Infective Endocarditid; Role of Anti-MRSA

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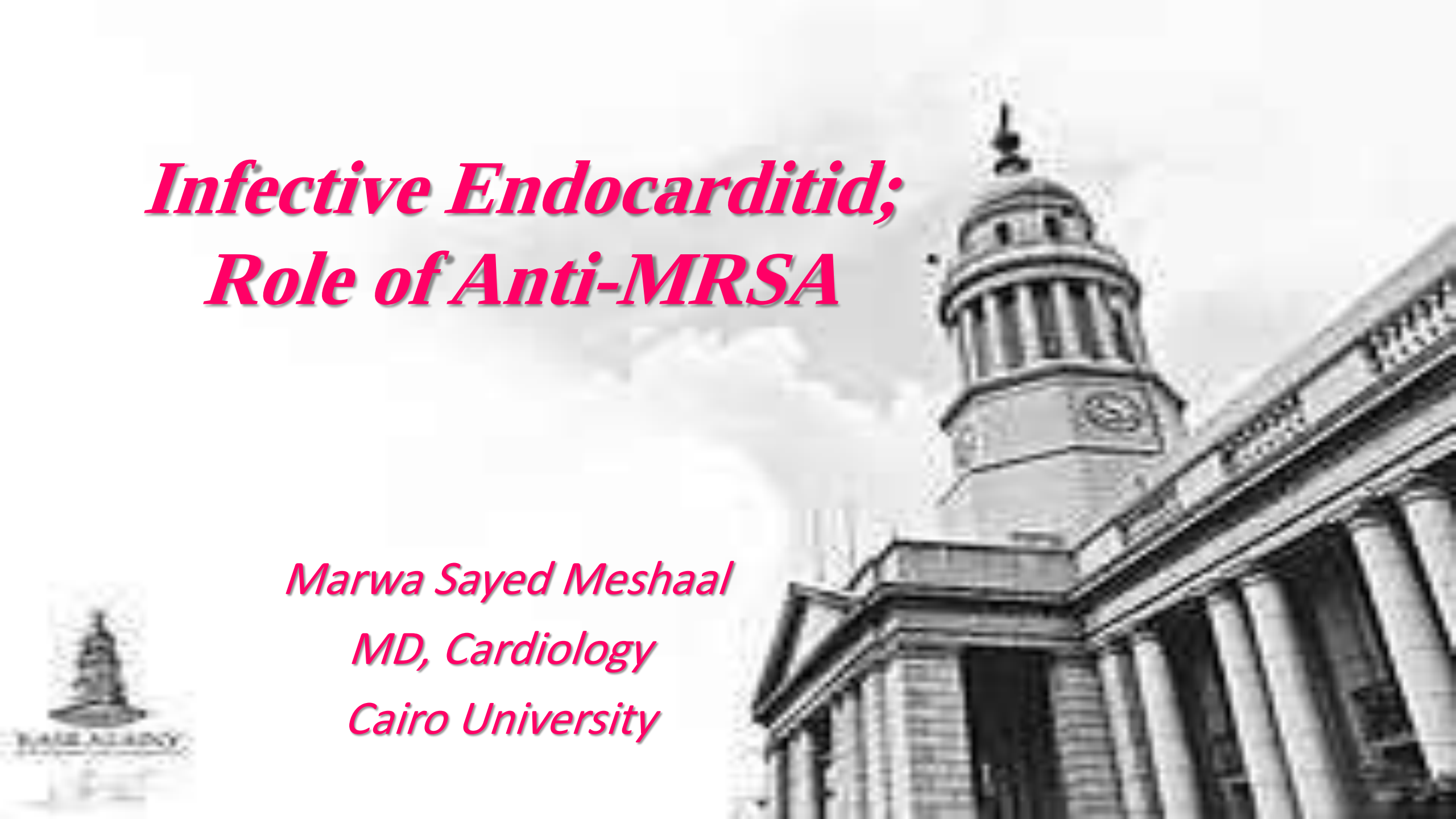

Antimicrobial Treatment

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- Corner stone in treating IE patient is complete eradication of the infective organism
- Surgery only contributes to the cure by removing the main/all bulk of the infected tissues
- Yet remains the main role for the ***antimicrobial*** to achieve complete cure
- Bactericidal/fungicidal drugs should be used
- Combination therapy are usually preferred to monotherapy to ensure eradication of tolerant organisms

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- ***Tolerant microbes*** are not resistant, they escape the drug killing effect, keep dormant and resume activity after drug discontinuation
- This explains the need for combination therapy and long term treatment
- Use of large doses for long time
- Bactericidal/ Fungicidal agents
- Parenteral route is usually required

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- So Are We Done with These Monsters ?

Unfortunately , NOT YET

With development f more drug resistance, we are in a continuous need for new potent bactericidal and fungicidal drugs

Desperate Need for New Antibiotics

- Infectious diseases have been a challenge throughout the ages
- Currently, more than 2 million North Americans acquire infections associated with antibiotic resistance every year, resulting in 23,000 deaths
- In Europe, nearly 700,000 cases of antibiotic-resistant infections directly develop into over 33,000 deaths yearly
- AMR results in reduced efficacy of antibacterials, making treatment of patients difficult, costly, or even impossible

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- Infective end … norbidity and prolonge…
- Mortality du… 5%
- Further 9% t… st year after discharge
- Thinking of …

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- Common community-acquired infections, e.g. CAP, which used to be readily treatable can be an aggressive life threatening
- With this growing risk of highly virulent community acquired infections, goes without saying the growing risk of more aggressive HCAI
- And many can be a threat to develop IE in predisposed patients
- Most antibiotic classes we have today were introduced in the 1940–1960s
- ***With current lack of new antimicrobials to replace those become ineffective more urgency is need to protect the existing ones***

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MRSA Endocarditis

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- MRSA infection goes back to 1961 when it was first described
- Occurs in by mutation of a penicillin-binding protein, a chromosome-encoded protein
- Methicillin resistance in S. aureus is defined as ***Oxacillin*** MIC≥ 4 micrograms/mL
- This resistance is transferred between S. aureus organisms by bacteriophages

- Incidence and prevalence of MRSA have been increasing dramatically, both HA-MRSA and CA-MRSA
- This organism used to respond to Vancomycin, which remains its treating drug of choice
- Decreased vancomycin sensitivity is not uncommon nowadays
    - Vancomycin intermediate sensitivity (VISA) at MIC level 2-4 mg/L
    - Vancomycin resistance (VRSA) MIC level ≥ 4mg/L

MRSA in Endocarditis

- Although the overall IE incidence has remained stable, incidence of IE caused by Staphylococcus aureus has increased
- S. aureus is now the most common causative organism in IE
- Progressive increase in rates of MRSA; both hospital and community acquired
- MRSA Endocarditis is commonly encountered with *PVE*, patients with *HAE, CDRE,* immunosuppressed patients and *IDU*
- ***Daptomycin was valuable antibiotic addition in ESC and AHA 2015 guidelines, established role in ESC 2023 IE guidelines***

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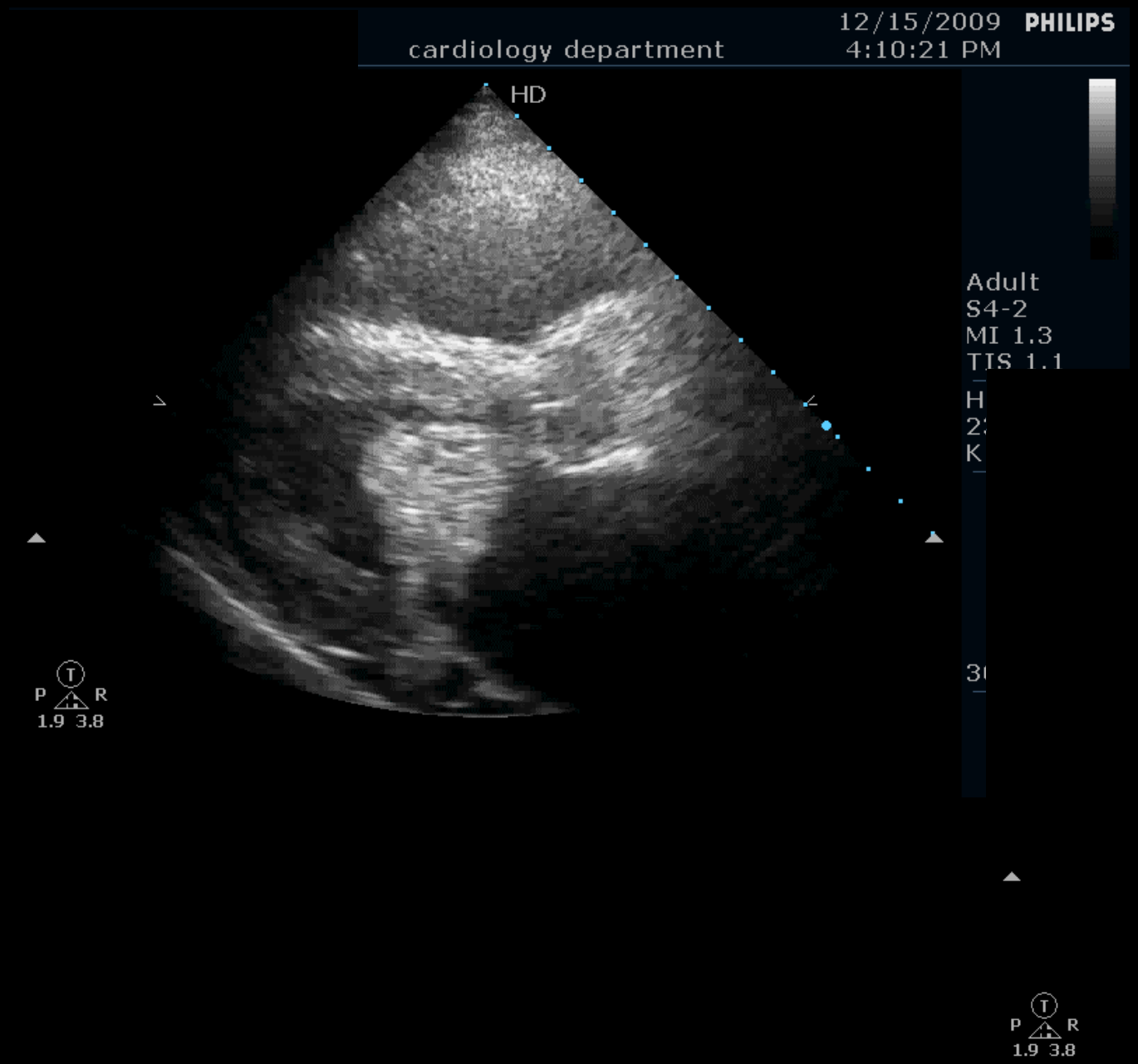
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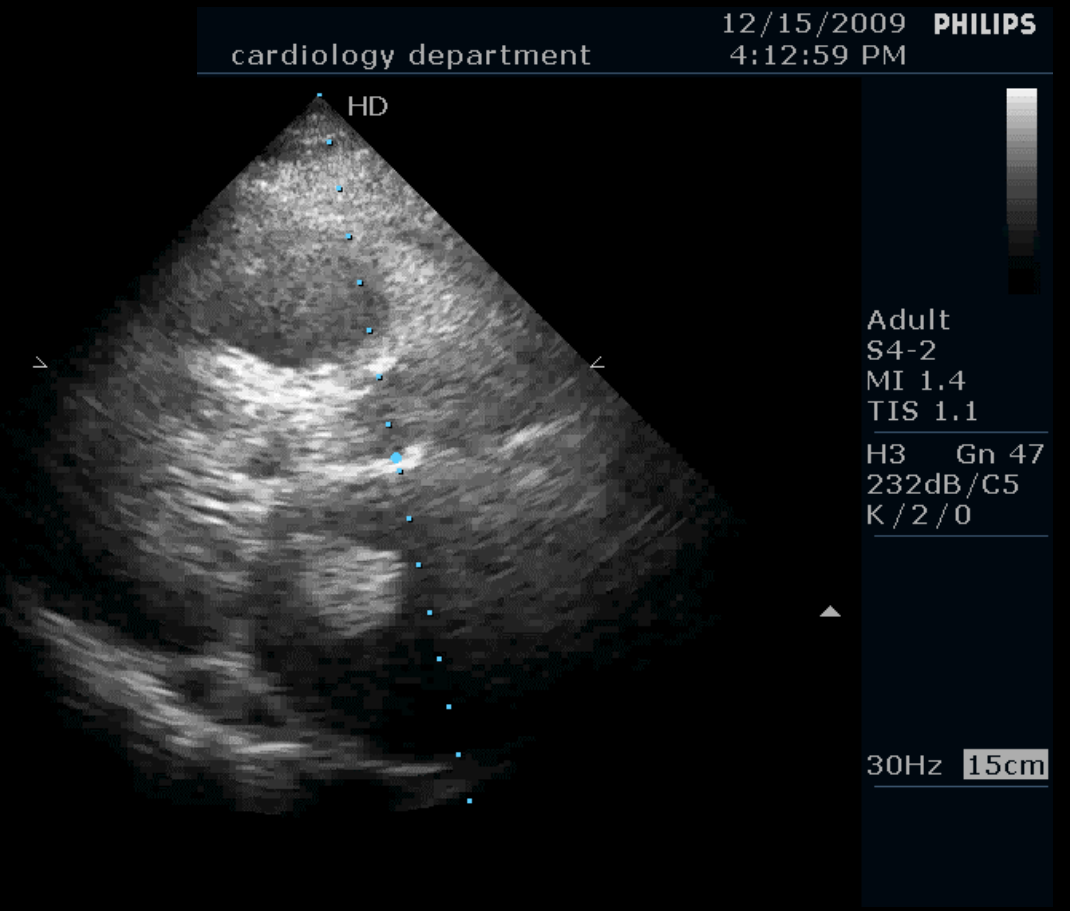
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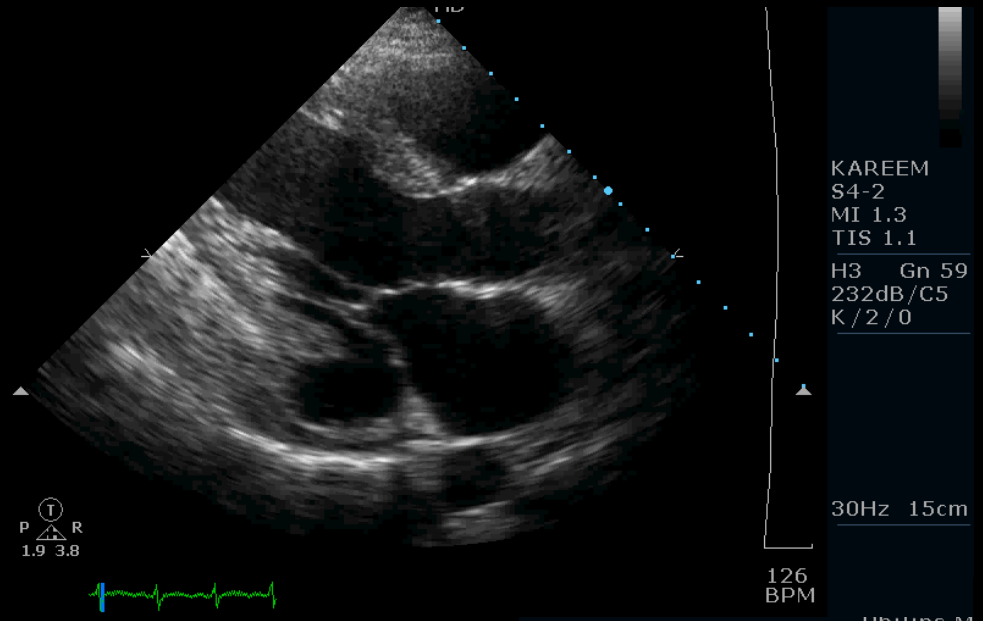
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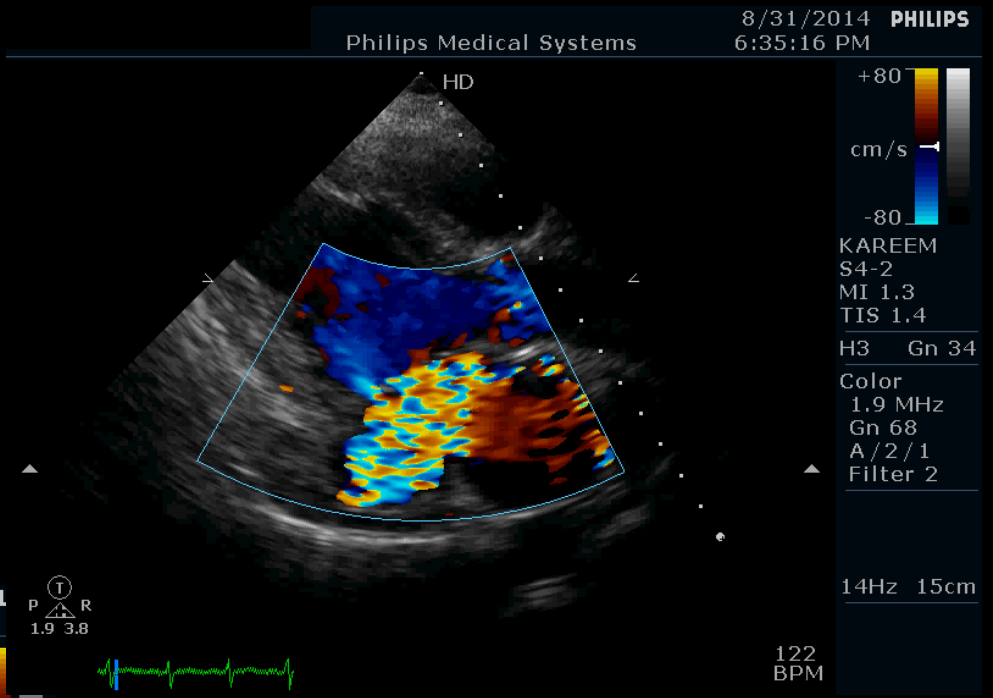
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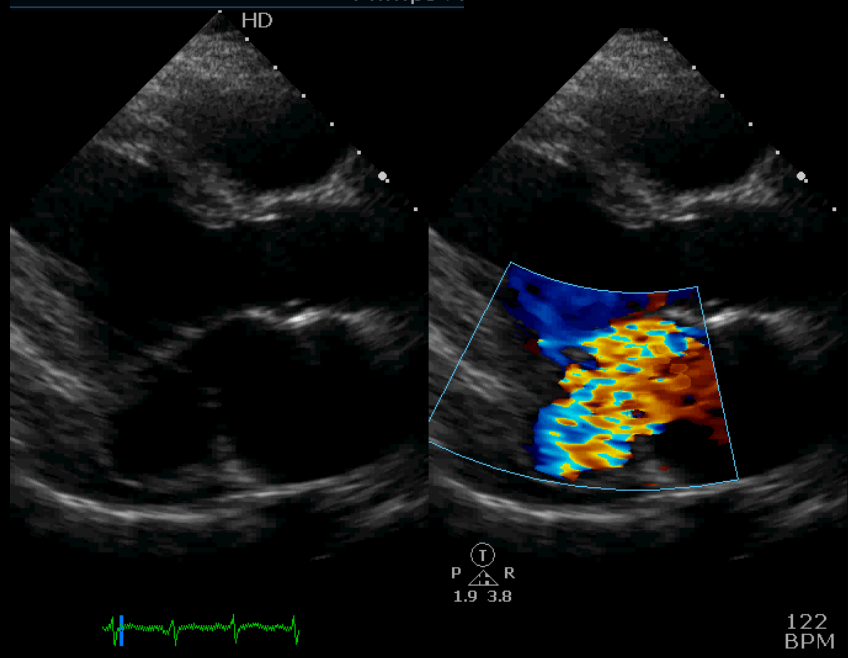
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DAPTOMYCIN

- Daptomycin is a cyclic lipopeptide
- It binds to bacterial cell membranes and causes a rapid depolarization of membrane potential
- This loss of membrane potential causes inhibition of DNA, RNA, and protein synthesis, which results in bacterial cell death
- Daptomycin exhibits rapid, concentration-dependent bactericidal activity against Gram positive bacteria
- It has the advantage of being a once-daily dosed, rapidly bactericidal

- Needs to be administered in appropriate doses and combined with other antibiotics to avoid further resistance in patients with IE
- Given at high doses (10 mg/kg), and experts recommend to add beta-lactams (ampicillin, ertapenem or ceftaroline) or Fosfomycin, or gentamicin
- Cohort studies of S. aureus and CoNS, IE have shown that daptomycin is at least as effective as vancomycin in treating IE
- And in two cohort studies of MRSA bacteraemia with high vancomycin MICs (>1 mg/L), daptomycin was associated with better outcomes including survival

2023 ESC Guidelines For the Management of Endocarditis

European Heart Journal (2023) 44, 3948–4042
https://doi.org/10.1093/eurheartj/ehad193

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Vancomycin-resistant *Enterococcus* spp.[f]			
In patients with IE due to vancomycin-resistant *Enterococcus* spp., daptomycin combined with beta-lactams (ampicillin, ertapenem, or ceftaroline) or fosfomycin is recommended using the following doses:[369]		I	C
Adult antibiotic dosage and route			
Daptomycin	10–12 mg/kg/day i.v. in 1 dose		
Ampicillin	300 mg/kg/day i.v. in 4–6 equally divided doses		
Fosfomycin	12 g/day i.v. in 4 doses		
Ceftaroline	1800 mg/day i.v. in 3 doses		
Ertapenem[g]	2 g/day i.v. or i.m. in 1 dose		
Paediatric antibiotic dosage and route			
Daptomycin	10–12 mg/kg/day i.v. in 1 dose (age-adjusted)		
Ampicillin	300 mg/kg/day i.v. in 4–6 equally divided doses		
Fosfomycin	2–3 g/day i.v. in 1 dose		
Ceftaroline	24–36 mg/kg/day in 3 doses		
Ertapenem[g]	1 g/day i.v. or i.m. in 1 dose [if younger than 12 years, 15 mg/kg/dose (to a maximum of 500 mg) twice daily]		

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III. What is the management of MRSA bacteremia and infective endocarditis?

Bacteremia and Infective Endocarditis, Native Valve

19. For adults with uncomplicated bacteremia (defined as patients with positive blood culture results and the following: exclusion of endocarditis; no implanted prostheses; follow-up blood cultures performed on specimens obtained 2–4 days after the initial set that do not grow MRSA; defervescence within 72 h of initiating effective therapy; and no evidence of metastatic sites of infection), vancomycin (**A-II**) or daptomycin 6 mg/kg/dose IV once daily (**AI**) for at least 2 weeks. For complicated bacteremia (defined as patients with positive blood culture results who do not meet criteria for uncomplicated bacteremia), 4–6 weeks of therapy is recommended, depending on the extent of infection. Some experts recommend higher dosages of daptomycin at 8–10 mg/kg/dose IV once daily (**B-III**).

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin Resistant Staphylococcus aureus Infections in Adults and Children 2011

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Drug to Drug interaction

- ***HMG-CoA Reductase Inhibitors*:**
  - Experience with the coadministration of HMG-CoA reductase inhibitors and Daptomycin for injection in patients is limited
  - may cause myopathy, which is manifested as muscle pain or weakness associated with elevated levels CPK
  - therefore, consideration should be given to suspending use of HMG-CoA reductase inhibitors temporarily in patients receiving Daptomycin

Drug-Laboratory Test Interactions

- significant concentration-dependent false prolongation of prothrombin time (PT) and elevation of International Normalized Ratio (INR) when certain recombinant thromboplastin reagents are utilized for the assay.

Safety &Adverse Drug Reactions

- ***Myopathy and Rhabdomyolysis*:**
  - increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal have been reported
  - CPK levels should be monitored regularly

- ***Eosinophilic Pneumonia:***
  - Patients developing fever, dyspnea, hypoxic respiratory insufficiency and diffuse pulmonary infiltrates or organizing pneumonia
  - Daptomycin should be discontinued immediately

- ***Drug reaction with Eosinophilia and systemic Symptoms (DRESS):***
  - Patients who develop skin rash, fever, peripheral eosinophilia, and epatic, renal, pulmonary)

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Ray Of Hope

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Thank you