

# Le Infezioni Nosocomiali:

## Evidenze emergenti per una gestione ottimale

**ANTONIO VENA**

Clinical Infectious Diseases

University of Genoa

San Martino Polyclinic Hospital- Genoa, Italy



Università degli Studi di Genova  
Dipartimento di Scienze della Salute (DISSAL)  
Genoa, Italy

Clinica Malattie Infettive  
Ospedale Policlinico San Martino IRCCS  
Genoa, Italy



# Disclosures

- Research grants/speaker

- MSD
- Gilead
- Astellas
- Pfizer
- Menarini
- Shionogi



Università degli Studi di Genova  
Dipartimento di Scienze della Salute (DISSAL)  
Genoa, Italy

Clinica Malattie Infettive  
Ospedale Policlinico San Martino IRCCS  
Genoa, Italy



# Patient safety in the healthcare

SPECIAL ARTICLE

## The Safety of Inpatient Health Care

David W. Bates, M.D., David M. Levine, M.D., M.P.H.,

- Retrospective study; 2,800 admissions (random sample) from 11 Massachusetts hospitals in 2018.
  - AEs during hospitalization (unintentional physical harm from care requiring substantial intervention, prolonged recovery, or resulting in death): **24%!**
  - Of the 978 AEs, up to one-third were severe; 5% associated with death.
    - Adverse drug events (39%), surgical or procedural events (30.4%), patient care-related events (e.g., falls, pressure ulcers) or **health care–associated infections**.
    - LOS doubled in cases with AEs (9 days vs. 4 days).

Bates DW N Engl J Med 2023; 388: 142



Università degli Studi di Genova  
Dipartimento di Scienze della Salute (DISSAL)  
Genoa, Italy

Clinica Malattie Infettive  
Ospedale Policlinico San Martino IRCCS  
Genoa, Italy



# 1- Nosocomial bloodstream infections and CR-BSI

Excess length of stay and readmission following hospital-acquired bacteraemia: a population-based cohort study applying a multi-state model approach



Mortensen Viggo H et al. Clinical Microbiol Infect 2023

- Longer hospital stays, higher readmission rates and increased admission, especially if the origin was intravascular
- **Cardiovascular origin**
  - Excess length of stay 18 days
  - 16% readmission rate
  - HR of discharge alive 0.2

	Count
<b>Overall</b>	<b>3457</b>
hospital-acquired bacteraemia	
Source of infection	
Thoracic, including pneumonia	124
<b>Heart and vascular</b>	<b>78</b>
Abdomen	314
Liver and biliary system	365
Urinary tract	574
Skin, soft-tissue, and bone	121
<b>Intravenous catheter</b>	<b>259</b>
Miscellaneous <sup>a</sup>	43
Unknown	1579

**URGENT NEED TO PREVENT THESE EPISODES**

# RC-BSI IN HEMODIALYSIS

- CVCs account for 20% of vascular access for HD, but they cause 70% of all BSI in this group of pts.
- In 2021, only in the USA, 36,000 CR-BSI cases.
- Hospitalization cost per episode: \$17,000–32,000.



**Taurolidine** is a broad-spectrum antimicrobial compound (Bacteria and Fungi) derived from taurine, with a unique mechanism of action that does not induce resistance.



Università degli Studi di Genova  
Dipartimento di Scienze della Salute (DISSAL)  
Genoa, Italy

Clinica Malattie Infettive  
Ospedale Policlinico San Martino IRCCS  
Genoa, Italy



# Taurolidine/Heparin Lock Solution and Catheter-Related Bloodstream Infection in Hemodialysis

A Randomized, Double-Blind, Active-Control, Phase 3 Study

- **Design:** RCT performed in 70 centers in the U.S.
- **Method:** Lock solution 13.5 mg/ml of taurolidine + 1000 U/ml of heparin (T/H) compared to standard heparin at 1000 U/ml (H).
  - After each HD session, aspirated before the next session.
- **Patients:** 795 patients undergoing chronic HD with CVC.
- **Primary outcome:** Time to CVC-related BSI infection, assessed by a blinded clinical adjudication committee.

Agarwal AK. Clin J Am Soc Nephrol 2023



Università degli Studi di Genova  
Dipartimento di Scienze della Salute (DISSAL)  
Genoa, Italy

Clinica Malattie Infettive  
Ospedale Policlinico San Martino IRCCS  
Genoa, Italy

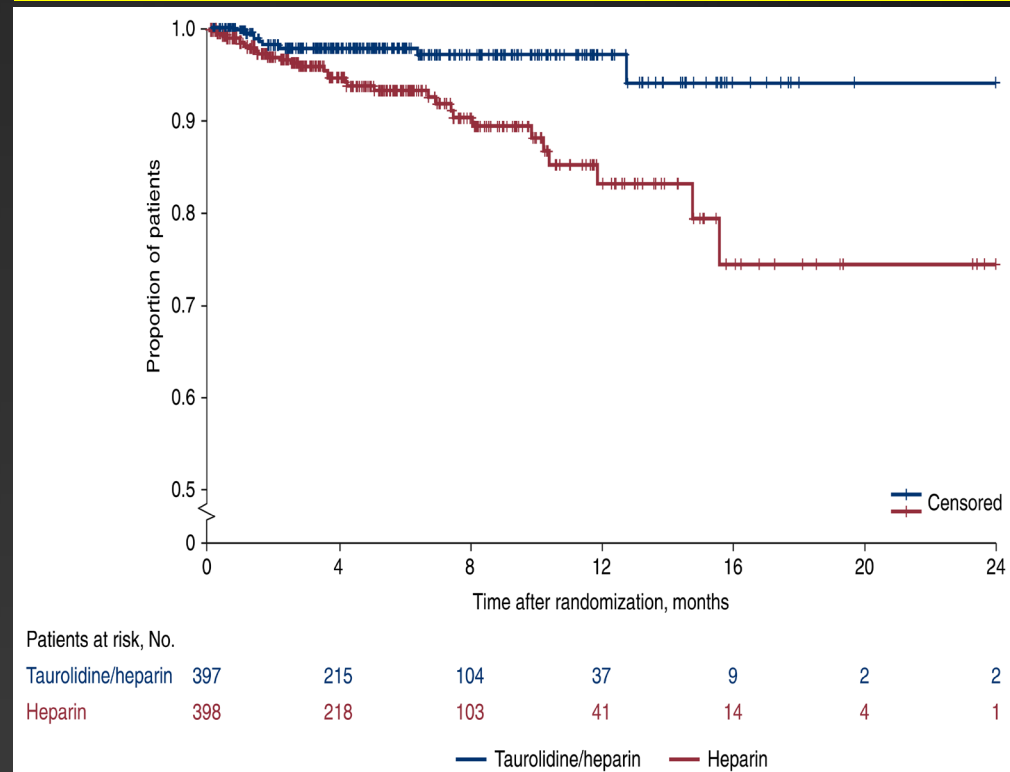




# Prevention of CVC-related BSI in HD patients

- **Results:** Early termination of the study after 44,000 CVC days due to significant outcome differences.
  - **2%** in T/H vs **7%** in H
  - BRC rates: **0.13 vs 0.46** per 1,000 CVC days in T/H and H
- No safety issues
- Similar % of CVC removals due to any reason or dysfunction

**71% reduction in CR-BSI**



Agarwal AK. Clin J Am Soc Nephrol 2023



Università degli Studi di Genova  
Dipartimento di Scienze della Salute (DISSAL)  
Genoa, Italy

Clinica Malattie Infettive  
Ospedale Policlinico San Martino IRCCS  
Genoa, Italy



# Topical gentamicin for the prevention of tunneled hemodialysis catheter-related infections: a randomized double-blind study

To compare the infection rates achieved with the application of either topical gentamicin or placebo to the exit-site of tunneled catheters filled with locking solution in chronic hemodialysis patients



**Double-blind, randomized clinical trial**



**Dialysis Center of Botucatu Medical School Hospital**



**July 2018 to August 2019.  
Followed up for at least 90 days.**



**Prevalent hemodialysis patients with chronic kidney disease, who had a long-term central venous catheter (CVC).**

91 patients  
Mean (60,4%)  
60,4 (+ 15,4) years  
Diabetes (40,7%)

The study was approved by the Research Ethics Committee of São Paulo State University-UNESP

**Intervention**

**G1: placebo to exit site**  
N= 50



**G2: 0.1% gentamicin to exit site**  
N=41

**Primary outcomes**  
CVC-related infections

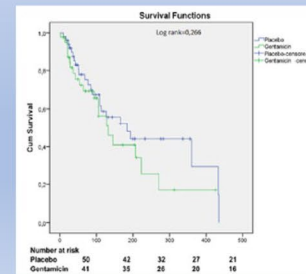
**G1:**  
ESI: 30%  
BSI: 22%



**G2:**  
ESI: 34%  
BSI: 17,1%

ESI: exit site infections  
BSI: bloodstream infection

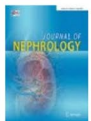
**Results**



No difference in either ESI or BSI incidence density per 1000 catheter-days- between groups

No significant difference in infection-free time (86 days) between groups

**Conclusions:** Our study showed that the application of topical 0.1% gentamicin on the exit site did not reduce the rate of infectious complications related to tunneled CVCs filled with locking solution, when compared to topical placebo in chronic kidney disease patients from a dialysis center.



**Journal of NEPHROLOGY**



Official journal of the Italian Society of Nephrology

Caetano C. J. Nephrology 2023



Università degli Studi di Genova  
Dipartimento di Scienze della Salute (DISSAL)  
Genoa, Italy

Clinica Malattie Infettive  
Ospedale Policlinico San Martino IRCCS  
Genoa, Italy





# My main messages for catheter related-BSI

---

- **The lock therapy with taurolidine/heparin compared to heparin alone was associated with a significantly lower number of CRBs in pts undergoing HD. Hemodialysis catheters should be "locked" between sessions using taurolidine-heparin.**
  - Based on this study, the FDA has approved T/H for this population.
  - The SHEA/IDSA/APIC guidelines recommend that antimicrobial lock solutions should be considered not only for these patients but also for those with **chronic CVCs at high risk of complications** (or those who have experienced recurrent CRBs and have limited vascular access).
- **The application of 0.1% topical gentamicin at the exit site of tunneled catheters filled with lock solution did NOT reduce infectious complications compared to topical placebo in patients undergoing chronic hemodialysis.**

## ***2- Staphylococcus aureus BSI***

---

- **It continues to be a critically important cause of morbidity and mortality:**
  - Annual increase of 9.4% of patients with BSI requiring ICU admission.
  - In-hospital mortality remains at 21%.
- **Efforts to reduce mortality have not been successful, and no combo therapy has proven more effective than monotherapy.**
  - New Treatments
  - Infectious disease specialist involvement is essential.

# New antibiotic therapy for *S.aureus* BSI

## ORIGINAL ARTICLE

### Ceftobiprole for Treatment of Complicated *Staphylococcus aureus* Bacteremia

T.L. Holland, S.E. Cosgrove, S.B. Doernberg, T.C. Jenkins, N.A. Turner,  
H.W. Boucher, O. Pavlov, I. Titov, S. Kosulnykov, B. Atanasov, I. Poromanski,  
M. Makhviladze, A. Anderzhanova, M.E. Stryjewski, M. Assadi Gehr,  
M. Engelhardt, K. Hamed, D. Ionescu, M. Jones, M. Saulay, J. Smart, H. Seifert,  
and V.G. Fowler, Jr., for the ERADICATE Study Group\*



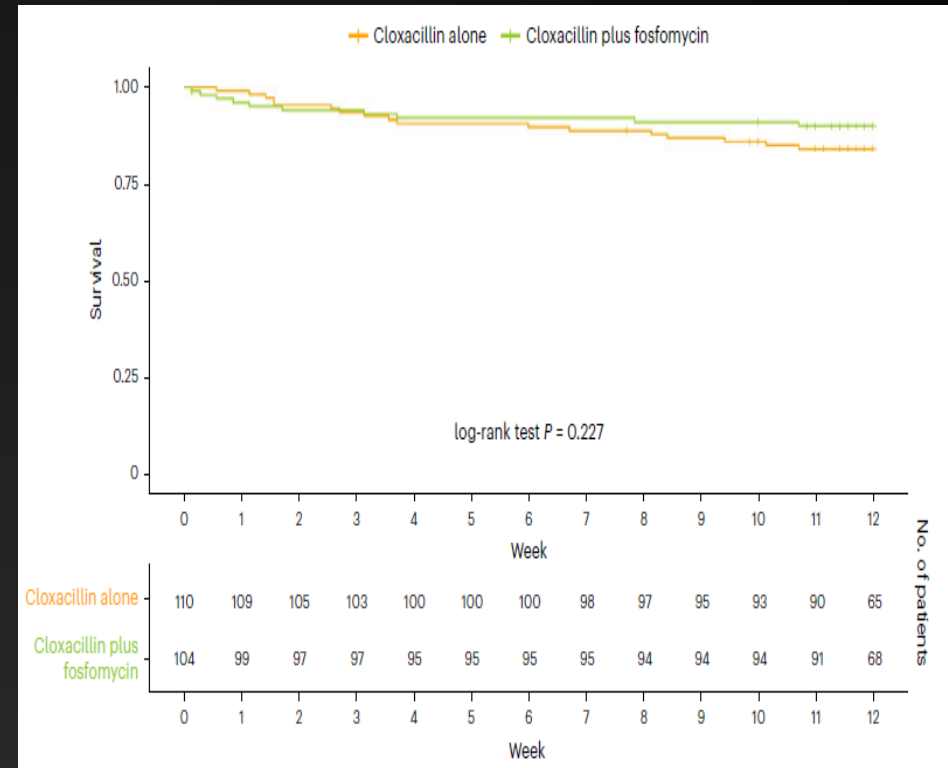
Università degli Studi di Genova  
Dipartimento di Scienze della Salute (DISSAL)  
Genoa, Italy

Clinica Malattie Infettive  
Ospedale Policlinico San Martino IRCCS  
Genoa, Italy



# Cloxacillin plus fosfomycin versus cloxacillin alone for methicillin-susceptible *Staphylococcus aureus* bacteremia: a randomized trial

- Multicenter, open-label, randomized, superiority trial
- **Primary endpoint:** Success at 7-day (alive, clinical improvement/stable, afebrile, and neg. BCs)
- **Success rates:** 79.8% vs 74.5%
- **Mortality and adverse events:** Similar across groups



# Comparative Effectiveness of Ceftriaxone versus Antistaphylococcal Penicillins for MSSA Bacteremia

- Ceftriaxone is often tempting to use for completing the treatment of MSSA BSI, but it is associated with a higher risk of therapeutic failure or death compared to antistaphylococcal penicillins.

**Buis et al.** Prospective cohort, 268 adults w MSSA BSI (Netherlands).

- **30-day mortality:** 8% with cloxacillin, 17% with cefuroxime (HR 1.37), and **29% with ceftriaxone** (HR 1.93).

**Yetmar et al.** Retrospective cohort, 223 adults (Mayo Clinic).

- Therapeutic failure at 90 days (mortality or microbiological recurrence): 27% for ceftriaxone vs. 9% for other regimens (HR 2.66).
- Median total treatment duration: 31 days (24 in outpatient care).





# My main messages for *S.aureus*-BSI

---

- Ceftobiprole is not inferior to daptomycin for *S. aureus* bacteremia.
- Combination therapy with cloxacillin and fosfomycin is not recommended.
- Ceftriaxone should not be used.

# 3- Ventilator associated pneumonia

- It is essential to reduce the incidence of VAP, a topic that has been debated for many years.
  - Attempts to use antimicrobials have not shown clear success.

*The NEW ENGLAND JOURNAL of MEDICINE*

ORIGINAL ARTICLE

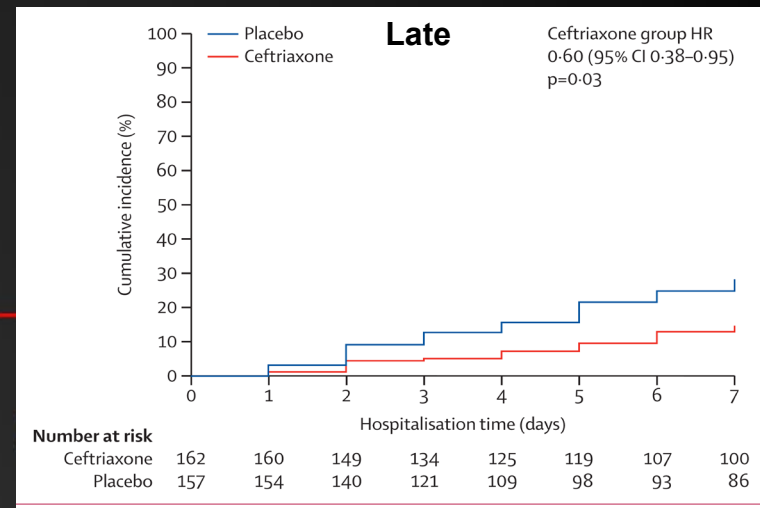
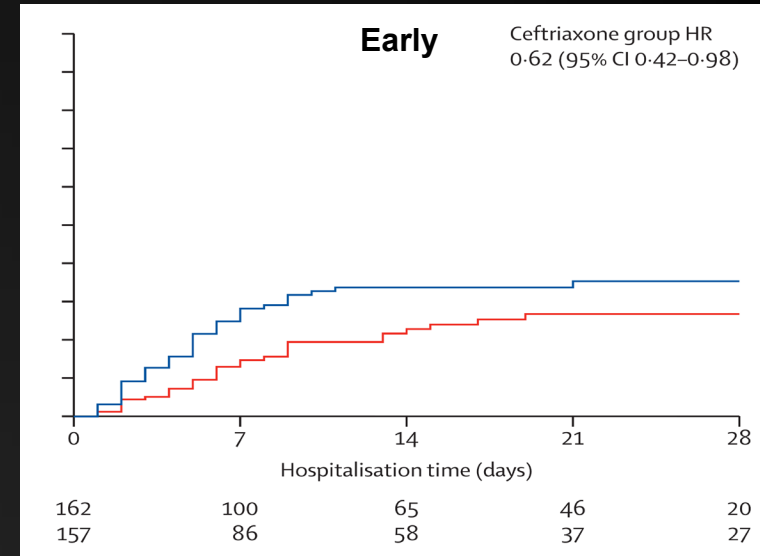
## Inhaled Amikacin to Prevent Ventilator-Associated Pneumonia

Stephan Ehrmann, M.D., Ph.D., François Barbier, M.D., Ph.D., Julien Demiselle, M.D.,

# Ceftriaxone to prevent early ventilator-associated pneumonia in patients with acute brain injury: a multicentre, randomised, double-blind, placebo-controlled, assessor-masked superiority trial

## PROPHY-VAP Trial

- Early single injection of ceftriaxone to prevent early VAP in **acute brain injury patients**.
  - **14% vs. 32%**; HR 0.60, P = 0.030.
  - Decreased exposure to antibiotics.
  - Reduced hospital and ICU stay.
  - Increased 28-day survival.
  - No local or systemic side effects during ICU stay.



Dahyot-Fizelier C. Lancet Respir Med 2024



Università degli Studi di Genova  
Dipartimento di Scienze della Salute (DISSAL)  
Genoa, Italy

# My main messages for VAP

---

- In mechanically ventilated patients ( $\geq 72$  hours), 3 days of inhaled amikacin reduced VAP incidence over 28 days of follow-up.
  - The trial lacked sufficient power to assess other outcomes, such as mortality or LOS, or to demonstrate the impact of inhaled amikacin on reducing resistance pressure.
- A single dose of ceftriaxone reduced early ventilator-associated pneumonia and **28-day mortality** in patients with acute brain injury and was well-tolerated.

## 4- Post- Surgical site Infections

---

- Surgical site infections are common and associated with increased mortality and healthcare costs, estimated at \$10 billion annually in the US
- Postoperative infection, especially deep incisional or periprosthetic, is particularly concerning in total knee arthroplasty (TKA) or total hip arthroplasty (THA).
- Addressing methicillin-resistant staphylococci in surgeries with prosthetic material is a critical and challenging question for ID physicians



# Trial of Vancomycin and Cefazolin as Surgical Prophylaxis in Arthroplasty

- **Objective:** To evaluate whether adding vancomycin to cefazolin prophylaxis provides additional benefit (by covering MR- MSSA).
- **Design:** Multicenter, double-blind, placebo-controlled, superiority trial.
- **Patients:** adults w/o known MRSA colonization undergoing arthroplasty in 11 Australian centers.
  - 1.5 g of vancomycin or placebo in addition to cefazolin prophylaxis.
  - Pre-operative nasal and groin cultures.
- **Primary Endpoint:** Surgical site infection within **90 d** post-surgery.

Peel TN. N Engl J Med 2023; 389: 1488-98



Università degli Studi di Genova  
Dipartimento di Scienze della Salute (DISSAL)  
Genoa, Italy

Clinica Malattie Infettive  
Ospedale Policlinico San Martino IRCCS  
Genoa, Italy



# Study population

- 4239 patients-50% TKA and 50% THA
- Diabetes mellitus: approximately 12% in both study groups



Peel TN. N Engl J Med 2023; 389: 1488-98



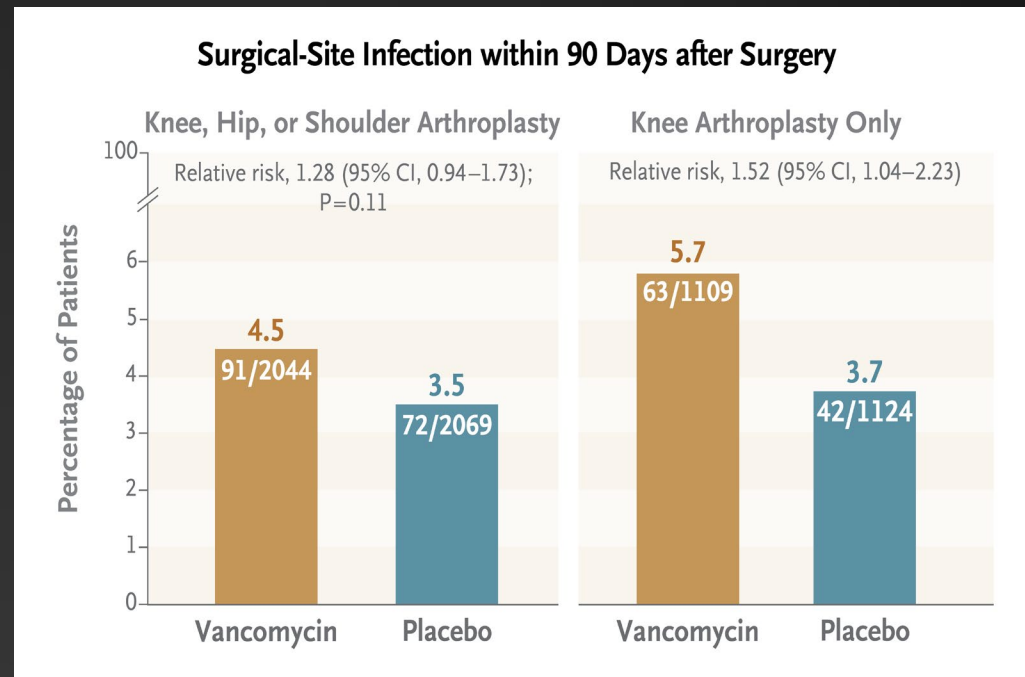
Università degli Studi di Genova  
Dipartimento di Scienze della Salute (DISSAL)  
Genoa, Italy

Clinica Malattie Infettive  
Ospedale Policlinico San Martino IRCCS  
Genoa, Italy



# Surgical-Site Infection within 90 Days

- Knee, hip, or shoulder : 4.5% **VAN** vs. 3.5% placebo;  $p=0.11$ .
- Knee arthroplasty only: **5.7%** **VAN** vs. 3.7% placebo.
- Hip arthroplasty only: 3% VAN vs. 3% placebo.



Potential **increase** in surgical site infection risk was noted with vancomycin in TKA

Peel TN. N Engl J Med 2023; 389: 1488-98



Università degli Studi di Genova  
Dipartimento di Scienze della Salute (DISSAL)  
Genoa, Italy

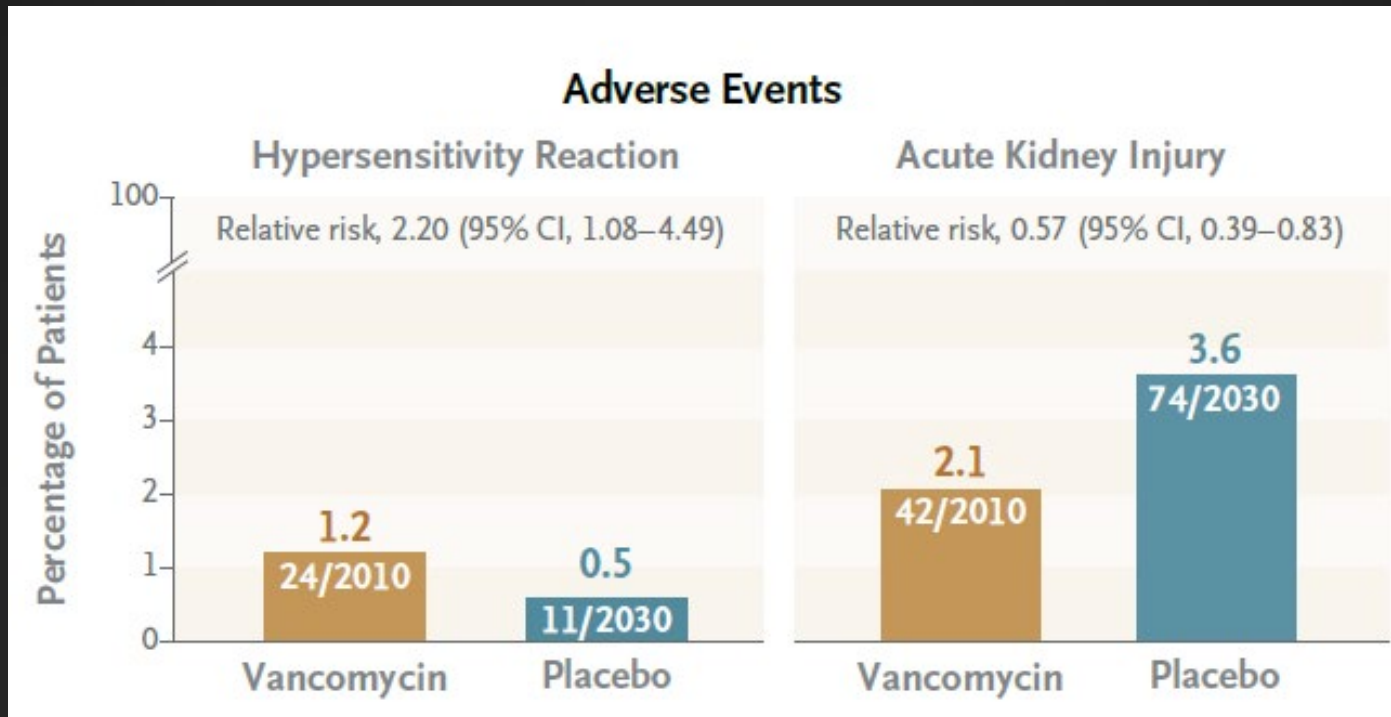
Clinica Malattie Infettive  
Ospedale Policlinico San Martino IRCCS  
Genoa, Italy



# Adverse Effects

Peel TN. N Engl J Med 2023; 389: 1488-98

## Vancomycin (1.7%) vs. Placebo (1.7%)



Vancomycin prophylaxis was associated with a higher risk of hypersensitivity reactions and a **lower risk of acute kidney injury**.



# My main messages for SSI

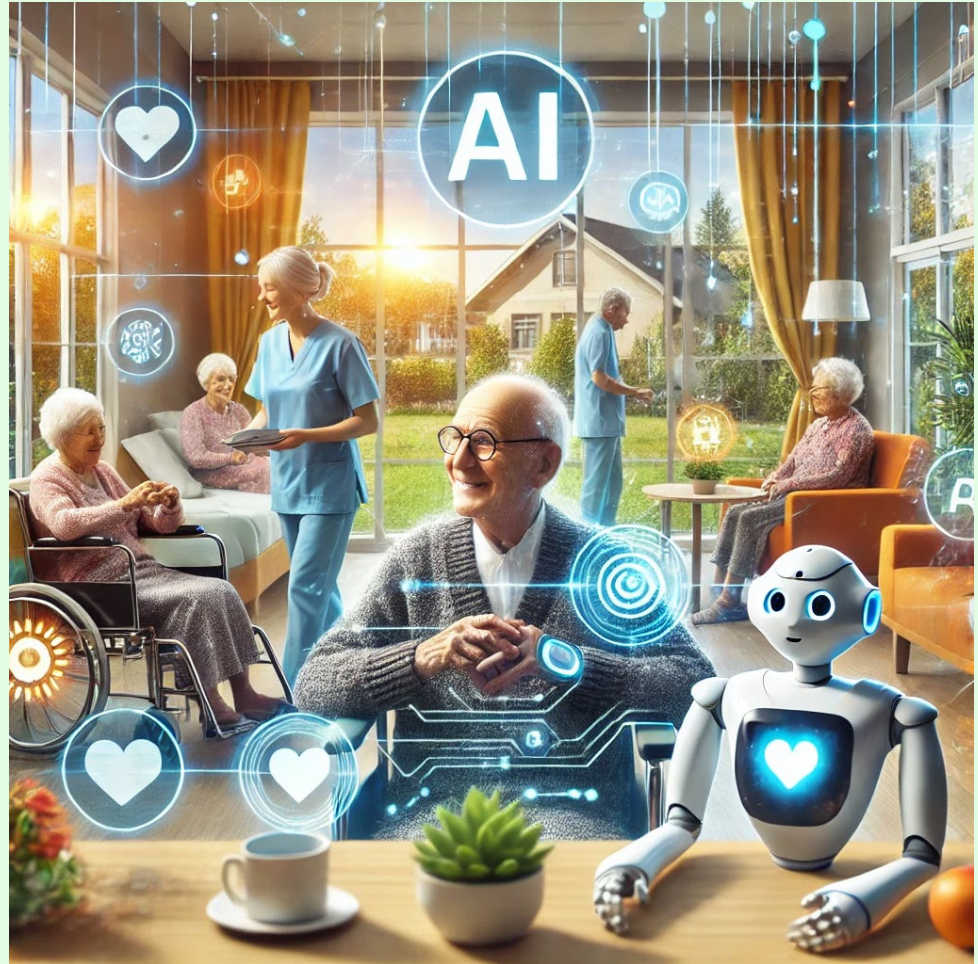
---

- In patients *without known MRSA colonization* undergoing arthroplasty, adding vancomycin to cefazolin prophylaxis DOES NOT offer superior prevention of surgical site infections.
- **Limitations:**
  - The study was interrupted due to the COVID-19 pandemic.
  - The prevalence of MRSA colonization was low, limiting the applicability to colonized patients.
  - Most surgical site infections were superficial.



# 5- Prevention of Nosocomial Infections in Older Adults

**Importance of preventing hospital admissions in the elderly population.**



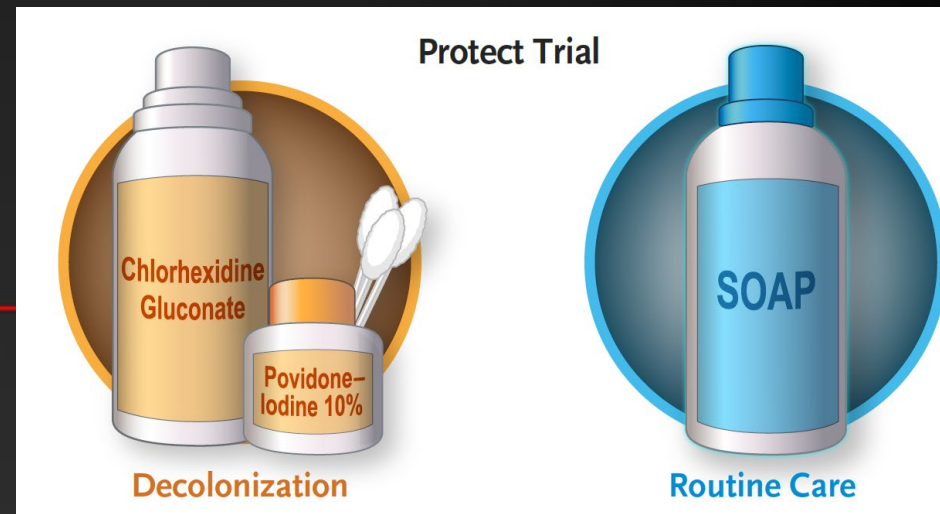
# Decolonization in Nursing Homes to Prevent Infection and Hospitalization

- **Objective:** Investigate whether systematic decolonization reduces hospital admissions.
- **Method:** Cluster-randomized trial across nursing homes.
- **Intervention:** Standard bathing/showers vs. bathing with **chlorhexidine + povidone-iodine nasal application/** 12h <5 d after admission, followed by weekly tx.
- **Timeline:** 18-m reference period, 18 months of intervention.

Miller et al. N Engl J Med 2023; 389: 1488-98



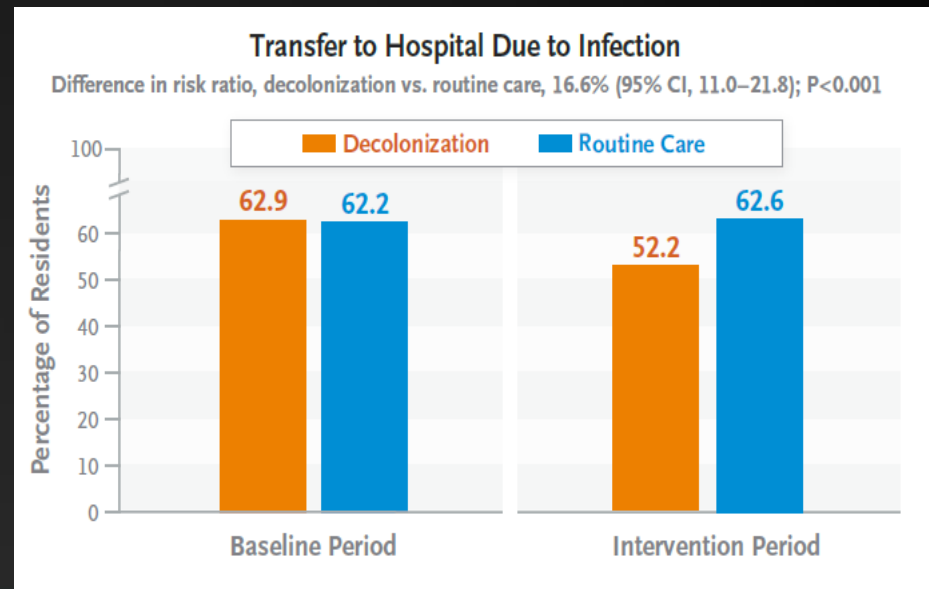
Università degli Studi di Genova  
Dipartimento di Scienze della Salute (DISSAL)  
Genoa, Italy



# Results

- **Primary Outcome:** Hospitalization due to infection.
- **Secondary Outcome:** Hospitalization for any reason.
- 28 nursing homes in California, involving 28,956 residents.

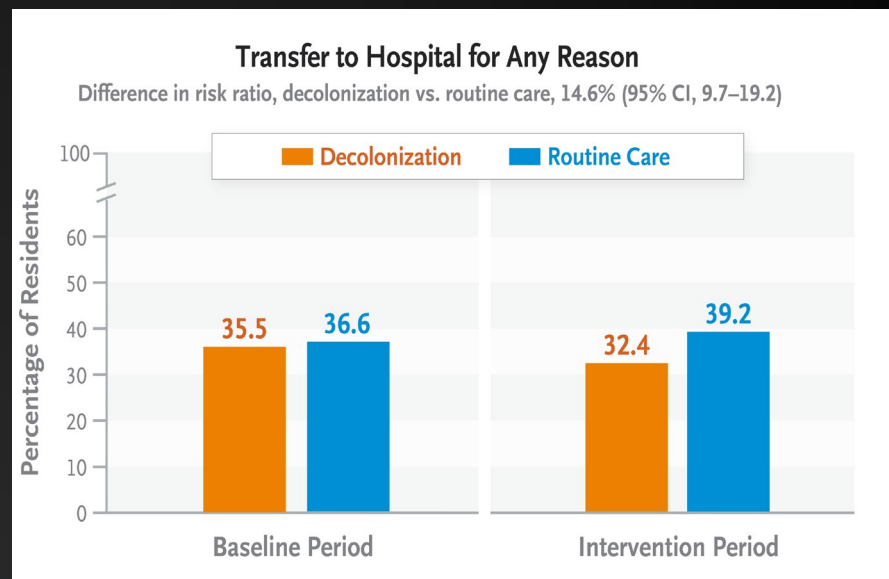
- **Hospitalization due to Infection:**
  - **Routine Care:** 62.2% vs 62.6% (RR 1.00)
  - **Decolonization Group:** 62.9% vs 52.2%. **16.6% RR reduction (95% CI: 11.0–21.8;  $P < 0.001$ ).**



# Additional Results

- **Primary Outcome:** Hospitalization due to infection.
- **Secondary Outcome:** Hospitalization for any reason.
- 28 nursing homes in California, involving 28,956 residents.

- **Hospitalization for any reason:**
  - **Routine Care:** 36.6% vs 39.2% (RR 1.08)
  - **Decolonization Group:** 35.5% vs 32.4%. 14.6% RR reduction (95% CI: 9.7–19.2)



# Number needed to treat

**NNT prevent one infection-related hospitalization: 9.7**

**A 100-bed nursing home would prevent 2 infection-related admissions per month.**

**Adverse Events:** 35 potential Aes in the decolonization group across 772,113 interventions during the study period (34 rashes).

Miller et al. N Engl J Med 2023; 389: 1488-98



Università degli Studi di Genova  
Dipartimento di Scienze della Salute (DISSAL)  
Genoa, Italy

Clinica Malattie Infettive  
Ospedale Policlinico San Martino IRCCS  
Genoa, Italy





# My main messages for older patients

---

- Chlorhexidine bathing and periodic nasal decolonization significantly reduce the risk of infection-related hospitalizations in residents of long-term care facilities.
- **Advantages over culture-based decolonization. More feasible, but:**
  - Increased material costs.
  - Facilities with intervention received more training and support from the study team.
  - Non-blinded study design.
  - Adverse effects of prolonged chlorhexidine use?