may have been missed if cultures were not obtained from difficult-to-sample body sites (e.g. sputum, abscesses). Third, their dataset had a high degree of missing vital signs, requiring the investigators to impute vitals for their primary analyses. However, sensitivity analyses excluding vital signs were consistent with the primary analysis. Lastly, continuation of anti-MRSA or anti-pseudomonal therapy are acceptable in some situations even if resistant pathogens are not isolated (e.g., anti-pseudomonal beta-lactams in patients with neutropenic fever, vancomycin in some patients with severe skin/soft tissue infections and in patients with beta-lactam allergies).

BOTTOM LINE

In this large US cohort, de-escalation of anti-MRSA and anti-pseudomonal antibiotics in patients with suspected sepsis was uncommon. De-escalation was associated with clinical and microbiologic factors and associated with lower odds for adverse outcomes. In addition, timely de-escalation may induce less disruption of the gut microbiome, which is increasingly recognized as an important modulator of the immune response to sepsis and patient outcomes. These findings underscore both the opportunity and complexity of de-escalating broad-spectrum antibiotics in patients with suspected sepsis.

7

Biomarker-Guided Antibiotic Duration for Hospitalized Patients With Suspected Sepsis: The ADAPT-Sepsis Randomized Clinical Trial

JAMA published online December 9, 2024
DOI: 10.1001/jama.2024.26458

This trial was named Biomarker-Guided Duration of Antibiotic Treatment in Hospitalized Patients With Suspected Sepsis (ADAPT-Sepsis) trial. Investigators enrolled 2,760 adults with suspected sepsis at 41 National Health Service (NHS) hospitals. Included patients had been initiated intravenous antibiotics within 24 hours of admission to a critical care or ICU and were expected to continue antibiotics for at least 72 hours.

From January 1, 2018, June 5, 2024, 918 patients were randomly assigned to a daily PCT-guided protocol, 924 to a daily CRP-guided protocol, and 918 to standard care. The biomarker-guided protocols were based on daily blood draws. Group assignments were blinded from patients, their relatives, clinical teams, and investigators.

The primary outcome for efficacy was total duration of antibiotics from randomization to 28 days, and 28-day all-cause mortality was the primary safety outcome. Secondary outcomes included antibiotic duration for the initial sepsis period. The trial aimed to detect a 1-day reduction in total antibiotic duration and show noninferiority with a 5.4% safety margin.

Among the randomized patients (mean age, 60.2 years; 60.3% male; average Sequential Organ Failure Assessment [SOFA] score, 7), there was a significant reduction in the total duration of antibiotic treatment from randomization to 28 days in the PCT-guided protocol group compared with the standard-care group (mean total duration, 10.7 days for standard care vs 9.8 days for daily PCT-guided protocol; mean difference, 0.88 days; 95% confidence interval [CI], 0.19 to 1.58). No difference was seen between standard care and daily CRP-guided protocol (mean total duration, 10.6 days for daily CRP-guided protocol; mean difference, 0.09 days; 95% CI, −0.60 to 0.79).

Although there was a significant reduction in the duration of antibiotics for the initial sepsis period for both biomarker protocols compared with standard care (daily PCT-guided protocol: mean difference, 1.13 days; 95% CI, 0.58 to 1.68 and daily CRP-guided protocol: mean difference, 0.71 days; 95% CI, 0.16 to 1.26), the initial reduction was not maintained by day 28 in the CRT-guided protocol group.

Analysis of all-cause mortality at 28 days found the daily PCT-guided protocol was noninferior to standard care (19.4% of patients receiving standard care vs 20.9% of PCT-guided patients; absolute difference, 1.57 percentage points; 95% CI, −2.18 to 5.32). The treatment difference for the daily CRP-guided protocol was inconclusive (19.4% for standard care vs 21.1% for CRP; absolute difference, 1.69 percentage points; 95% CI, −2.07 to 5.45).

Supported by data on the implementation of these protocols, it is likely that the differential clinical effectiveness findings for daily PCT-guided and daily CRP-guided protocols are explained by the differences in the utility of these biomarkers to track inflammation caused by bacterial infection in the setting of critical illness, where PCT concentrations are known to increase earlier and normalize more rapidly than CRP in response to treatment.

The investigators added that while the PCT-guided protocol's reductions in antibiotic duration were modest, they are equivalent to a 10% reduction in antibiotic use for sepsis, which they say could provide significant cost and labor savings and might also reduce the development of antimicrobial resistance and other adverse events.

BOTTOM LINE

Care guided by measurement of PCT reduces antibiotic duration safely compared with standard care, but CRP does not. All-cause mortality for CRP was inconclusive. Although biomarkers had a small effect on individual-patient basis, the public health effect is large since a 10% reduction of broad-spectrum antibiotics can provide a significant benefit in terms of less antibiotic exposure, reduced antibiotic adverse events, decrease development of antibiotic resistance, and decreased cost.

8

Description of national antibiotic prescribing rates in U.S. long-term care facilities, 2013–2021

Antimicrobial Stewardship & Healthcare Epidemiology 2024, Vol. 4, Iss. 1, e209:1-4
DOI: 10.1017/ash.2024.457

In this study investigators from the CDC analyzed data on antibiotics dispensed in 1,900 unique US long-term care (LTC) facilities from 2013 to 2021. Overall antibiotic use was reported as the percent of LTC residents receiving an antibiotic per year, antibiotic courses per 1,000 resident-days, and antibiotic days of therapy (DOT) per 1,000 resident-days overall. The investigators also looked at median antibiotic duration and antibiotic class.

Over the study period, the percentage of LTC residents receiving an antibiotic decreased from 51% to 44%, total use rates in antibiotic courses/1,000 resident-days fell by 8%, and total use rates in antibiotic DOT/1,000 resident days fell by 8%. The steepest declines occurred from 2019 to 2021, likely because of changes in antibiotic prescribing practices during the Covid-19 pandemic.

Prescribing rates decreased across several antibiotic classes, most notably fluoroquinolones (49%) and macrolides (30%). Concurrently, prescribing rates of tetracyclines and cephalosporins increased by 56% and 22%, respectively. Increased prescribing of tetracyclines and cephalosporins may be due to clinicians avoiding fluoroquinolones; however, the increased prescribing of cefdinir (228%) should be further evaluated. The median antibiotic course duration was 7 days.

Since the admission date was not available, antibiotic courses started at the facility as well as continuations from hospital-initiated courses were included. They were also unable to stratify rates of antibiotic use by type of resident stay, an important predictor of antibiotic use in LTC settings.

Dr. Septimus's Annotations

The study authors note that the decline in LTC antibiotic prescribing rates coincides with the 2017 Centers for Medicare & Medicaid Services (CMS) rule requiring that LTCs have a system for tracking antibiotic use. The findings also highlight potential opportunities to improve antibiotic treatment duration, which did not change over the study period.

Evidence supports shorter duration of treatment for most common infections, and studies demonstrate that every day of additional antibiotic therapy is associated with increased risk of adverse events. [Ann Intern Med 2021; 174:822–827] In addition, prolonged antibiotic durations contribute 18% of total DOT and provide another opportunity to optimize antimicrobial therapy.

BOTTOM LINE

Overall antibiotic prescribing rates in long-term care decreased from 2013 to 2021, mostly due to decreases in fluoroquinolones and macrolides, but more needs to be done.

9

Highlights Antibiotic Awareness Week.

Infectious Disease News | November 18, 2024

1. More than 39 million could die from antibiotic resistance by 2050 [Lancet. 2024; doi:10.1016/S0140-6736(24)01867-1]
2. Threat of antimicrobial resistance on the rise in low-, middle-income countries Resistance to third-generation cephalosporins in E. coli and resistance to carbapenems in A. baumannii are on the rise, with notable increases sub-Saharan Africa and South Asia. [ESCMID Global Congress; April 27-30, 2024]
3. Trial: 7 days of antibiotics for bloodstream infections noninferior to 14 days Another study suggested that shorter courses of antibiotics for bloodstream infections are as effective as longer ones in a multinational randomized trial. [N Engl J Med published online November 20, 2024] Reviewed in December 2024 ID Watch
4. The WikiGuidelines collaborative published its third clinical practice guidance — this one on the prevention, diagnosis and management of UTIs. [JAMA Network Open. 2024;7(11): e2444495] Reviewed in December 2024 ID Watch
5. Study identifies high-volume prescribers at risk for inappropriate use of antibiotics. The top 10% of outpatient prescribers by antibiotic volume contributed 42% of all antibiotic claims. The top 25% contributed 55.5% of the claims for three specific broad-spectrum antibiotics. [Abstract 155. Presented at: Society for Healthcare Epidemiology of America Spring Conference; April 16-19; Houston]
6. CDC: Resistant hospital infections increased 20% during Covid-19 pandemic. Antimicrobial-resistant hospital infections caused by seven pathogens increased a combined 20%. [https://www.cdc.gov/antimicrobial-resistance/data-research/threats/update-2022.html] Reviewed October 2024 ID Watch
7. Computer prompt cuts extended-spectrum antibiotic use for abdominal infections by 35%. Abdominal infections are commonly treated with unnecessary extended-spectrum antibiotics. In the intervention arm, physicians who ordered extended-spectrum antibiotics for adult non-ICU patients being treated for abdominal infections received a computerized prompt displaying the patient's individual risk for a multidrug-resistant organism. If the risk was below 10%, the prompt recommended standard-spectrum antibiotics instead of extended-spectrum drugs. [Abstract 444. Presented at: IDWeek; Oct. 16-19, 2024; Los Angeles]

8. Antimicrobial resistance linked to a million African deaths in 1 year- Antimicrobial resistance accounted for more than 25% of the 3.83 million infection-related deaths in Africa in 2019. The four most common pathogens were each linked to well over 100,000 deaths — S pneumoniae (195,000), K pneumoniae (184,000), E coli (147,000) and S aureus (136,000) — and responsible for roughly half the AMR-related deaths in Africa in 2019. [Lancet Glob Health 2024;12: e201-e216]
9. Study: New antibiotics underprescribed for difficult-to-treat infections. [Ann Intern Med. 2024; doi:10.7326/M23-2309] More than 40% of patients with difficult-to-treat (DTR) pathogens were prescribed older, generic agents despite the FDA approval of several new gram-negative antibiotics. Among 362,142 hospital encounters for gram-negative infections, 0.7% were categorized as DTR pathogens, according to the study. Patients with DTR pathogens were treated exclusively with traditional generic agents in 41.5% of DTR episodes, including 79.3% of DTR episodes where these older agents were agents with known suboptimal safety and/or efficacy such as polymyxins, aminoglycosides, and tigecycline.

Infectious Diseases Society of America 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections.

Clinical Infectious Diseases published online August 7, 2024
DOI: 10.1093/cid/ciae403

The following represent some key changes to the 2023 IDSA AMR Guidance Document.

ESBL-E

- Fosfomycin is not be suggested for pyelonephritis and complicated urinary tract infections (cUTI); however, the uncertainty of the additive benefit of additional doses of oral fosfomycin for these indications was highlighted in light of recent clinical data.
- Amoxicillin-clavulanic acid continues to not be a preferred agent for uncomplicated ESBL-producing cystitis; however, it was acknowledged that there may be occasions where it is prescribed if resistance or toxicities preclude the use of alternative oral antibiotics and there is a preference to avoid IV antibiotics. It is advised that caution be given to patients about the potential increased risk of recurrent infection if amoxicillin-clavulanic acid is administered for this indication.
- Additional details on the mechanistic reasons why piperacillin-tazobactam is not anticipated to be as effective for ESBL-E infections are reviewed.
- Piperacillin-tazobactam continues to not be preferred for the treatment of pyelonephritis and cUTI; however, it was acknowledged that if piperacillin-tazobactam was initiated for pyelonephritis or cUTI and clinical improvement occurs, the decision to continue piperacillin-tazobactam should be made with the understanding that theoretically there may be an increased risk for microbiological failure with this approach.
- A re-review of available data and newer data indicate that ceftolozane-tazobactam is likely to be effective against ESBL-E; however, it suggested that this agent be preserved for the treatment of DTR *P aeruginosa* or polymicrobial infections (e.g., both DTR *P. aeruginosa* and ESBL-E).

AmpC-E

- The term “moderate to high risk” clinically significant AmpC production was replaced with “moderate risk” throughout.
- It was clarified that even without upregulation of AmpC production, basal production of AmpC β-lactamases by organisms with inducible ampC expression leads to intrinsic resistance to ampicillin, amoxicillin-clavulanate, ampicillin-sulbactam, and first- and second-generation cephalosporins.
- The suggestion that cefepime is not advised for Enterobacter cloacae, Citrobacter freundii, and

Klebsiella aerogenes with cefepime MICs of 4-8 µg/mL because of concerns for an increased risk of ESBL production in this cefepime MIC range.

CRE

- An increase in the prevalence of CRE isolates producing metallo-beta-lactamases (MBL) in the United States (e.g., NDM, VIM, IMP) has been observed.
- Dosing suggestions for ceftazidime-avibactam in combination with aztreonam are updated in Table 1. Both agents are suggested to be administered every 8 hours to facilitate simultaneous administration in clinical practice.

DTR *P. aeruginosa*

- For infections caused by *P. aeruginosa* isolates not susceptible to any carbapenem agent but susceptible to traditional β-lactams (e.g., cefepime), administration of a traditional agent as high-dose extended-infusion therapy continues to be suggested, although the panel no longer emphasizes the importance of repeating AST on the initial isolate before administration of the traditional agent given the frequency with which this susceptibility profile occurs.
- A new question (i.e., Question 4.2) has been added "Are there differences in percent activity against DTR *P aeruginosa* across available β-lactam agents?" Differences in DTR *P. aeruginosa* susceptibility percentages to the newer β-lactams are described along with regional differences in enzymatic mechanisms of resistance that contribute to some of these differences.
- Once-daily tobramycin or amikacin were added as alternative treatment options for only pyelonephritis or cUTI caused by DTR *P aeruginosa* given the prolonged duration of activity of these agents in the renal cortex and the convenience of once daily dosing.

CRAB

- Sulbactam-durlobactam, in combination with meropenem or imipenem-cilastatin, was added as the preferred agent for the treatment of CRAB infections.
- High-dose ampicillin-sulbactam in combination with at least one other agent has been changed from a preferred to an alternative regimen if sulbactam-durlobactam is not available.
- The suggested dosing of high-dose ampicillin-sulbactam has been adjusted to be 27 grams of ampicillin-sulbactam (18 grams ampicillin, 9 grams sulbactam) daily.

S. *maltophilia*

- Questions have been adjusted to list agents in order of preference (i.e., cefiderocol [with a second agent at least initially], ceftazidime-avibactam and aztreonam, minocycline [with a second agent], TMP-SMX [with a second agent], or levofloxacin [with a second agent].
- A description of a CLSI endorsed method (i.e., broth disk elution method) to test for activity of the combination of ceftazidime-avibactam and aztreonam for *maltophilia* activity is discussed.
- Tigecycline has been removed as a component of combination therapy.
- Updated guidance from the CLSI advising against the testing of ceftazidime for S *maltophilia* infections has been added.

Dr. Septimus's Annotations

I find it extremely helpful that IDSA has made this a living document and updated yearly. They continue to caution the use of piperacillin-tazobactam for ESBL infections. For AmpC the suggestion that cefepime is not advised for *Enterobacter cloacae*, *Citrobacter freundii*, and *Klebsiella aerogenes* with cefepime MICs of 4-8 µg/mL because of concerns for an increased risk of ESBL production in this cefepime MIC range is an important addition. Sulbactam-durlobactam, in combination with meropenem or imipenem-cilastatin, was added as the preferred agent for the treatment of

CRAB infections. For *Stenotrophomonas* cefiderocol [with a second agent at least initially] and ceftazidime-avibactam and aztreonam are the preferred agents for true invasive infection. One of the challenges with *Stenotrophomonas* is determining if it is colonization versus infection.

BOTTOM LINE

The updated "Infectious Diseases Society of America 2024 Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections" provides clinicians with the best updated information on the treatment of these difficult infections. Diagnostic and antimicrobial stewardship plus infection prevention is critical in our battle against multi-drug-resistant gram-negative infections.

11

Using interpretable machine learning to predict bloodstream infection and antimicrobial resistance in patients admitted to ICU: Early alert predictors based on EHR data to guide antimicrobial stewardship.

PLOS Digital Health 2024. 3(10): e0000641.
DOI: 10.1371/journal.pdig.0000641

Investigators from King's College London and clinicians at Guy's and St Thomas' NHS Foundation Trust collaborated in this interdisciplinary study to help improve outcomes of critically ill patients. Data from 1,142 patients at Guy's and St Thomas' NHS Foundation Trust were used for the study. They examined various infection control protocols and personalized treatment strategies, guided by laboratory tests, aim to detect bloodstream infections (BSI) and assess the potential for antimicrobial resistance (AMR). These include individual components of the APACHE-II score, laboratory data, symptoms, past medical history, and medical therapies that patients were undergoing at the time of admission to the ICU. In this study, they used a machine learning (ML) approach based on Multi-Objective Symbolic Regression (MOSR), an evolutionary approach to create ML models in the form of readable mathematical equations in a multi-objective way to overcome the limitation of standard single-objective approaches. This method leverages readily available clinical data collected upon admission to intensive care units (ICUs), with the goal of predicting the presence of BSI and AMR. They further assess its performance by comparing it to established ML algorithms using both naturally imbalanced real-world data and data that has been balanced through oversampling techniques.

Their findings reveal that traditional ML models exhibit subpar performance across all training scenarios. In contrast, MOSR, specifically configured to minimize false negatives, outperforms other ML algorithms and consistently delivers reliable results.

Their dataset comprised only 1142 patients. This limited size may affect the robustness and generalizability of their findings. In addition, the absence of external validation limits the broader applicability of their approach currently.

Dr. Septimus's Annotations

The widespread use of antibiotics can accelerate the emergence of AMR. Additionally, inadequate infection control (IC) measures can further transmit AMR, posing a significant issue to other patients in the ICU. [Ther Adv Drug Saf 5 (2014) 229–24111] and exposes patients to elevated risks of increased morbidity and mortality. JAMA 2009. 302: 2322-2329]

The investigators used an innovative ML approach known as Multi-Objective Symbolic Regression (MOSR), which was designed to predict bloodstream infections and evaluate antibiotic resistance risks using readily available clinical data from ICU admissions. Unlike conventional models, MOSR consistently outperforms its counterparts, delivering reliable results even when faced with data imbalances. Making significant steps forward in this field, the team showed how AI and

machine learning can provide same-day triaging for patients in ICU, particularly in environments with limited resources. The technology is also much more cost-effective than manual testing.

Current assessments of ICU patients can be time consuming and require lengthy laboratory tests, requiring bacteria to be cultured in a laboratory, taking up to 3-5 days. This can have a significant impact on clinical outcomes, especially ICU patients, who have life-threatening conditions. Having access to this information sooner would enable clinicians to make quicker, more informed decisions on care—including whether to use antibiotics. Appropriate use of antibiotics has a strong relationship with improved patient outcomes. This study provides further evidence on the potential benefits of AI in health care relating to the critical issues of AMR and BSIs

BOTTOM LINE

This research indicates a promising path forward in enhancing Antimicrobial Stewardship (AMS) strategies. The Multi-Objective Symbolic Regression (MOSR) approach can be readily implemented on a large scale, offering a new machine learning (ML) tool to find solutions to these critical healthcare issues.

12

The economic burden of nosocomial infections for hospitals: evidence from Germany.

BMC Infectious Diseases 2024; 24: 1294
DOI: 10.1186/s12879-024-10176-8

They analyzed cost data obtained from routine records maintained by the accounting department of a German hospital's surgical and orthopedic units from 2018 to 2019 for the "HygArzt" research project. To ensure balance, they employed genetic matching. We estimated the differences in length of stay (LOS) and daily revenue between patients with and without nosocomial infections (NI) using linear regression. Finally, they calculated the opportunity cost borne by the hospital by treating NI patients instead of non-NI patients. All costs are reported in 2018 Euros.

The final sample included 81 patients with NI matched 207 patients without NI. The majority of the NI patients (77.0%) had surgical site infection (SSI). Compared to non-NI patients, they observed that NI patients had a longer LOS (10 days, $p < 0.001$) and lower daily revenue (€400, $p < 0.001$). They also found that comorbidities and the frequency of operations had a significant impact on the LOS. Using a baseline of 30 to 50% preventable NIs, successful prevention of a single NI could potentially reduce the length of hospital stay by 3 to 5 days and increase hospital revenue by approximately €120 to €200 per day per prevented NI. Consequently, the hospital saves 3 to 5 more bed-days to backfill and generate more revenue, and/or make more efficient resource allocation by changing bed-capacity and staffing. The resulting opportunity costs can potentially exceed €1,000 per preventable case.

Conclusion NIs pose a substantial economic burden for hospitals. From a health economics' perspective, there are strong economic incentives for hospitals to implement infection control interventions. More importantly, prevention of NIs is a patient safety issue.

13

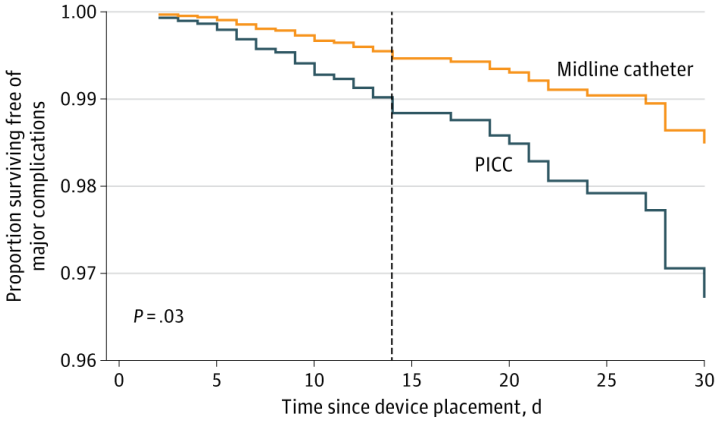
Midline vs Peripherally Inserted Central Catheter for Outpatient Parenteral Antimicrobial Therapy

JAMA Internal Medicine published online November 11, 2024
DOI: 10.1001/jamainternmed.2024.5984

Investigators conducted a retrospective cohort study of 2800 patients discharged with outpatient parenteral antimicrobial therapy (OPAT) from 69 Michigan hospitals between 2017 and 2023. Most catheter devices were placed on the day of, or the day before, hospital discharge. They excluded vancomycin. Among 2800 total devices placed, 2000 were midline catheters, and 800 were PICCs. The primary composite outcome, major device complications (i.e.,

catheter-related bloodstream infections, catheter-related venous thromboembolism, upper-extremity deep venous thrombosis, or pulmonary embolism), occurred in 44 patients (1.6%), including 16 (0.8%) with midline catheters and 28 (3.4%) with PICCs. Among patients with dwell times ≤14 days, major complications were significantly less frequent in the midline-catheter group than in the PICC group (adjusted hazard ratio, 0.29); complication rates were similar in the two groups among patients with longer dwell times.

Major Complications in Patients Receiving Outpatient Parenteral Antimicrobial Therapy by Device Type



Dr. Septimus's Annotations

Current guidelines recommend midline catheters over peripherally inserted central catheters (PICCs) when antibiotic infusions are anticipated to be completed within 14 days. However, evidence supporting this guidance is limited in the setting of increasing OPAT use. This study reinforces guideline recommendations that midline catheters, rather than PICCs, should be preferred for patients who require short-duration OPAT. Clinicians also should know which antibiotics and other infusates are not compatible with midline catheters due to their potential to cause tissue damage upon extravasation. An excellent evidence-based resource for identifying the appropriate catheter is the Magic recommendations. [Ann Intern Med.2015;163 (6) (suppl): S1-S40]

This study did not capture catheter-related complications that may have occurred after device removal or beyond 30 days of follow-up. They did not have information on dosing and combination regimens of antimicrobial agents; larger studies examining effects of dosing frequency or complex therapies are needed to fully determine the safety of these 2 devices.

Lastly, the clinician should also determine if the patient can transition to oral therapy with a bioavailable antimicrobial which can further decrease the risk of any IV related complication.

BOTTOM LINE

In this study of vascular access devices placed for outpatient parenteral antimicrobial therapy (OPAT), the risk of major device complications was lower with midline catheters compared with PICCs, particularly for devices that dwelled for 14 or fewer days. These findings suggest that midline catheters are safe alternatives to PICCs for OPAT, especially for treatment durations of 14 or fewer days. **See next review**

Implementing oral antibiotics for bone and joint infections: Lessons learned and opportunities for improvement.

Open Forum Infectious Diseases published online November 16, 2024
DOI: 10.1093/ofid/ofae683

In 2023, the investigators implemented a new institutional guideline to preferentially treat patients with bone and joint infections with oral antibiotics. The post-guideline cohort was compared with a historical pre-guideline cohort via retrospective chart review. The primary outcome was the proportion of patients discharged exclusively on oral antibiotics. Secondary outcomes included 90-day treatment failure, length of stay, and adverse effects.

PATIENT SELECTION

Consider IV to oral transition when the following criteria are met irrespective of duration of IV lead-in:

- Patient is clinically stable
- Patient can readily absorb oral medications
- Culture data is available showing in-vitro susceptibility or antibiogram demonstrates reliable susceptibility to recommended regimens
- Absence of ongoing bacteremia and concomitant infections that may warrant IV antibiotics
- If indicated, source control has been achieved to the extent possible through surgical procedure

Other factors may influence antibiotic decision making. These include, but are not limited to, prior history of infections at the same site, repeated surgeries, history of radiation or use of current immunosuppression, patient and/or provider preference.

ANTIBIOTIC OPTIONS

- Selection of oral antibiotics should be based on in-vitro susceptibility, allergy history, drug interactions, and risk of side effects. The oral options that are most well-studied as well as recommended regimens based on pathogens are listed below. The preferences below are based on available data, clinical experience, cost, and side effect profiles.

Table of recommended antibiotics by organisms, color coded by level of evidence (High Moderate Low)

Organism	*Staphylococcus* species [a,b]	*Streptococcus*	*Enterococcus*	Enteric GNR	*Pseudomonas*	*C. acnes*
Preferred options	Levofloxacin + Rifampin TMP-SMX Clindamycin	Amoxicillin	Amoxicillin	Quinolones TMP-SMX	Quinolones	Amoxicillin
Alternative options	Doxycycline Linezolid	Clindamycin Levofloxacin Linezolid	Linezolid	Amox/clav Amoxicillin		Doxycycline Levofloxacin Clindamycin

Most patients with bone and joint infections are seen by the surgical infectious diseases consult service, but some patients, such as those with diabetic foot infections or vertebral osteomyelitis, are admitted to a medicine team and seen by the medical infectious disease service.

One hundred and eighty-six patients (53 pre-guideline and 133 post-guideline) were included in the analysis. Patients in the post-guideline cohort were more likely to be discharged exclusively on oral antibiotics (25% vs. 70%, p<0.01), with no difference in 90-day treatment failure (8% vs. 9%, p=0.75). Patients in the post-guideline cohort had a shorter length of stay than pre-guideline (median days: 8 vs. 7, p=0.04) and trended towards fewer PICC-related adverse events (6% vs. 1% p=0.07).

Dr. Septimus's Annotations

Recent literature, particularly the Oral Versus Intravenous Antibiotics for Bone and Joint Infection (OVIVA) trial, demonstrated that the use of PO antibiotics was safe and effective for the treatment of bone and joint infections.[N Engl J Med. 2019;380:425-436] The current study also found a significant decrease in length of stay and intravenous catheter complications in those who received PO compared to IV antibiotics. Despite the literature base supporting the use of PO therapy for bone and joint infections, there are few real-world examples of institutions implementing the findings of the OVIVA trial. Further, many physicians including ID physicians are still reluctant to use PO antibiotics for definitive therapy for osteoarticular infections. [Emerging Infections Network (EIN) survey] In the current study patients with vertebral osteomyelitis and prosthetic joint infections were less likely to be discharged on PO antibiotics. The reluctance to treat these conditions with PO antibiotics is consistent with what is observed nationally. In the same nationally conducted survey, only 22% and 28% of respondents reported using oral antibiotics as definitive therapy for vertebral osteomyelitis and orthopedic hardware infections, respectively. [Emerging Infections Network (EIN) survey] The lack of PO antibiotic utilization is not due to lack of evidence given that recent guidelines, including those for vertebral osteomyelitis and hardware infections, are now specifically recommending PO antibiotics if organism susceptible to a bioavailable antibiotic. [JAMA Netw Open. 2022;5(5): e2211321; Infect Dis Now. 2023;53(3):104647; J Orthop Trauma. 2020;34(1):30-41]

Though not statistically significant, in the post-implementation cohort there were more treatment failures in the PO group compared to the IV group, which were driven primarily by patients with diabetic foot infections. Diabetic foot infections are complex and difficult to treat requiring multi-disciplinary care. [Clin Infect Dis. 2023;77(3): e1-e13] While antibiotics are frequently used, they may not be the most important factor in determining risk of relapse. [Open Forum Infect Dis. 2022;9(9): ofac407] All diabetic foot patients who failed in this study also had peripheral vascular disease which may have not only affected drug delivery but healing and source control.

This study was not designed to compare regimens, and the optimal regimens for different pathogens or types of infection remains unclear. The follow-up period of 90-days for evaluation of clinical outcomes was shorter than comparable studies, though this did not impact their primary outcome of proportion of patients discharged on PO antibiotics. Lastly, this was a single-center retrospective study with a relatively low number of patients evaluated.

BOTTOM LINE

An institutional guideline was effective in increasing the proportion of patients with bone and joint infections discharged on oral antibiotics. They demonstrated similar clinical outcomes while reducing length of hospital stay and a trend towards fewer IV-related adverse events.

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2-[^{18}F]F-p-Aminobenzoic Acid Specifically Detects Infective Endocarditis in Positron Emission Tomography

The Journal of Infectious Diseases published online November 8, 2024
DOI: 10.1093/infdis/jiae547

Recent guidelines have recommended additional techniques such as positron emission tomography/computed tomography with the tracer [18F] fluorodeoxyglucose (FDG-PET/CT). [Clin Infect Dis, 2023; 518–526] However, this approach only detects increased metabolic activity and does not specifically target bacteria. Another potential marker is p-aminobenzoic acid (PABA), which is only accumulated by prokaryotes.

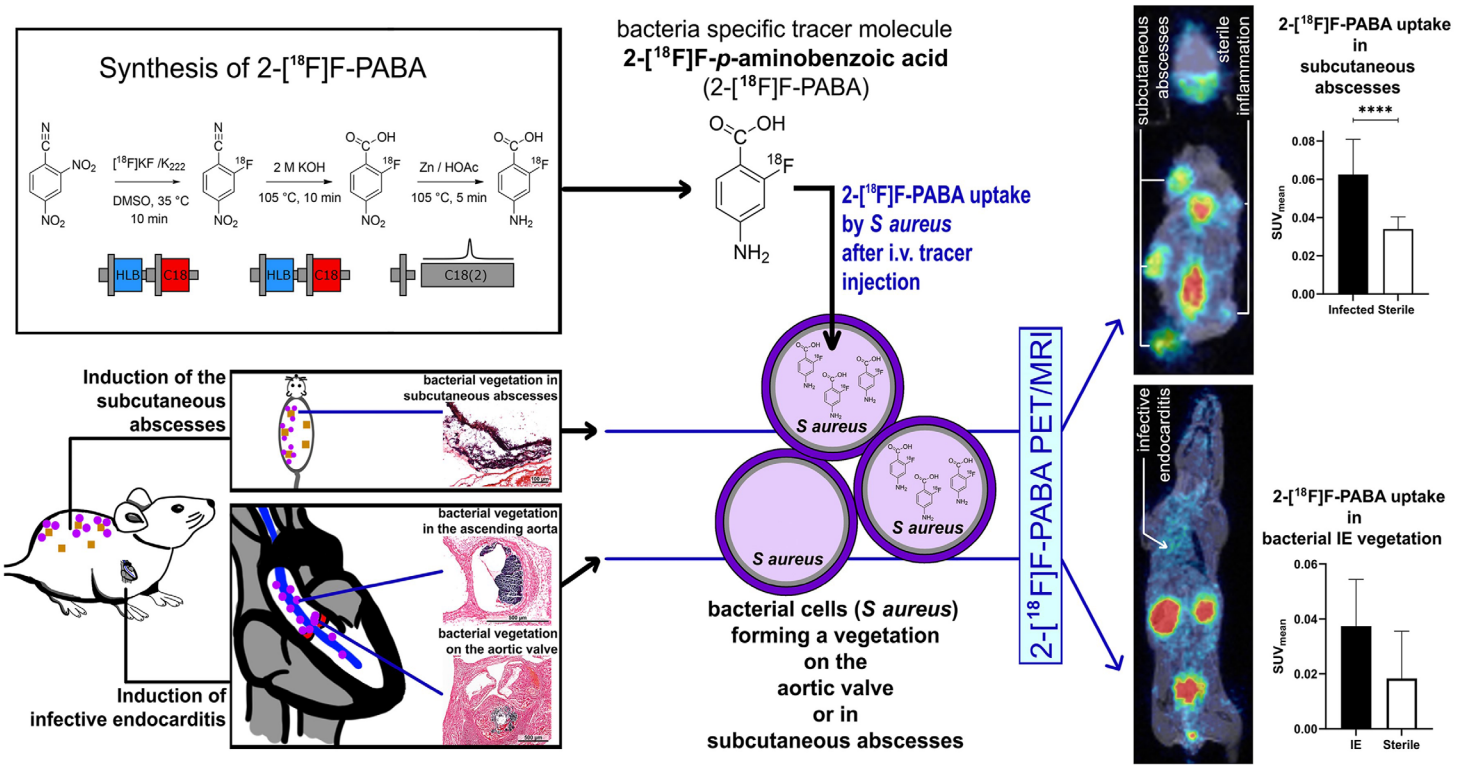
To assess 2-[18F]F-PABA as a tracer, a murine infective endocarditis (IE) model was created by lodging a suture thread in the left ventricular outflow tract followed 24 hours later with an intravenous injection of S aureus. Control mice had placement of the suture alone. Subsequent 2-[18F]F-PABA-PET/MRI scanning demonstrated a nonsignificant twofold higher uptake of tracer in the region of the suture compared with control. Tracer enrichment in the gallbladder, bladder, spine, and sternum acted as a potential interfering signal.

Dr. Septimus's Annotations

The advantage of 2-[18F]F-PABA as a tracer is that it can only be accumulated by bacteria, thereby indicating active infection. In this study, the imaging signal was not strong and only S. aureus was tested as an inoculum — moreover, 2-[18F]F-PABA is not currently available and FDG-PET/CT is recommended as an imaging modality in the 2023 revision of the Duke criteria. [Clin Infect Dis, 2023; 518–526] The revised Duke criteria conclude that FDG PET/CT as a Minor Criterion until more data on the routine use of early PET/CT scans become available. FDG PET/CT was included as a Major Criterion in the 2015 European Society of Cardiology IE diagnostic criteria for PVE, a change that improved the diagnostic yield compared with the modified Duke Criteria. [Eur Heart J 2015; 36:3075–128] Thus, the current indication for [18F]FDG PET/CT is for patients with a high clinical suspicion of PVE but nondiagnostic echocardiography. At this time if available, FDG-PET/CT can be used in cases where the diagnosis of IE has not been otherwise established.

BOTTOM LINE

This study highlights the great potential of 2-[18F]F-PABA imaging for the direct detection of IE. Future studies are necessary to further investigate the clinical potential of this molecular imaging approach.



16

Association between adjunctive rifampin and gentamicin use and outcomes for patients with staphylococcal prosthetic valve endocarditis: a propensity-score adjusted retrospective cohort study.

Infection published online October 23, 2024
DOI: 10.1007/s15010-024-02421-8

Staphylococcal prosthetic valve endocarditis (PVE) is associated with high morbidity and mortality. Guidelines of the American Heart Association and the European Society of Cardiology recommend treatment with rifampin, gentamicin, or both in addition to oxacillin or cefazolin (for methicillin-susceptible *Staphylococcus aureus* [MSSA]) or vancomycin (for methicillin-resistant S. *aureus* [MRSA]). However, supporting evidence is limited and benefits have been questioned. Investigators conducted a retrospective multicenter cohort study involving 373 patients admitted with staphylococcal PVE (S. *aureus*, 61%; coagulase-negative *Staphylococcus*, 39%) between 2003 and 2021.

Rates of susceptibility to oxacillin, rifampin, and gentamicin were 49%, 97%, and 87%, respectively. In all, 74% of participants received ≥1 dose of rifampin (median duration, 36 days) and 60% received ≥1 dose of gentamicin (median duration, 14 days). Gentamicin use declined throughout the study period, whereas rifampin use remained stable. Rifampin was discontinued early in 13% of recipients and gentamicin in 13% due to side effects. Propensity-score adjusted analysis revealed that neither adjunctive rifampin nor adjunctive gentamicin reduced PVE recurrence or mortality, whereas ID consultation and surgical treatment were beneficial.

Dr. Septimus's Annotations

The association between adjunctive rifampin use and outcome was assessed using propensity-score adjusted analysis. Although a significantly lower proportion of patients experienced an outcome in the rifampin group in the crude analysis, no significant association was observed in the propensity-score adjusted analysis. This lack of association is in line with a multicenter study in France which reported similar survival and relapse rates in patients treated with or without rifampin. [Clin Infect Dis. 2021;72(9):e249–55] Similarly, our analyses did not show an association between gentamicin use and lower mortality or recurrence, which is compatible with findings reported in the multicenter study in Spain.[Infect Chemother. 2018;24(7):555–62] This study supplements the evidence that guideline-recommended adjunctive treatment with gentamicin, rifampin, or both for staphylococcal PVE lack benefit, but may have side effects. However, the results of a retrospective study with possible unidentified confounders should not change our practice yet, but rather, should encourage a randomized prospective study.

BOTTOM LINE

In this study no significant association was observed between adjunctive rifampin or gentamicin use and improved outcomes in patients with Staphylococcus prosthetic valve endocarditis. Randomized prospective studies are needed to confirm this observation.

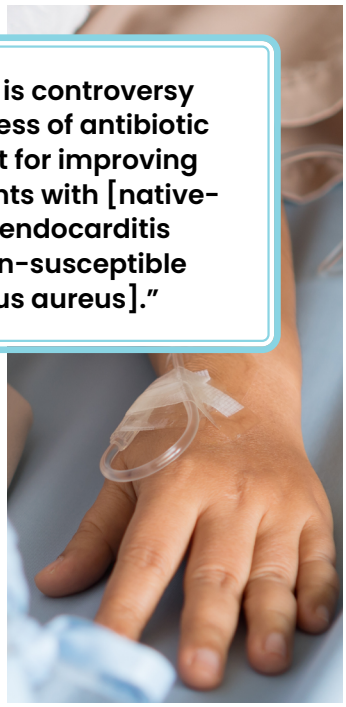
17

Efficacy and safety of antistaphylococcal penicillin or cephazolin-based combinations versus monotherapy for methicillin-susceptible Staphylococcus aureus infective endocarditis: A propensity score analysis of nationwide prospective cohort

Journal of Infection published online October 23, 2024
DOI: 10.1016/j.jinf.2024.106352

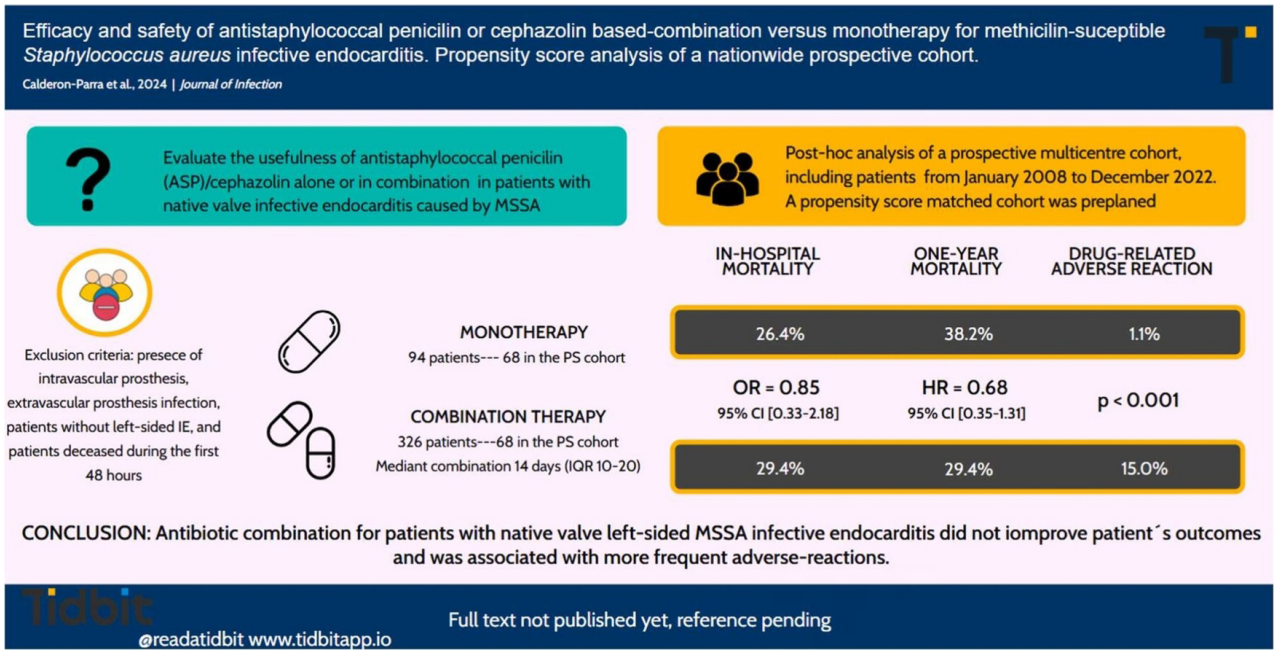
The investigators aimed to evaluate the usefulness of antistaphylococcal penicillin (ASP) or cefazolin-based combinations versus monotherapy in patients with native-valve infective endocarditis (IE) due to methicillin-susceptible Staphylococcus aureus (MSSA). They performed a post-hoc analysis of a multicenter prospective cohort. They include patients from 2008 to 2022 with definite native-valve, left-side IE due to MSSA treated primarily with ASP/cefazolin. Patients were categorized according to whether they initially received monotherapy or combination therapy for more than 72 hours. A propensity score-matched cohort was used.

"Currently, there is controversy about the usefulness of antibiotic combination best for improving outcomes of patients with [native-valve infective endocarditis due to methicillin-susceptible Staphylococcus aureus]."



Out of 420 included cases, 94 (22.4%) received monotherapy and 326 (77.6%) combination. The most frequent companion antibiotics were aminoglycosides (126, 93 of them gentamicin), daptomycin (107), rifampin (53) and vancomycin. Median combination duration was 14 days (interquartile range 10–20). Sixty-eight combination cases were matched with 68 monotherapy controls. Baseline characteristics were well balanced. There were no differences in in-hospital or one-year mortality between groups (OR 0.85, 95%CI 0.33–2.18 and HR 0.68, 95%CI 0.35–1.31, respectively). Endocarditis relapses and

persistent bacteremia rates were similar (0% vs 1.5%, p = 1.000; and 19.1% vs 13.2%, p = 0.352, respectively). Drug- related adverse events were more frequent in the combination group (15.0% vs 1.1%, p < 0.001).



Dr. Septimus's Annotations

Currently, there is controversy about the usefulness of antibiotic combination best for improving outcomes of patients with MSSA IE. Some experts propose that this infection requires a synergic and bactericidal combination therapy with an ASP or cefazolin plus a non-beta-lactam antibiotic (most commonly vancomycin, daptomycin, rifampin or an aminoglycosides). [J Antimicrob Chemother. 2021; 76:1539-1546] Clinically, combination therapy has been previously evaluated in MSSA and methicillin-resistant Staphylococcus aureus (MRSA) bacteremia, demonstrating a reduction in bacteremia duration primary with IE due to MRSA. [JAMA. 2020; 323:527-537] Yet, these trials have failed to show better patient-center outcomes when compared to ASP or cefazolin monotherapy for MSSA. [Microorganisms. 2022; 10:848] Nevertheless, these studies have not focused on patients with left-sided IE due to MSSA.

The results in this study are in line with previous clinical trials performed in MSSA bacteremia that showed that different ASP/cefazolin-based combinations were not associated with better outcomes, including aminoglycoside, [J Infect Chemother. 2018 Jul; 24:555-562] daptomycin, [Clin Infect Dis. 2019; 69:1480-1488] vancomycin, and rifampin combination. [Enferm Infecc Microbiol Clin. 2015; 33:625.e1-625.e23] In general, these studies have only shown a slight reduction bacteremia duration, without affecting more important clinical outcomes. [Clin Infect Dis. 2009; 48:713-721 Frequently, combination arms presented more frequent adverse events. The most notably exception is the use of rifampin for biofilm-associated infections (i.e., prosthetic arthritis or prosthetic endocarditis), which has been shown to reduce relapses. [Microorganisms. 2022; 10:848] In this study almost half of the patients received cardiac surgery.

This study is based on an observational cohort, with the limitation inherit to this design, especially selection bias. However, they tried to mitigate selection bias by using a robust statistical analysis including a propensity score matching approach. This cohort was not specifically designed to evaluate treatment effects, certain variables important to treatment selection and/or outcomes could not be gathered, i.e., positivity of first control blood cultures

(first 48–72 hours). Median combination duration was only 14 days. Lastly their main analysis included all combination treatments options. Further studies should evaluate other specific antibiotics, i.e., daptomycin or ertapenem-based combinations.

BOTTOM LINE

Antibiotic combinations for patients with native valve left-sided MSSA endocarditis did not improve patient's outcomes. Drug-related adverse events were more frequent in combination patients.

18

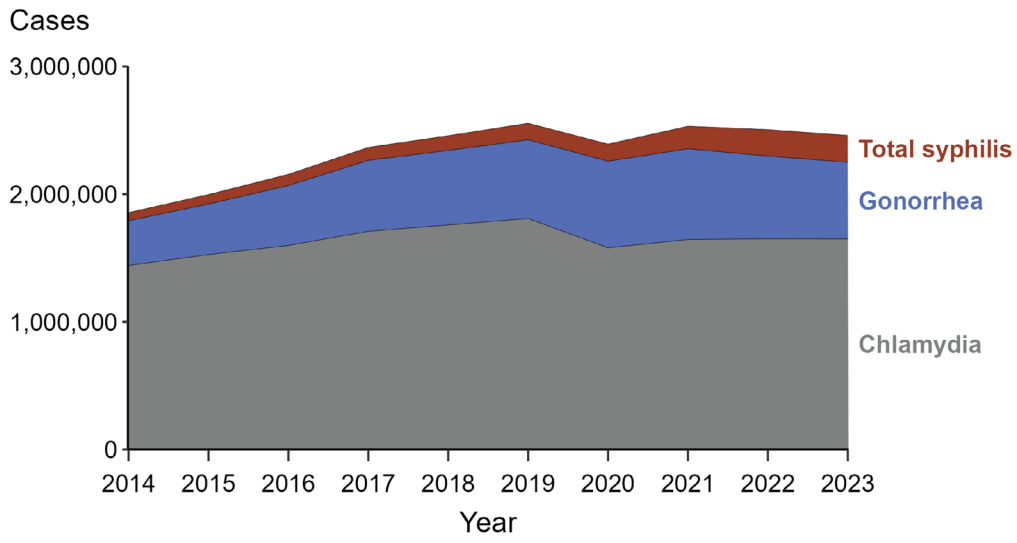
National Overview of STIs in 2023.

CDC November 12, 2024

The incidence of bacterial sexually transmitted infections (STIs) climbed sharply during the last decade, with especially high numbers for syphilis (including congenital syphilis). Now, a 2023 CDC surveillance report of case numbers for syphilis (209,253), gonorrhea (601,319), and chlamydia (1,648,568) suggests that the trend may be abating.

Syphilis rates were 1% higher in 2023 than 2022, but cases of primary and secondary syphilis declined by 10%, especially among men who have sex with men. Cases of congenital syphilis continued to rise in number (3882 cases). Gonorrhea rates fell by 8% for the second year in a row, with the largest reduction among women. Chlamydia rates remained flat. In general, however, these STI rates mask stark ethnic and racial disparities. Syphilis incidence (including congenital syphilis) was highest among American Indian and Alaskan Native peoples. Rates of gonorrhea and chlamydia were highest among African Americans.

Reported Cases by STI and Year, United States, 2014–2023



Dr. Septimus's Annotations

Although rates of bacterial STIs have largely stabilized, case counts remain high. These encouraging overall trends may reflect the investment made by the American Rescue Plan Act (ARPA) of 2021 when it provided $600 million over 3 years to bolster the workforce comprising disease-intervention specialists for STIs (offsetting the public health efforts

that were redirected toward Covid-19). Additionally, the rollout of doxycycline postexposure prophylaxis for persons at high risk is likely having an impact on STI rates. Even so, I remain concerned that these rates may rise again if the investment into public health is not maintained over the long term.

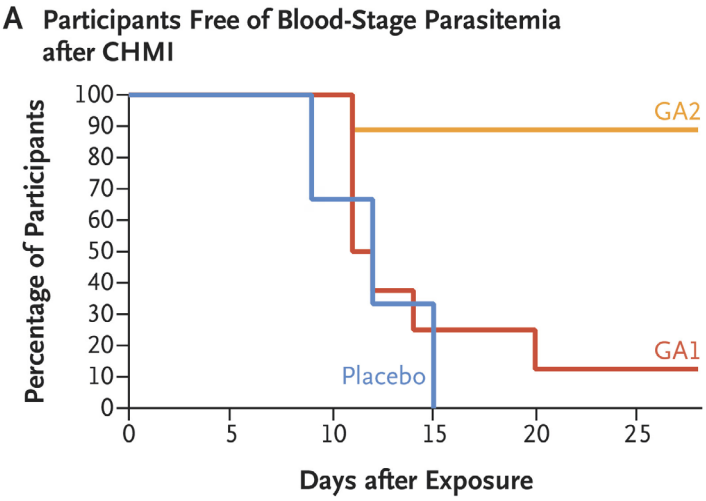
19

Safety and Efficacy of Immunization with a Late-Liver-Stage Attenuated Malaria Parasite.

The New England Journal of Medicine 2024; 391: 1913-23.
DOI: 10.1056/NEJMoa2313892

The investigators conducted a controlled double-blind clinical trial to evaluate the safety, side effect profile, and efficacy of immunization, by means of mosquito bites, with a second-generation genetically attenuated parasite (GA2) — a mei2 single knockout *P. falciparum* NF54 parasite (sporozoite form) with extended development into the liver stage. After an open-label dose-escalation safety phase in which participants were exposed to the bites of 15 or 50 infected mosquitoes (stage A), healthy adults who had not had malaria were randomly assigned to be exposed to 50 mosquito bites per immunization of GA2, an early-arresting parasite (GA1), or placebo (bites from uninfected mosquitoes) (stage B). After the completion of three immunization sessions with 50 mosquito bites per session, they compared the protective efficacy of GA2 against homologous *P. falciparum* controlled human malaria infection with that of GA1 and placebo. The primary end points were the number and severity of adverse events (in stages A and B) and blood-stage parasitemia greater than 100 *P. falciparum* parasites per milliliter after bites from GA2-infected mosquitoes (in stage A) and after controlled human malaria infection (in stage B).

Protective efficacy against sub sequent controlled human malaria infection was observed in 8 of 9 participants (89%) in the GA2 group, in 1 of 8 participants (13%) in the GA1 group, and in 0 of 3 participants in the placebo group. A significantly higher frequency of *P. falciparum* specific polyfunctional CD4+ and Vδ2+ γδ T cells were observed among participants who received GA2 than among those who received GA1, whereas GA2 and GA1 induced similar antibody titers targeting the *P. falciparum*. Although they demonstrated a strong proinflammatory CD4+ T-cell response in both groups, induction of *P. falciparum*–specific poly functional effector memory CD4+ T cells was more robust in participants who received bites from GA2-infected mosquitoes than in those who received bites from GA1-infected mosquitoes. Adverse events were similar across the trial groups. circumsporozoite protein.



CHMI= controlled human malaria infection

Dr. Septimus's Annotations

This trial showed evidence of higher cellular immunogenicity and protective efficacy with a late arresting genetically attenuated parasite (GA2) compared with an early-arresting parasite (GA1), which indicates a potential role for late-liver-stage antigens in eliciting protective immunity to malaria. Protection was not associated with antibodies to PfCSP, AMA1, or PfMSP1 but was related to the induction of P. falciparum–specific polyfunctional CD4+ T cells and Vδ2+ γδ T cells.

The protection induced by late-arresting GA2 in this trial (89%) is higher than that seen in previous trials involving replication-incompetent, early arresting attenuated sporozoites. The protection induced by bites from GA2-infected mosquitoes in this trial is reminiscent of that from parasites coadministered with chemoprophylaxis, in which three exposures to bites of 15 infected mosquitoes resulted in 100% efficacy against homologous controlled human malaria infection, which supports the hypothesis that extended immune responses. [N Engl J Med 2009; 361:468-77; Proc Natl Acad Sci USA 2013; 110: 7862-7]

The conclusions from this trial are limited by the small sample size and the large number of immunologic analyses. More studies with greater numbers of participants are required to better understand the safety profile of GA2.

BOTTOM LINE

In this small trial, second-generation genetically attenuated parasite GA2 was associated with a favorable immune induction profile and protective efficacy, findings that require further evaluation.

20

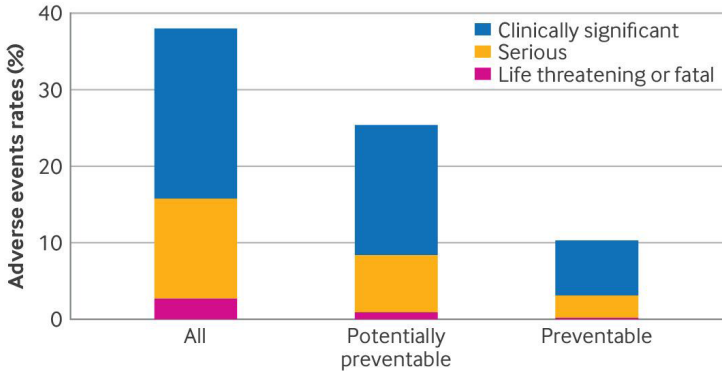
Safety of inpatient care in surgical settings: cohort study.

The BMJ 2024; 387: e080480
DOI: 10.1136/ bmj-2024-080480

To determine the frequency, severity and preventability of surgical complications, investigators from Harvard Medical School and Boston-based Brigham and Women's Hospital reviewed a sample from a dataset of 64,121 adults admitted for surgery across 11 Massachusetts hospitals. Nurses and physicians reviewed 1,009 patient records.

Adverse events during inpatient perioperative care were assessed using a trigger method, identifying information previously associated with similar events, and from a comprehensive review of electronic health records. Trained nurses reviewed all records and flagged admissions with possible adverse events, which were then adjudicated by physicians, who confirmed the occurrence and characteristics of the events. Adverse events were classified as major if they resulted in serious harm requiring substantial intervention or prolonged recovery, involved a life-threatening event, or led to a fatal outcome. Potentially preventable events included those definitively, probably, or possibly preventable. Severity was determined using an ascending ordinal classification. Adverse events were defined as clinically significant (caused unnecessary harm but resulted in rapid recovery), serious (caused harm that resulted in substantial intervention or prolonged recovery), life threatening (caused a potentially fatal situation that required immediate intervention), and fatal (resulted in death).

Severity of adverse events weighted rates for each admitted patient according to preventability.



The researchers found that, among 593 adverse events, 476 were either potentially or definitely preventable. The most common adverse events were related to surgical procedures (49.3%), adverse drug events (26.6%), healthcare-associated infections (12.4%), patient care events (11.2%) and blood transfusion reactions (0.5%). The professions most frequently involved in adverse events were attending physicians, nurses, residents, and advanced level practitioners. Adverse events occurred most frequently in general care units, followed by operating rooms, intensive care units and recovery rooms.

"'While emphasizing safety as a collective responsibility for all health professionals is important, it is essential to recognize the expertise of those ultimately responsible for patient care, such as attending physicians.'"

Dr. Septimus's Annotations

"While emphasizing safety as a collective responsibility for all health professionals is important, it is essential to recognize the expertise of those ultimately responsible for patient care, such as attending physicians." In modern healthcare systems where organizational and administrative factors often drive delivery of care, concern is growing that physicians have limited input into decision making processes. It is equally important to engage the perspectives of frontline staff and promote collaborative approaches to care delivery. We must strive toward a system that prioritizes patient safety.

BOTTOM LINE

The findings of this study suggest that adverse events remain frequent and preventable in surgery, rendering perioperative care as a high-risk environment for patients. This highlights the urgent need to enhance patient safety across the continuum of care.

21

CDC Proposed Mask Guidance

Healthcare Infection Control Practices Advisory Committee (HICPAC) November 15, 2024

During a Nov. 15 meeting, HICPAC discussed the CDC's four key questions on this guidance and voted on responses for each. They determined that:

1. N95 respiratory masks should not be universally recommended for all airborne pathogens.
2. Surgical masks are sufficient for common respiratory pathogens that spread over short distances.
3. Healthcare workers may voluntarily wear N95 respirators, but this language should not be included as a formal recommendation.
4. A blanket recommendation for universal mask use to prevent pathogen transmission from the mask-wearer is unnecessary.

Transmission-Based Precautions to Prevent Transmission through the Air

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

a. AIIR = Airborne Infection Isolation Room for Containment of Air in a Designated Space
b. Although an AIIR is not routinely recommended, an AIIR may be suggested for certain pathogens listed in Appendix A (2007), and for pathogens with uncertain transmission characteristics

Disclaimer. The findings and conclusions herein are draft and have not been formally disseminated by the Centers for Disease Control and Prevention and should not be construed to represent any agency determination or policy.

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

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

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

HICPAC initially approved the draft recommendations in November 2023. After facing pushback from nurses and other industry members, the CDC in January requested additional clarifications from the advisory group on its isolation precautions guideline, including whether N95s should be required and under what specific circumstances.

BOTTOM LINE

CDC's Healthcare Infection Control Practices Advisory Committee (HICPAC) voted in favor of recommendations that remain largely unchanged despite ongoing criticism. HICPAC recommendations will be sent to the CDC in preparation for a public comment period.

Testing and Masking Policies and Hospital-Onset Respiratory Viral Infections

JAMA Network Open 2024; Vol. 7, Iss. 11: e2448063
DOI: 10.1001/jamanetworkopen.2024.48063

Most hospitals have stopped testing all patients for SARS-CoV-2 upon admission and requiring masking. Ten hospitals in the Mass General Brigham hospital system ended both these precautions simultaneously in May 2023 but restarted masking for health care workers in January 2024 during a winter respiratory viral surge. The investigators characterized the association of these changes with the relative incidence of hospital-onset SARS-CoV-2, influenza, and respiratory syncytial virus (RSV).

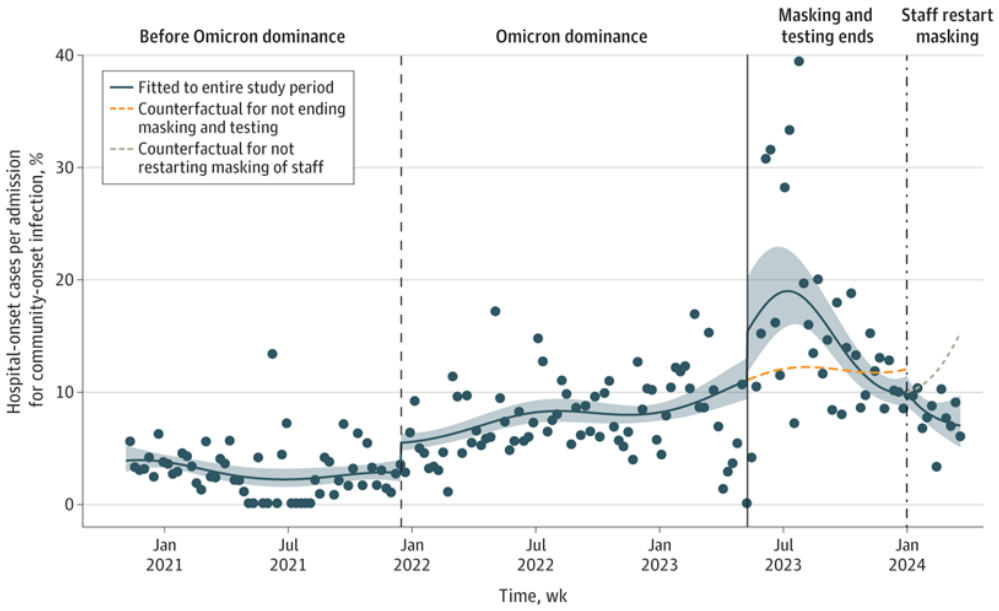
"In this study, discontinuing universal masking and SARS-CoV-2 testing was associated with a significant increase in hospital-onset respiratory viral infections relative to community infections."

They analyzed all patients admitted between November 6, 2020, and March 21, 2024, to 10 hospitals (2 tertiary hospitals, 7 community hospitals, 1 eye and ear hospital) using a Poisson interrupted time-series design. They identified hospital-onset infections (first positive PCR test more than 4 days after admission) and community-onset infections (first positive within 4 days) for SARS-CoV-2, influenza, and RSV. The study had 4 periods: pre-Omicron with universal testing and masking; Omicron with universal testing and masking; Omicron without universal testing and masking; and Omicron after restarting masking for health care workers alone. Periods with universal testing included both admission testing and serial retesting of patients who were SARS-CoV-2-negative. They reviewed 100 randomly selected hospital-onset SARS-CoV-2 cases admitted after universal testing ended, to assess whether community-onset cases were being misclassified as hospital onset using 3 yes or no characteristics: new symptoms of respiratory infection, known exposure to SARS-CoV-2, and PCR cycle threshold of less than 30.

Among 641,483 admissions (357,263 women [55.7%]; median [IQR] age, 61 [38-74] years), there were 30,071 community-onset and 2075 hospital-onset SARS-CoV-2, influenza, and RSV infections. While universal testing was in effect, admission SARS-CoV-2 tests were collected for 386,257 of 415,541 admissions (92.9%), compared with 39,765 of 149,712 admissions (26.5%) after stopping universal testing. The median (IQR) interval between tests in admissions of 8 days or more was 4.4 (3.4-6.1) days during universal testing vs 11.1 days (8.4-17.0) days after stopping universal testing.

The mean weekly ratio between hospital-onset and community-onset infections increased from 2.9% prior to Omicron dominance to 7.6% (95% CI, 6.0%-9.1%) during Omicron dominance. After universal masking and testing ended, it increased to 15.5% (95% CI, 13.6%-17.4%), then fell to 8.0% (95% CI, 5.0%-11.0%) following resumption of masking among health care workers. Under the adjusted Poisson model, cessation of universal masking and testing was associated with a 25% increase in hospital-onset respiratory viral infections compared with the preceding Omicron-dominant period (rate ratio [RR], 1.25; 95% CI, 1.02-1.53), and resumption of masking among staff was associated with a 33% decrease in hospital-onset respiratory viral infections (RR, 0.67; 95% CI, 0.52-0.85).

Weekly New Hospital-Onset Cases of SARS-CoV-2, Influenza, and RSV Infection Per Admission for Community-Onset Infection at 10 US Hospitals



Dr. Septimus's Annotations

Nosocomial respiratory viral infections remain associated with increased length of stay and higher mortality in hospitalized populations. [Ann Intern Med. 2024; 177:1078-1088; J Infect Public Health. 2022; 15:1118-1123; Infect Control Hosp Epidemiol. 2023; 44:433-439] In this study, discontinuing universal masking and SARS-CoV-2 testing was associated with a significant increase in hospital-onset respiratory viral infections relative to community infections. Restarting the masking of health care workers was associated with a significant decrease. There were no controls, there were variations in compliance, and difficulty separating the effects of testing vs masking.

BOTTOM LINE

This study supports the use of targeted universal masking. Data suggests that masking and testing were 2 potentially effective measures to protect patients who are hospitalized from nosocomial viral infections, particularly when community respiratory virus incidence rates were elevated.

23

Benefit of early oseltamivir therapy for adults hospitalized with influenza A: an observational study.

Clinical Infectious Diseases published online November 28, 2024
DOI: 10.1093/cid/ciae584

To assess the clinical benefit of the current guidelines, which recommend to treat adults hospitalized with acute influenza with oseltamivir as early as possible after admission, investigators prospectively enrolled adults aged 18 years and older who were hospitalized with laboratory-confirmed influenza at 24 hospitals during between October 1, 2022, and July 21, 2023. They used a multivariable proportional odds model to compare peak pulmonary disease severity — assessed by oxygen support, standard supplemental oxygen, high-flow oxygen/noninvasive ventilation, invasive mechanical ventilation or death — after the day of hospital admission. Patients who either started oseltamivir treatment the day of admission (early) were then compared with those who did not (late or not treated), and evaluated for odds

of ICU admission, acute kidney replacement therapy or vasopressor use, and in-hospital death.

In total, 840 patients with influenza were analyzed — 415 of whom started oseltamivir on the day of admission and 425 who did not. Patients treated early with oseltamivir had lower peak pulmonary disease severity (adjusted OR = 0.6; 95% CI, 0.49-0.72) compared with those treated later or not treated at all. These patients also had lower odds of ICU admission (aOR = 0.24; 95% CI, 0.13-0.47), acute kidney replacement therapy or vasopressor use (aOR = 0.4; 95% CI, 0.22-0.67) and in-hospital death (aOR = 0.36; 95% CI, 0.18-0.72).

Reduced odds of negative outcomes among patients hospitalized with flu who were treated with oseltamivir at admission vs. those treated later:

Dr. Septimus's Annotations

Their findings reinforce the current Infectious Diseases Society of America (IDSA) and CDC guidelines for hospitalized influenza patients, which recommend starting antiviral treatment with oseltamivir as soon as possible after admission. [Clin Infect Dis 2019;68:e1–e47] Compared with patients who had oseltamivir started later during hospitalization or never initiated, those who had oseltamivir initiated on the day of hospital admission were less likely to experience a broad range of severe clinical outcomes during their hospital course, including progression of pulmonary disease severity, invasive mechanical ventilation, extrapulmonary organ failure, and in-hospital death. This study and prior studies suggest that there is some treatment benefit for oseltamivir among adults hospitalized with influenza even when initiated >48 hours after symptom onset and that initiation of treatment as early as possible likely maximizes that benefit. [Clin Infect Dis 2012; 55:1198–1204; Euro Surveill 2023;28: pii=2200340]

Influenza severity and antiviral effectiveness may differ by influenza type or subtype, and the results observed here may not be generalizable to seasons during which influenza A(H1N1) pdm09 or B viruses are predominant. There were also some potentially relevant variables that were not collected, including outpatient antiviral treatment prior to hospital admission, or other treatments (i.e., with macrolides, statins, corticosteroids, or immunomodulators) before or during hospitalization. Lastly, despite their statistical approach including adjustment for baseline disease severity, age, site, sex, and influenza vaccination status, residual confounding in the relationship between early initiation of oseltamivir and clinical outcomes is possible.

BOTTOM LINE

Among adults hospitalized with influenza, treatment with oseltamivir on day of hospital admission was associated reduced risk of disease progression, including pulmonary and extrapulmonary organ failure and death.

24

Prophylaxis Options in Children With a History of Recurrent Urinary Tract Infections: A Systematic Review

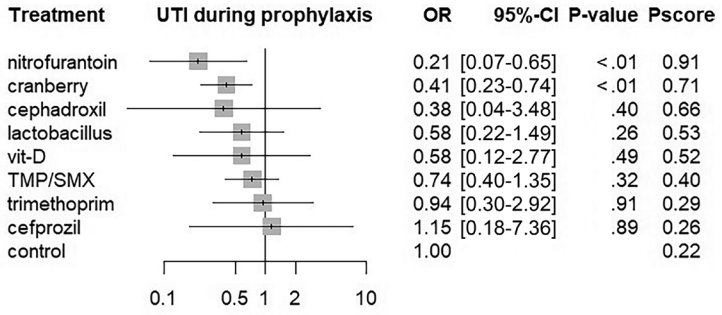
Pediatrics 2024, Vol. 154, Iss. 6: e2024066758
DOI: 10.1542/peds.2024-066758

The authors conducted a systematic review and meta-analysis of randomized controlled trials comparing prophylaxis options for the prevention of UTI and kidney scarring in children with a history of recurrent UTI (rUTI). They conducted

a systematic literature search through major electronic databases (PubMed/Medline, Scopus and Cochrane Library) up to November 26th, 2023. The primary outcome was the effect of the different prophylaxis options on the incidence of symptomatic UTI in children with rUTI during prophylactic treatment.

Their meta-analysis included 3335 participants from 23 studies. Cranberry products and nitrofurantoin lead to lower odds of symptomatic UTI episodes during prophylaxis compared with the control group and control, trimethoprim-sulfamethoxazole, or trimethoprim groups accordingly. Nitrofurantoin may be the best option for UTI incidence reduction compared with all available documented interventions. Unfortunately, no prophylaxis option has been shown to reduce kidney scarring.

Symptomatic UTI episodes during prophylaxis (other interventions versus "control," random effects model).



Dr. Septimus's Annotations

UTIs are the most common cause of bacterial infection in children. [Pediatrics. 2021;147(2): e2020012138] Febrile UTI and acute pyelonephritis (APN) in children may contribute to kidney scar formation with the subsequent risk of future complications. [JAMA Pediatr. 2014;168(10):893–900] Acute pyelonephritis is the main cause of permanent kidney damage, and approximately 10% to 30% of cases will develop kidney scarring. Current practice suggests that in children with RUTI, long-term, low-dose antibiotic prophylaxis may prevent further episodes of UTI and future complications. [N Engl J Med. 2009;361(18):1748–1759] Vesicoureteral reflux (VUR), bladder instability, previous infections, and female sex are the main risk factors of rUTI. In a recent Cochrane Systematic Review, long-term antibiotic prophylaxis may have a small impact on UTI prevention, however, with a concurrent increase in the risk for antibiotic resistance, concluding that they should be reserved only for children at risk for rUTI. [Cochrane Database Syst Rev. 2019;4(4):CD001534]

This review demonstrated cranberry products and nitrofurantoin lead to lower odds of symptomatic UTI episodes during prophylaxis compared with the control group and control, TMP-SMX, or trimethoprim groups. Nitrofurantoin may be the best option for UTI incidence reduction compared with all available interventions in the literature. These results agree with the results of individual studies that were described in the discussion section.10,50,51

This review has limitations that should be discussed. A few RCTs did not include only children with a history of rUTI. Additionally, the risk of bias (RoB) in more than half of the included studies raised many concerns (high RoB). Another issue is that definitions of RUTI in different studies included were not consistent. (difference in threshold [cfu/mL] of positive urine culture, episodes of rUTI definition and urine sampling method).

BOTTOM LINE

The latest data in this review suggests there may be a clinical benefit of nitrofurantoin and cranberry supplements for recurrent UTI (rUTI) prophylaxis in the general pediatric population.

25

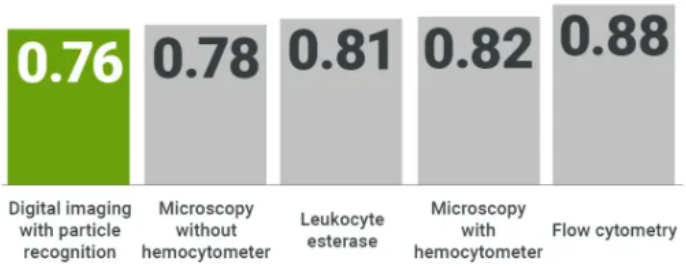
Accuracy of Screening Tests for the Diagnosis of Urinary Tract Infections in Young Children

Pediatrics 2024, Vol. 154, Iss. 6, e2024066600
DOI: 10.1542/peds.2024-066600

They included children between 1 and 36 months of age undergoing bladder catheterization for suspected UTIs. Using a positive urine culture result as the reference standard, they compared the sensitivity of 5 modalities for assessing pyuria at the cutoffs most often used clinically for detecting children with a positive culture result: leukocyte esterase on a dipstick, white blood cell (WBC) count on manual microscopy with and without using a hemocytometer, automated WBC enumeration using flow cytometry, and automated WBC enumeration using digital imaging with particle recognition.

A total of 4188 children were included. Out of 4188 children, 3,377 (81%) had a fever, and 407 (9.7%) had positive urine cultures. Among febrile children, the sensitivity of the 2 most widely available modalities, the leukocyte esterase test and WBC enumeration using digital imaging, had sensitivity values of 84% (95% confidence interval, 0.80–0.87) and 75% (95% confidence interval, 0.66–0.83), respectively. Pyuria combined with bacteriuria had a slightly higher sensitivity (i.e., > 90% for 4 of the 5 modalities examined). Pyuria was less common with pathogens other than E coli.

Sensitivity of automated dispstick and urinalysis tests:



Dr. Septimus's Annotations

The AAP published guidelines requiring the presence of pyuria and at least 50,000 colony-forming units of a single pathogen to diagnose a UTI in children aged 2 to 24 months. Subsequent studies reported that many children may be left with untreated UTIs due to this requirement [J Pediatr. 2019; doi: 10.1016/j.jpeds.2019.10.019.] and the organization retired these guidelines in 2021. WikiGuidelines recently released updated recommendations for UTI diagnosis and treatment which cautioned providers not to use urinalysis alone to determine whether to order a urine culture.[JAMA Netw 2024.44495] [ID watch December 2024]

BOTTOM LINE

These findings suggest that for febrile children <36 months of age undergoing bladder catheterization for suspected UTI, pyuria will be absent in ~20% of children who are eventually shown to have pure growth of a pathogen on a culture. This raises questions about the appropriateness of requiring pyuria for the diagnosis of UTIs.

26

Impact of clinician feedback reports on antibiotic use in children hospitalized with community-acquired pneumonia.

Clinical Infectious Diseases published online December 3, 2024
DOI: 10.1093/cid/ciae593

The study evaluated the impact of electronically delivered audit and feedback reports on antibiotic prescribing for community-acquired pneumonia (CAP) at the hospital's two locations from December 2021 through November 2023. While electronic feedback reports have been shown to improve adherence to evidence-based recommendations for antibiotic use in outpatient settings, their use has not been well-explored in inpatient settings.

The reports, which contained information on adherence to the recommended first-line antibiotic choice (ampicillin) and duration (5 days) for CAP, were distributed by email to all general pediatrics attendings, fellows, and advanced practice providers at the hospitals and reviewed in monthly meetings. The primary outcome of the study was the proportion of all CAP encounters that involved both the appropriate antibiotic choice and duration before and after the intervention.

A total of 800 CAP encounters occurred during the study period (413 preintervention and 387 postintervention). Adherence to appropriate antibiotic choice and duration increased from 52% of encounters preintervention to 80% postintervention. An interrupted time series analysis demonstrated an immediate 18% increase in the proportion of CAP encounters receiving both the appropriate antibiotic choice and duration (95% confidence interval [CI], 3% to 33%), with no further change over time (-0.3% per month, 95% CI, -2% to 2%).

Using a Poisson model adjusted for age, sex, race, season, site, and intensive care unit admission, the researchers found the intervention was associated with a 32% increase in the rate of appropriate antibiotic choice and duration (rate ratio, 1.32; 95% CI, 1.12 to 1.56). No difference in length of stay or revisits were detected postintervention.

Dr. Septimus's Annotations

CAP is among the most common indications for antibiotic treatment in pediatric inpatients. [JAMA Netw Open, 2021; 4:e2117816] Ampicillin is recommended as the first-line treatment for most children hospitalized with non-severe pneumonia.[Clin Infect Dis 2011; 53:e25-76] Multiple randomized trials and observational studies have demonstrated that five days of antibiotic treatment is as effective as longer durations for CAP in non-immunocompromised patients who are clinically stable within five days of starting therapy, a recommendation contained in the 2019 American Thoracic Society/ Infectious Diseases Society of America adult CAP guidelines. [Am J Respir Crit Care Med 2019; 200:e45–e67]

The investigator in this report demonstrated the effectiveness of group-level clinician feedback reports in improving adherence to antibiotic use guidelines among academic general pediatrics clinicians within a pediatric health system. These electronically delivered feedback reports, coupled with clinician education, an established local guideline, and regular review of the metrics at divisional QI meetings, resulted in a 32% increase in the rate of appropriate antibiotic use for CAP over the one-year postintervention period, driven by improved adherence to antibiotic duration recommendations.

BOTTOM LINE

The investigators demonstrated the effectiveness of audit and feedback reports, implemented with clinician education, monthly review of metrics, and a long-standing guideline in improving compliance with evidence-based recommendations for antibiotic selection and duration in children hospitalized with community acquired pneumonia.

Duration of viral persistence in human semen after acute viral infection: a systematic review

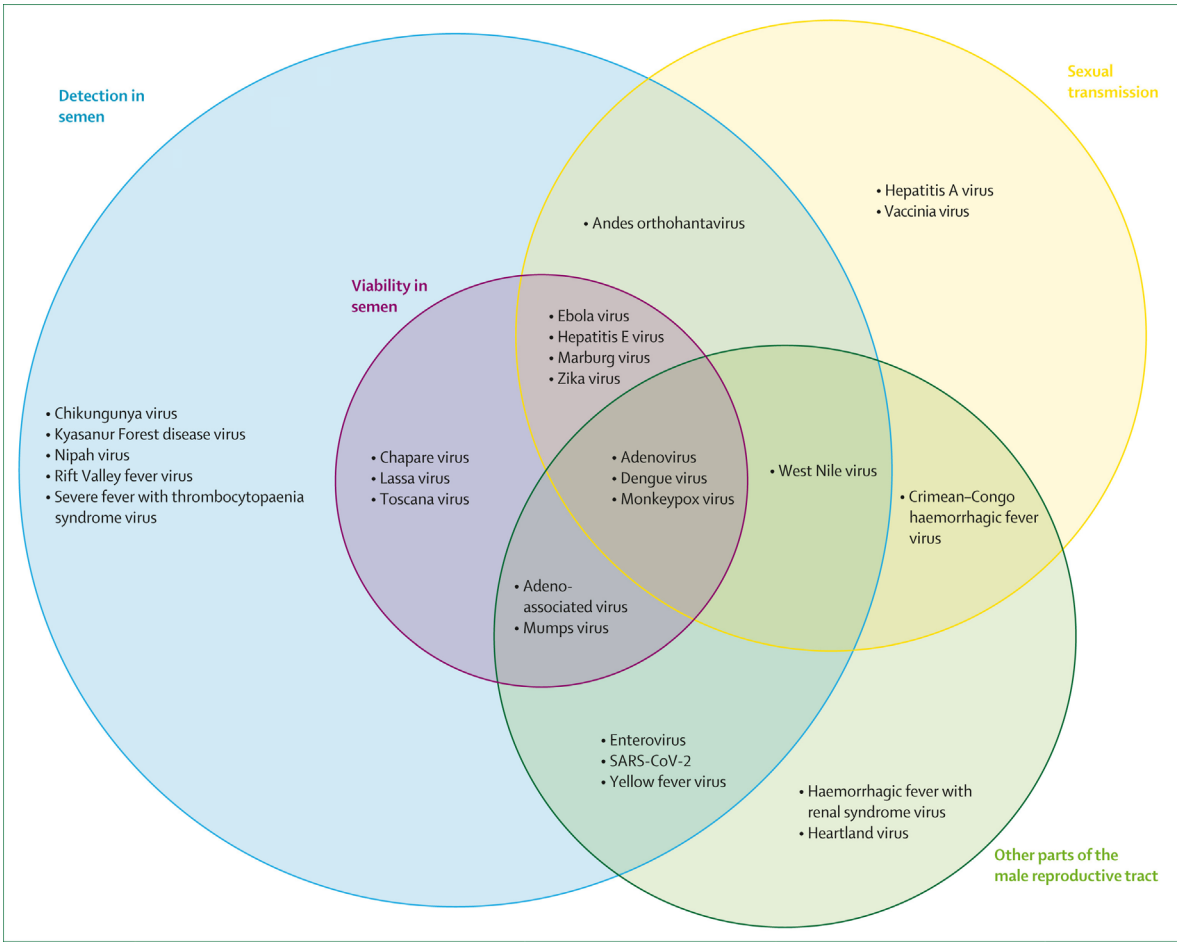
The Lancet Microbe published online December 10, 2024
DOI: 10.1016/j.lanmic.2024.101013

The investigators conducted a systematic review of viral persistence in semen. 373 original studies were included in this review after screening 29,739 articles from five databases.

Evidence was found of detection of 22 viruses in human semen following acute infection. In addition to the 22 viruses present in semen following acute infection, 3 others—Crimean-Congo hemorrhagic fever virus, hantavirus causing hemorrhagic fever with renal syndrome, and Heartland virus—were detected in other parts of the human male reproductive tract, but not in semen. Hepatitis A virus and vaccinia virus showed evidence for sexual transmission but no evidence for detection in the semen or elsewhere in the male reproductive tract.

Ebola virus had the longest viral persistence, detected 988 days after discharge from an Ebola treatment unit and 965 days after onset of illness, in separate studies. The maximum detection of Zika virus in semen was 941 days after onset of illness, but the median persistence was 57 days after onset of illness. The shortest duration was 8 days after onset of illness for Kyasanur Forest disease. Maximal detection time for other viruses was 21 days for yellow fever virus, 22 days for West Nile virus, and 37 days for dengue virus. They found considerable variability between individuals regarding the duration of persistence of virus in the semen, alongside substantial uncertainty in the duration of persistence in each individual.

Evidence for detection of all 27 viruses in the semen, their viability in the semen, sexual transmission, and detection in other parts of the male reproductive tract



Dr. Septimus's Annotations

This review only focused on viruses that cause acute infection, given the clinical and public health implications of persistence even after resolution of illness. Viral presence in the semen in the context of chronic infections, reviewed elsewhere on other publications, [Emerg Infect Dis 2017; 23: 1922–24; Microbiol Mol Biol Rev 2001; 65: 208–31] has been confirmed for HIV, hepatitis B, hepatitis C, cytomegalovirus ,Epstein–Barr virus, human simplex virus 1,human simplex virus 2, varicella zoster virus, transfusion-transmitted virus, GB virus C,BK virus, JC virus, simian virus 40, simian foamy virus, human T-cell lymphomavirus1,human herpesvirus 6,human herpes virus 7,and human herpesvirus 8.

BOTTOM LINE

In this new systematic review of 373 studies they confirm the detection of 22 viruses in human semen following acute infection, including pathogens with pandemic potential and shows that only 9 of the 22 viruses had evidence of sexual transmission.

28

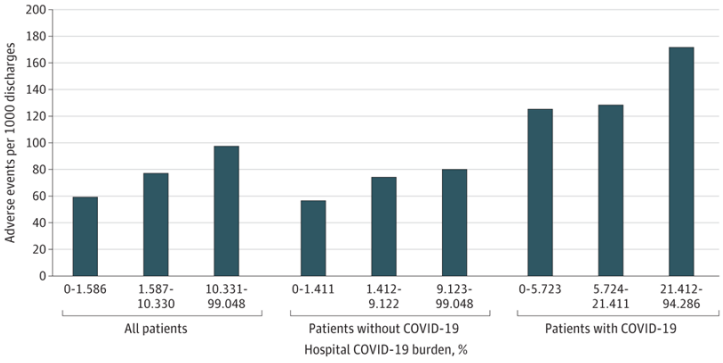
Hospital COVID-19 Burden and Adverse Event Rates

JAMA Network Open 2024; Vol. 7, Iss. 11: e2442936
DOI: 10.1001/jamanetworkopen.2024.42936

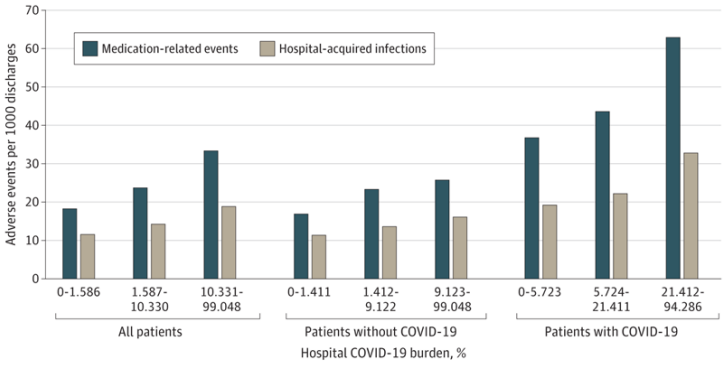
This cohort study used data from the Agency for Healthcare Research and Quality's(AHRQ) Quality and Safety Review System, a surveillance system that tracks the frequency of adverse events (AEs) among selected hospital admissions across the US. The study sample included randomly selected Medicare patient admissions to acute care hospitals in the US between September 1, 2020, and June 30, 2022. The main outcome was the association between frequency of AEs and hospital-specific weekly Covid-19 burden. Observed and risk-adjusted rates of AEs per 1000 admissions were stratified by the weekly hospital-specific COVID-19 burden (daily mean number of Covid-19 inpatients per 100 hospital beds each week), presented as less than the 25th percentile (lowest burden), 25th to 75th percentile (intermediate burden), and greater than the 75th percentile (highest burden). Risk adjustment variables included patient and hospital characteristics

In this cohort study of 40,737 hospital admissions among Medicare patients, increased hospital Covid-19 burden was associated with an increased adjusted risk of inpatient AEs among both patients with and without Covid-19. As the figures below indicate both medication related events and HAIs increased

Overall Observed Adverse Events per 1000 Discharges, by Hospital COVID-19 Burden



Medication-Related Events and Hospital-Acquired Infections



Dr. Septimus's *Annotations*

The Covid-19 pandemic introduced unprecedented demands on hospitals and their staff, including a surge in the volume of critically ill patients, burden related to isolation protocols, and staff shortages due to illness and other reasons. In this analysis the investigators found that the incidence of AEs occurring among hospitalized patients was associated with the weekly hospital specific Covid-19 burden from September 2020 through June 2022. Furthermore, this association was seen among patients hospitalized for any reason, including Covid-19, and among patients who did not have Covid-19. The Leapfrog Group reported that hospital-acquired infections increased to a 5-year high during the pandemic, with the mean CLABSI standard infection ratio (SIR) increased by 60%, the mean methicillin-resistant S. aureus (MRSA) SIR increased by 37%, and the mean CAUTI SIR increased by 19% compared with the period immediately prior to the Covid-19 pandemic. This data is concordant with data on hospital-acquired infections reported by the CDC. They also demonstrated that AE rates increased even among patients without Covid-19, removing the possibility that inadequate risk adjustment among patients with Covid-19—for example, due to their severity of illness—could have affected the validity of the results.

Their analysis was limited to the Medicare population, so it might not be applicable to a younger population. AEs were determined by medical record abstraction, so events that were not well documented might have been missed. As with all observational studies, causation cannot be proven.

BOTTOM LINE

This study found a statistically significant increase in adverse events (AE) rates in hospitalized Medicare patients during periods of high Covid-19 burden. This increase was seen in both patients with and without Covid-19.

29

Use of Additional Doses of 2024–2025 COVID-19 Vaccine for Adults Aged ≥65 Years and Persons Aged ≥6 Months with Moderate or Severe Immunocompromise: Recommendations of the Advisory Committee on Immunization Practices — United States, 2024

MMWR 2024; 73:1118-1123

In October 2024, Advisory Committee on Immunization Practices (ACIP) recommended that all persons aged ≥65 years and persons aged 6 months–64 years with moderate or severe immunocompromise receive a second 2024–2025 Covid-19 vaccine dose 6 months after their last dose. Further, ACIP recommended that persons aged ≥6 months with moderate or severe immunocompromise may receive additional doses based on shared clinical decision-making.

TABLE. Routine 2024–2025 COVID-19 vaccination schedule for persons aged ≥65 years,* by COVID-19 vaccination history† — United States, October 2024

COVID-19 vaccination history before 2024–2025 vaccine	No. of 2024–2025 COVID-19 doses recommended	2024–2025 vaccination schedule
≥1 mRNA vaccine dose (Moderna or Pfizer-BioNTech) or ≥2 Novavax doses or ≥1 Janssen dose	2	2024–2025 dose 1 (Moderna, Novavax, or Pfizer-BioNTech): ≥8 wks after last dose 2024–2025 dose 2 (Moderna, Novavax, or Pfizer-BioNTech): 6 mos (minimum interval = 2 mos) after 2024–2025 dose 1
1 Novavax dose	2	2024–2025 dose 1 (Novavax): 3–8 wks after last dose§ 2024–2025 dose 2 (Moderna, Novavax, or Pfizer-BioNTech): 6 mos (minimum interval = 2 mos) after 2024–2025 dose 1
Unvaccinated	2	2024–2025 dose 1 (Moderna or Pfizer-BioNTech): day 0 2024–2025 dose 2 (Moderna, Novavax, or Pfizer-BioNTech): 6 mos (minimum interval = 2 mos) after dose 1 or
	3	2024–2025 dose 1 (Novavax): day 0 2024–2025 dose 2 (Novavax): 3–8 wks after dose 1§ 2024–2025 dose 3 (Moderna, Novavax, or Pfizer-BioNTech): 6 mos (minimum interval = 2 mos) after dose 2

Dr. Septimus's Annotations

Covid-19 remains an important cause of morbidity and mortality, especially among adults aged ≥65 years and persons with moderate or severe immunocompromise; these persons are among those at highest risk for severe disease from Covid-19. Because SARS-CoV-2 circulates year-round and immunity from vaccination wanes, ACIP recommended a second 2024 2025 COVID-19 vaccine dose for all adults aged ≥65 years and for persons aged 6 months–64 years with moderate or severe immunocompromise, 6 months after their last dose of 2024 2025 COVID-19 vaccine (minimum interval = 2 months).

BOTTOM LINE

Advisory Committee on Immunization Practices (ACIP) recommended that all persons aged ≥65 years and persons aged 6 months–64 years with moderate or severe immunocompromise receive a second 2024–2025 Covid-19 vaccine dose 6 months after their last dose. These recommendations were based on persistent SARS-CoV-2 circulation throughout the year, higher risk for severe illness attributable to Covid-19 in adults aged ≥65 years and persons with moderate or severe immunocompromise.

30

Comparative effectiveness of treatments for recurrent Clostridioides difficile infection: a network meta-analysis of randomized controlled trials.

Frontiers in Pharmacology 2024; Vol. 15: 1430724
DOI: 10.3389/fphar.2024.1430724

A Bayesian network meta-analysis (NMA) of randomized control trials up to March 2024 was performed to investigate the efficacy of rCDI interventions. Seventeen trials were included, comprising 4,148 CDI patients with ten interventions, including fecal microbiota transplantation (FMT) by lower gastrointestinal (LGI), FMT by upper gastrointestinal (UGI), Autologous FMT (AFMT), vancomycin + FMT, vancomycin, placebo, fidaxomicin, Vowst (SER109), Rebyota (RBX2660), and monoclonal antibody. NMA showed that FMT by LGI had the highest efficacy in treating rCDIs with an odds ratio (95% confidence interval) of 32.33 (4.03, 248.69) compared with placebo. FMT by UGI also showed high efficacy, whereas the efficacy comparison between FMT by LGI and UGI was not statistically significant (ORs) (95% CI), 1.72 (0.65, 5.21). The rankogram and surface under the cumulative ranking curve(SUCRA)also showed FMT by LGI ranked at the top and FMT by UGI ranked second in the curative effect.

Other treatments evaluated in the study, including vancomycin, fidaxomicin, vancomycin plus FMT, placebo, and monoclonal antibodies, were found to be less effective for rCDI. Antibiotics like vancomycin and fidaxomicin showed lower efficacy, possibly due to their impact on the gut microbiota. New microbiota-based therapies, such as Vowst (SER109) and Rebyota (RBX2660), showed some potential but require further investigation.

Dr. Septimus's Annotations

The investigators ranked the treatments based on their effectiveness in treating rCDI and the safety profiles of each therapy. (1) FMT (LGI route); (2) FMT (UGI route); (3) Vowst; (4) Rebyota; (5) Fidaxomicin; (6) Autologous FMT; (7) Monoclonal Antibodies (Bezlotoxumab); (8) Vancomycin/ Placebo. Based on this review antibiotic therapy is the least effective for CDI patients, not only prone to relapse of CDI after discontinuation of antibiotics but also leading to low microbial diversity (i.e., dysbiosis) due to antibiotic exposure, impairing colonization resistance, which is a major function of a healthy microbiome. Fidaxomicin and vancomycin relieve symptoms by killing C. difficile, however, antibiotics did not affect dormant C. difficile spores, which rapidly germinated to become toxin-producing vegetative bacteria when dysbiosis persisted after cessation of treatment. Fidaxomicin and vancomycin

have comparable results in initial response, but fidaxomicin is associated with lower risk of rCDI. [N. Engl. J. Med. 364:422–431] Firmicutes and Bacteroidetes are the two dominant phyla in the gastrointestinal microbiota, while pro inflammatory proteobacteria account for a limited proportion of the healthy microbiota (Eckburg et al., 2005). Depletion of Firmicutes and their metabolites promoted the recurrence of CDI. Primary and secondary bile acids (BAs) play an essential role in the life cycle of C. difficile. Primary BA synthesized in the liver is secreted into the intestine and converted into secondary BA by commensal microorganisms. Primary BA promotes Clostridioides difficile germination of spores, whose vegetative growth is inhibited by certain secondary BAs. [PloS One 2016; 11 (1), e0147210] The concentration imbalance between primary BA and secondary BA leads to an increase in relative concentration, which provides favorable conditions for spore germination, bacterial replication, and toxin production [Annu. Rev. Microbiol. 2015; 69, 445–461] Therefore, the supplementation of firmicutes[FMT] is necessary, and the restoration of microbial diversity through microbial therapy can ensure the balance of BA and the germination and vegetative growth of spores, which also makes up for the fact that antibiotics can only kill C. difficile but are ineffective against spores' shortcomings.

Despite its significant benefits, FMT's safety is a concern due to the lack of standardized FDA compliant manufacturing and oversight.

BOTTOM LINE

This review demonstrates FMT's significant efficacy in rCDI(recurrent C difficile infection) management, regardless of administration route (lower or upper gastrointestinal). Antibiotics and monoclonal antibody treatments are less effective in managing rCDI, potentially due to disruptions in gut microbiota.

31

Estimated Effectiveness of Influenza Vaccines in Preventing Secondary Infections in Households

JAMA Network Open 2024; Vol. 7, Iss. 11: e2446814
DOI: 10.1001/jamanetworkopen.2024.46814

The investigators wanted to determine the estimated effectiveness of influenza vaccines in preventing secondary infections after influenza was introduced into households. During 3 consecutive influenza seasons (2017-2020), primary cases (the first household members with laboratory-confirmed influenza) and their household contacts in Tennessee and Wisconsin were enrolled into a prospective case-ascertained household transmission cohort study. Participants collected daily symptom diaries and nasal swabs for up to 7 days. Data were analyzed from September 2022 to February 2024. Specimens were tested using PCR to determine influenza infection. Longitudinal chain binomial models were used to estimate secondary infection risk and the effectiveness of influenza vaccines in preventing infection among household contacts overall and by virus type and subtype and/or lineage. Vaccination history were verified through review of medical and registry records.

In this case-ascertained cohort study of 699 primary cases and 1581 household contacts, the secondary infection risk of influenza infection among household contacts was18.8% (95%CI,15.9%to22.0%). The estimated effectiveness of influenza vaccines for preventing secondary infections among household contacts was 21.0%(95%CI,1.4%to 36.7%).The median age of participants with primary infections was 13 years, 54.5% were female, and 49.1% were vaccinated against flu. The median age in household contacts was 31 years, 52.7% were female, 50.1% were vaccinated, and 22.5% were diagnosed as having flu during follow-up. The median interval between index and secondary cases was 3 days. They did not collect acute and convalescent serum specimens to supplement detection of infections of systematically collected respiratory specimens or to assess the role of baseline immunological status on the susceptibility to infection. They were also not able to assess the effectiveness of specific vaccine formulations (e.g., high-dose vaccines).

Table 3. Vaccine Effectiveness Against Influenza Infection Among Household Contacts, Influenza Transmission Evaluation Study, Middle Tennessee and Central Wisconsin, 2017 to 2020[a]

Characteristic	Influenza A			Influenza B		
	Proportion of contacts infected, No./total No. (%)		Adjusted vaccine effectiveness (95% CI)	Proportion of contacts infected, No./total No. (%)		Adjusted vaccine effectiveness (95% CI)
	Vaccinated	Unvaccinated		Vaccinated	Unvaccinated	
Overall	134/534 (25.1)	133/486 (27.4)	5.0 (−22.3 to 26.3)	25/258 (9.7)	64/303 (21.1)	56.4 (30.1 to 72.8)
Age group						
<5 y	20/49 (40.8)	18/36 (50.0)	34.6 (−18.5 to 63.9)	6/28 (21.4)	4/20 (20.0)	−10.7 (−306.7 to 69.9)
5-17 y	39/165 (23.6)	59/183 (32.2)	23.8 (−18.7 to 51.1)	9/66 (13.6)	32/101 (31.7)	88.4 (75.1 to 94.6)
18-49 y	50/234 (21.4)	46/222 (20.7)	−13.1 (−71.6 to 25.5)	6/124 (4.8)	26/160 (16.3)	70.8 (28.5 to 88.1)
≥50 y	25/86 (29.1)	10/45 (22.2)	−44.9 (−210 to 32.3)	4/40 (10.0)	2/22 (9.1)	−58.7 (−798 to 71.9)
Site						
Central Wisconsin	73/270 (27.0)	85/304 (28.0)	0 (−39.1 to 28.2)	13/115 (11.3)	45/181 (24.9)	59.7 (24.4 to 78.5)
Middle Tennessee	61/264 (23.1)	48/182 (26.4)	16.5 (−23.7 to 43.7)	12/143 (8.4)	19/122 (15.6)	44.0 (−18.8 to 73.6)
Season						
2017-2018	16/96 (16.7)	16/77 (20.8)	21.6 (−61.4 to 62)	5/69 (7.2)	7/76 (9.2)	14.7 (−175.9 to 73.6)
2018-2019	71/258 (27.5)	58/243 (23.9)	−14.0 (−63.6 to 20.6)	0/41	1/26 (3.8)	NA[b]
2019-2020	47/180 (26.1)	59/166 (35.5)	24.4 (−13 to 49.5)	20/148 (13.5)	56/201 (27.9)	57.8 (28.2 to 75.1)

Abbreviation: NA, not applicable.

[a] Overall influenza type and/or subtype-specific vaccine effectiveness estimates were estimated using longitudinal chain binomial models and accounted for age group, site, household size, and season as appropriate. Other vaccine effectiveness estimates accounted for the other variables included in the table, as appropriate.

[b] Indicates estimates cannot be obtained due to 0 events.

Dr. Septimus's Annotations

This study showed that following introduction of influenza virus infections in households, there is a high risk of transmission to household members. During the study period, influenza vaccination was associated with a reduced risk of laboratory-confirmed influenza virus infection, especially influenza B virus. The estimates of VE against any influenza virus infection in the present study were lower than those generated from surveillance of medically attended illness. Previous cohorts have demonstrated VE against symptomatic laboratory-confirmed influenza acquired from community but not household settings. [Clin Infect Dis. 2013; 56:1363-1369] Lower VE in household settings suggests that additional measures should be considered to prevent the spread of influenza once it is introduced into the household if the goal is to prevent secondary infections

Complementary preventive measures could include isolation of ill household members, improved ventilation, hand hygiene, disinfection of surfaces, use of masks and covering coughs and sneezes, and antiviral prophylaxis.

BOTTOM LINE

This study demonstrated that following introduction of influenza virus infections in households, there is a high risk of transmission to household members. Children were commonly identified as primary cases and contact household children experienced the highest risk of secondary infection.

32

CDC Confirms First Severe Case of H5N1 Bird Flu in the United States

December 18, 2024

The CDC on Wednesday confirmed the first severe case of bird flu in the US. According to the CDC, a person in Louisiana was hospitalized with a severe case of avian influenza A(H5N1) virus infection after having contact with sick and dead birds in backyard flocks.

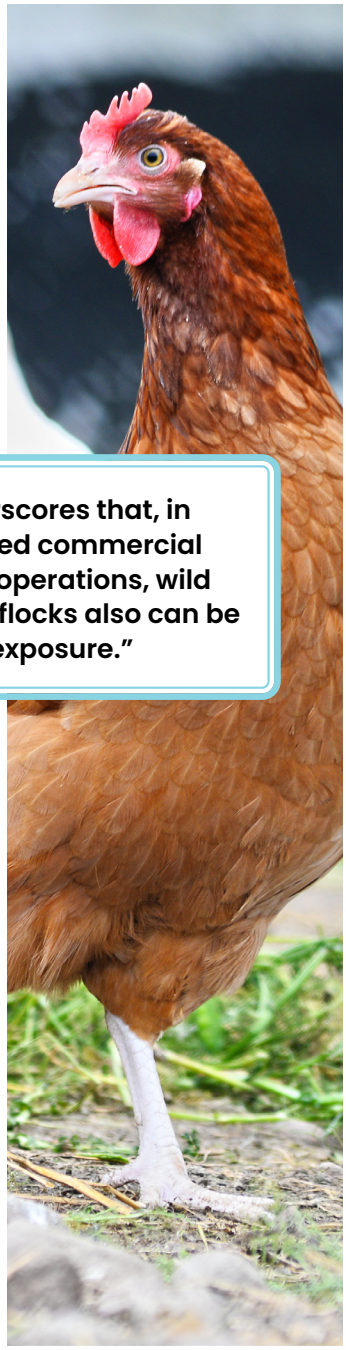
Although 61 total human cases of bird flu have been reported in the US since April, this is the first time a person has become severely ill, the CDC said. It was the first ever US case of H5N1 linked to backyard flock exposure.

Partial genetic testing of the virus showed that it is related to other H5N1 viruses recently detected in wild birds and poultry in the US and some human cases in British Columbia and Washington state, according to the CDC.

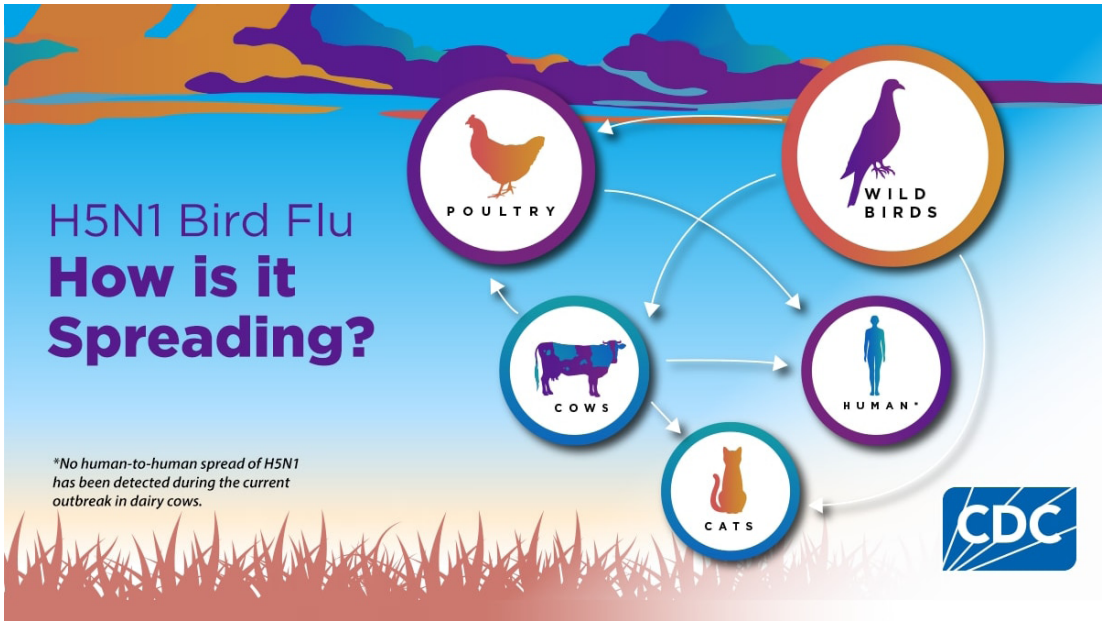
The CDC said no person-to-person transmission of H5N1 bird flu has been detected and that it considers the immediate risk to the public remains low.

Among the 60 other confirmed human cases of H5N1 in the US this year, 37 were linked to exposure to infected dairy cattle herds — including through raw milk — 21 had contact with sick birds at poultry farms, and two cases had unknown exposures. In all, 49 states have had bird flu outbreaks in poultry, and 16 have reported outbreaks in dairy cows.

This case underscores that, in addition to affected commercial poultry and dairy operations, wild birds and backyard flocks also can be a source of exposure.



"This case underscores that, in addition to affected commercial poultry and dairy operations, wild birds and backyard flocks also can be a source of exposure."



Dr. Septimus's Annotations

Partial viral genome data of the H5N1 avian influenza virus that infected the patient in Louisiana indicates that the virus belongs to the D1.1 genotype related to other D1.1 viruses recently detected in wild birds and poultry in the US and in recent human cases in British Columbia, Canada, and Washington state. This H5N1 bird flu genotype is different than the B3.13 genotype detected in dairy cows, sporadic human cases in multiple states, and some poultry outbreaks in the US.

This case underscores that, in addition to affected commercial poultry and dairy operations, wild birds and backyard flocks also can be a source of exposure. Infected birds shed avian influenza A viruses in their saliva, mucous, and feces. Other infected animals may shed avian influenza A viruses in respiratory secretions and other bodily fluids (e.g., in

unpasteurized cow milk or 'raw milk'). Because of this, the CDC recommended that backyard flock owners, hunters and other bird enthusiasts take precautions against infection, including avoiding contact with sick or dead animals, wearing personal protective equipment when contact cannot be avoided, and not touching surfaces or materials contaminated with saliva, mucous or animal feces from birds or other animals with confirmed or suspected bird flu.

BOTTOM LINE

Public health officials are increasingly concerned that a version of H5N1 could be our next pandemic. The virus is now widespread in wild birds and for months the virus has circulated in dairy cattle and poultry. Last week the Department of Agriculture announced they would begin testing the nation la milk supply to help identify infected herds.