L’infettivologo nell’Heart Team dell’Endocardite

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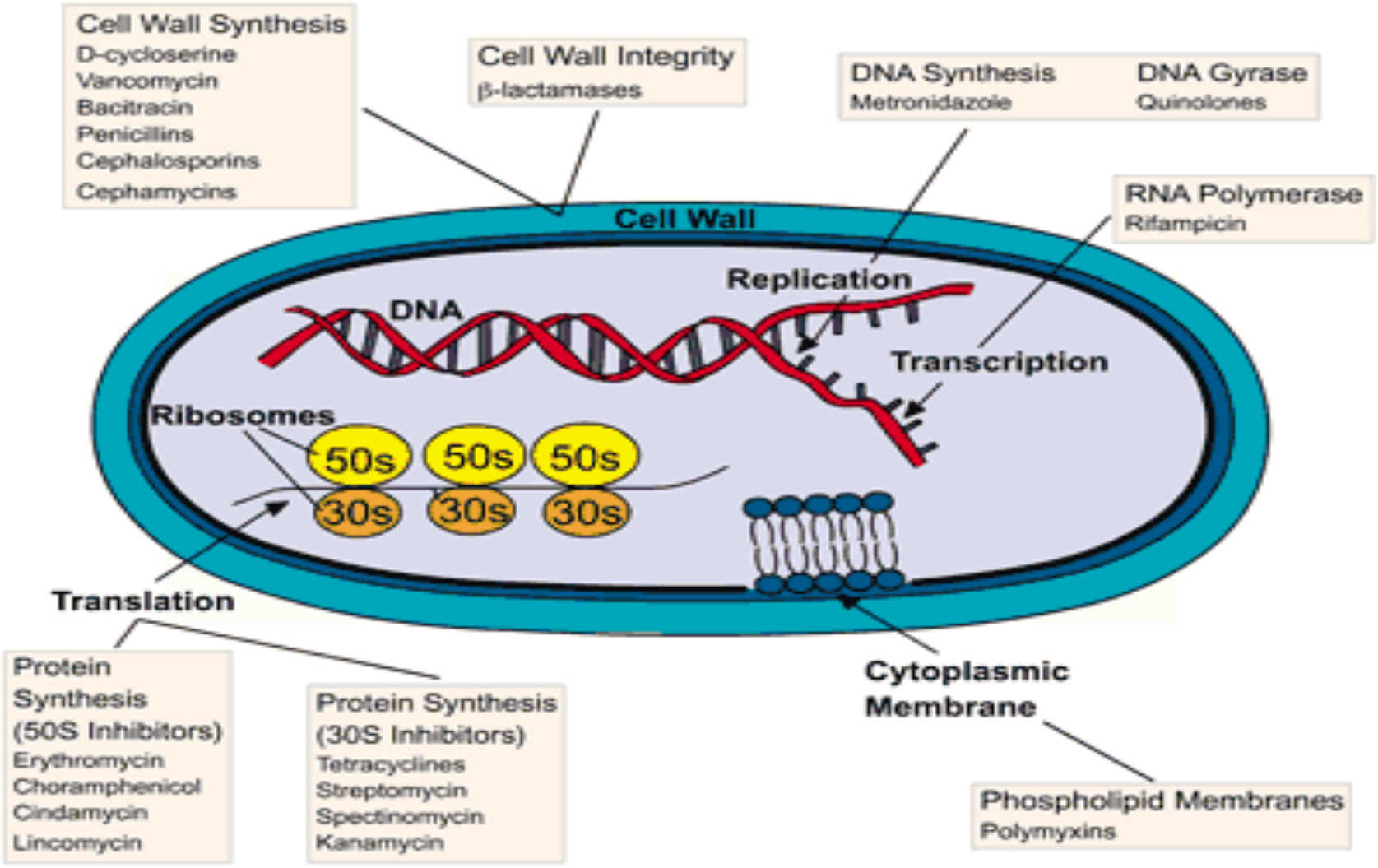
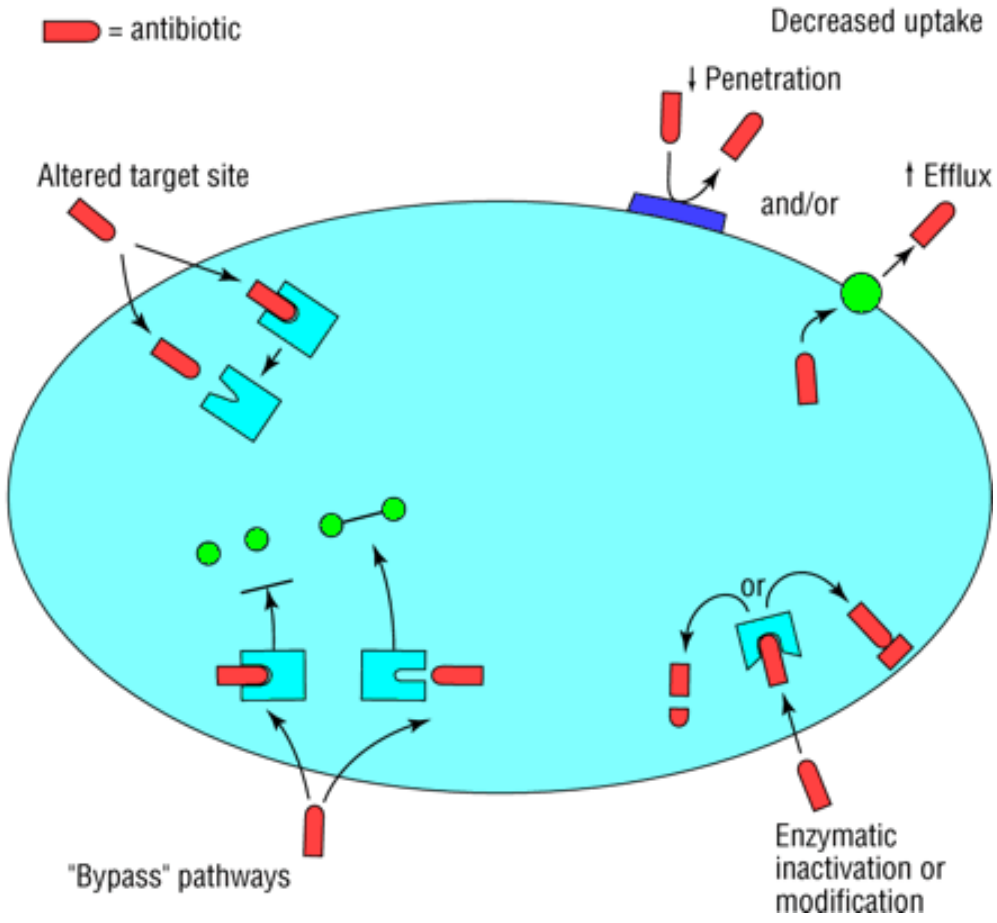
- I batteri sono sempre più resistenti ed aggressivi.

- Quanto incide il tipo di agente patogeno nella durata della terapia medica e sull'indicazione cardiochirurgica?

Antibiotics' Mechanisms of Action



Mechanisms of Resistance



- In addition to intrinsic resistance, bacteria can acquire or develop resistance to antibiotics.

- This can be mediated by several mechanisms, which fall into three main groups:
  - those that minimize the intracellular concentrations of the antibiotic as a result of poor penetration into the bacterium or of antibiotic efflux
  - those that modify the antibiotic target by genetic mutation or posttranslational modification of the target
  - those that inactivate the antibiotic by hydrolysis or modification

SOURCES OF THE RESISTANCE GENES

There are so many resistance genes that rely on many different mechanisms. Where did they come from?

History of Resistance

- Resistance mechanisms have been selected from millions of years.

- Microbes obtained from samples of Lechuguilla cave in New Mexico, an isolated cave for the past 4 million years, were found to be resistant to 14 different antibiotics.

Bhullar K, Waglechner N, Pawlowski A, Koteva K, Banks ED, Johnston MD, et al. Antibiotic resistance is prevalent in an isolated cave microbiome. PLoS One. 2012

Producing Organisms

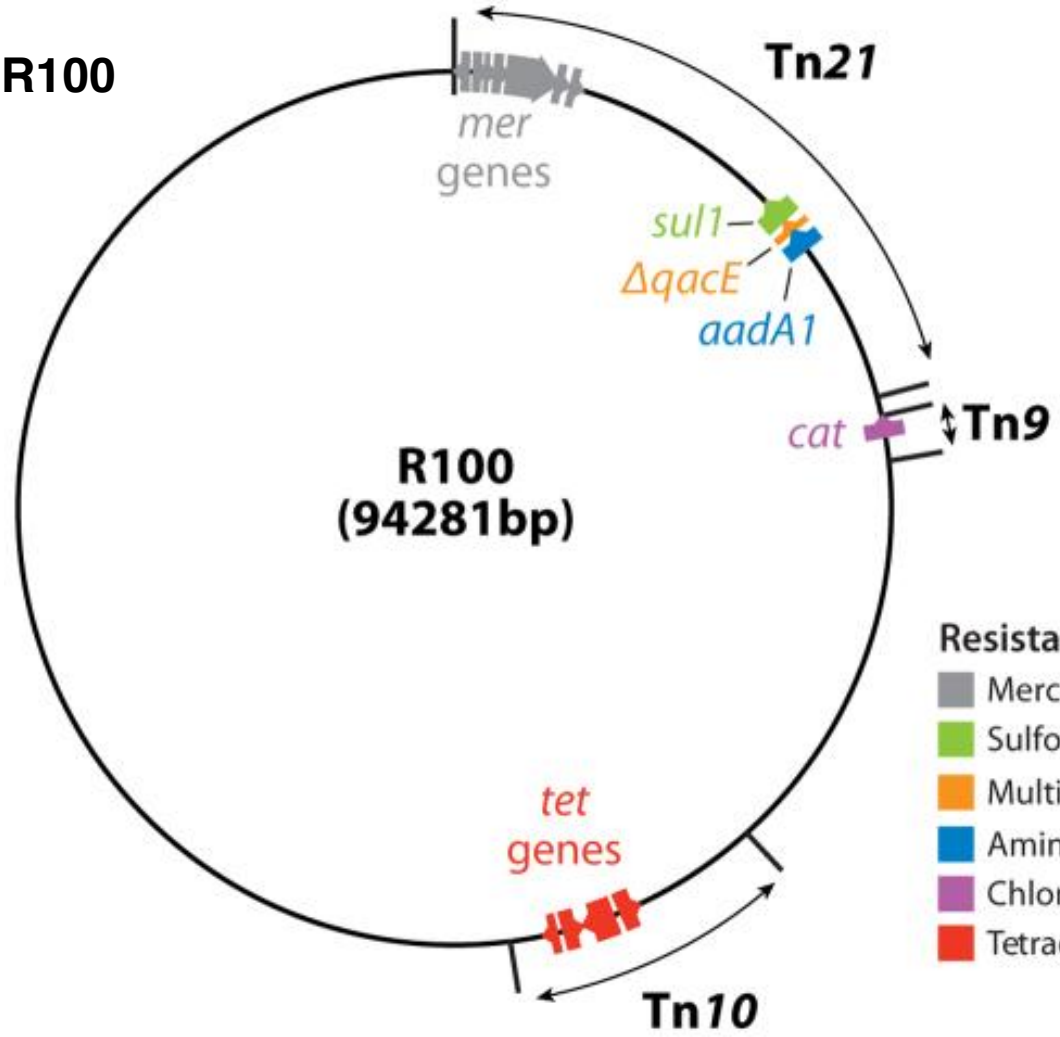
- Some of the aminoglycoside-resistant genes appear to be derived from streptomycetes producing these antibiotics.

- The genes coding for vancomycin resistance appear to originate in a similar way. the genes in the vancomycin-resistant clinical isolates of enterococci were found to be homologs of those found in the vancomycin-producing streptomycetes.

Marshall CG, Lessard IA, Park I, Wright GD. Glycopeptide antibiotic resistance genes in glycopeptide-producing organisms. Antimicrob. Agents Chemother. 1998;42:2215–20.

Transfer of Resistance

Plasmid R100



High mobility. The resistance genes when inserted into an integron become organized into a single operon, with the same orientation of transcription under a strong promoter supplied by the integron structure.

SUMMARY POINTS

- Multidrug resistance in bacteria is often caused by the accumulation of genes.
- Many of the resistance genes apparently have their evolutionary origins in the antibiotic-producing microbes.
- R plasmids are maintained extremely well and are often transferred efficiently from cell to cell.
- Another mechanism of multidrug resistance is the active pumping out of drugs by multidrug efflux pumps.
- In some gram-negative species, these mechanisms may become augmented by the decrease in outer membrane permeability through mutations in porin genes.

Types of infective endocarditis

- Native valve endocarditis (NVE)
  - Acute
  - Subacute
- Prosthetic valve endocarditis (PVE)
  - Early
  - Late
- Intravenous drug abuse (IVDA) endocarditis

Acute NVE

- Aggressive course with a rapidly progressive illness in persons who are healthy or debilitated.
- Virulent organisms are typically the causative agents, such as
  - S. aureus
  - Group B streptococci
- Underlying structural valve disease may not be present.

Examples of Pathophisiology

- Increased adherence to aortic valve by enterococci, S viridans, and S aureus
- Mucoid-producing strains of S aureus
- Dextran-producing strains of S viridans
- S viridans and enterococci that possess FimA surface adhesin
- Platelet aggregation by S aureus and S viridans and resistance of S aureus to platelet microbicidal proteins

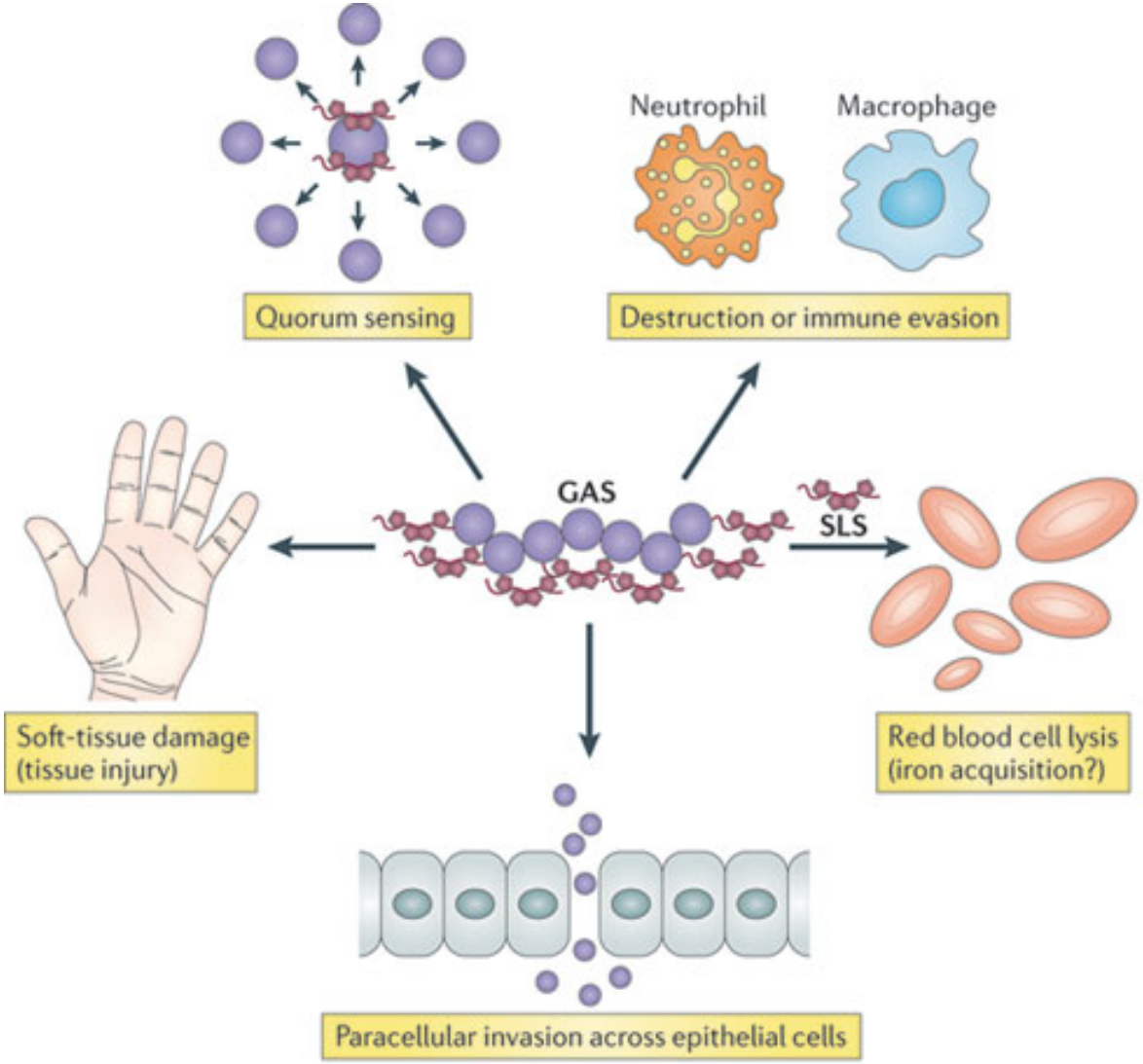
Steptococcal (Flash Eating Bacteria) exotoxins

- Hemolysins, Streptolysins O and S, Leukocidines.
- Surface proteins M-1 and M-3 increase the adhesion of streptococci to tissues and prevent phagocytosis by neutrophils.
- Streptococcal pyrogenic exotoxins (SPEs) A, B, and C and streptococcal superantigen (SSA) cause the release of cytokines.

Tissue Damage

- Impact on host phagocytes and a contribution to the paracellular translocation of GAS.
- SLS-associated gene A (*sagA*) mRNA and the associated 'pleiotropic effects locus' (*pel*) mRNA affect virulence through their impact on the expression of other virulence genes.
- SLS also functions as a signalling molecule, and it has been proposed to contribute to iron acquisition from the host.

Streptolysin S



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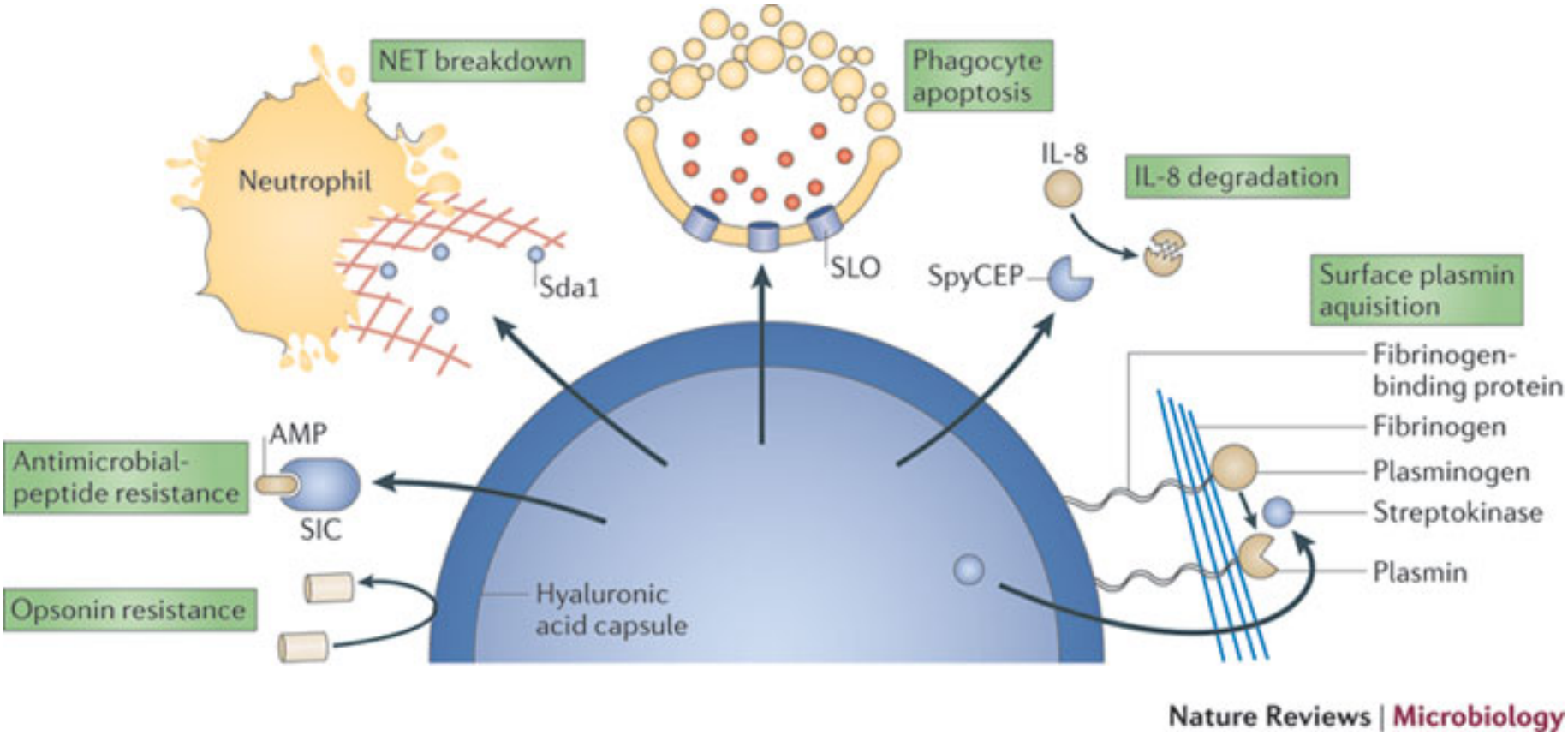
- Enhanced resistance to neutrophil-mediated killing is accomplished through the upregulation of multiple factors that facilitate neutrophil extracellular trap (NET) destruction

  - extracellular streptodornase D (Sda1))
  - Apoptosis by streptolysin O (SLO), interleukin-8 (IL-8) degradation IL-8 protease (SpyCEP)
  - reduced resistance to antimicrobial peptides by streptococcal inhibitor of complement (SIC) and the hyaluronic acid capsule.
  - Fibrinogen-binding proteins help capture plasminogen, which is converted to plasmin by bacterial streptokinase.
  - The protease activity of plasmin aids bacterial colonization of host tissues.

- Many of these virulence factors are upregulated in group A *Streptococcus* (GAS) strains with a mutation in the *covRS* operon, leading to hypervirulence.


NET breakdown
Neutrophil
Sda1
Phagocyte apoptosis
SLO
IL-8
IL-8 degradation
SpyCEP
Surface plasmin aquisition
Fibrinogen-binding protein
Fibrinogen
Plasminogen
Streptokinase
Plasmin
AMP
Antimicrobial-peptide resistance
SIC
Opsonin resistance
Hyaluronic acid capsule
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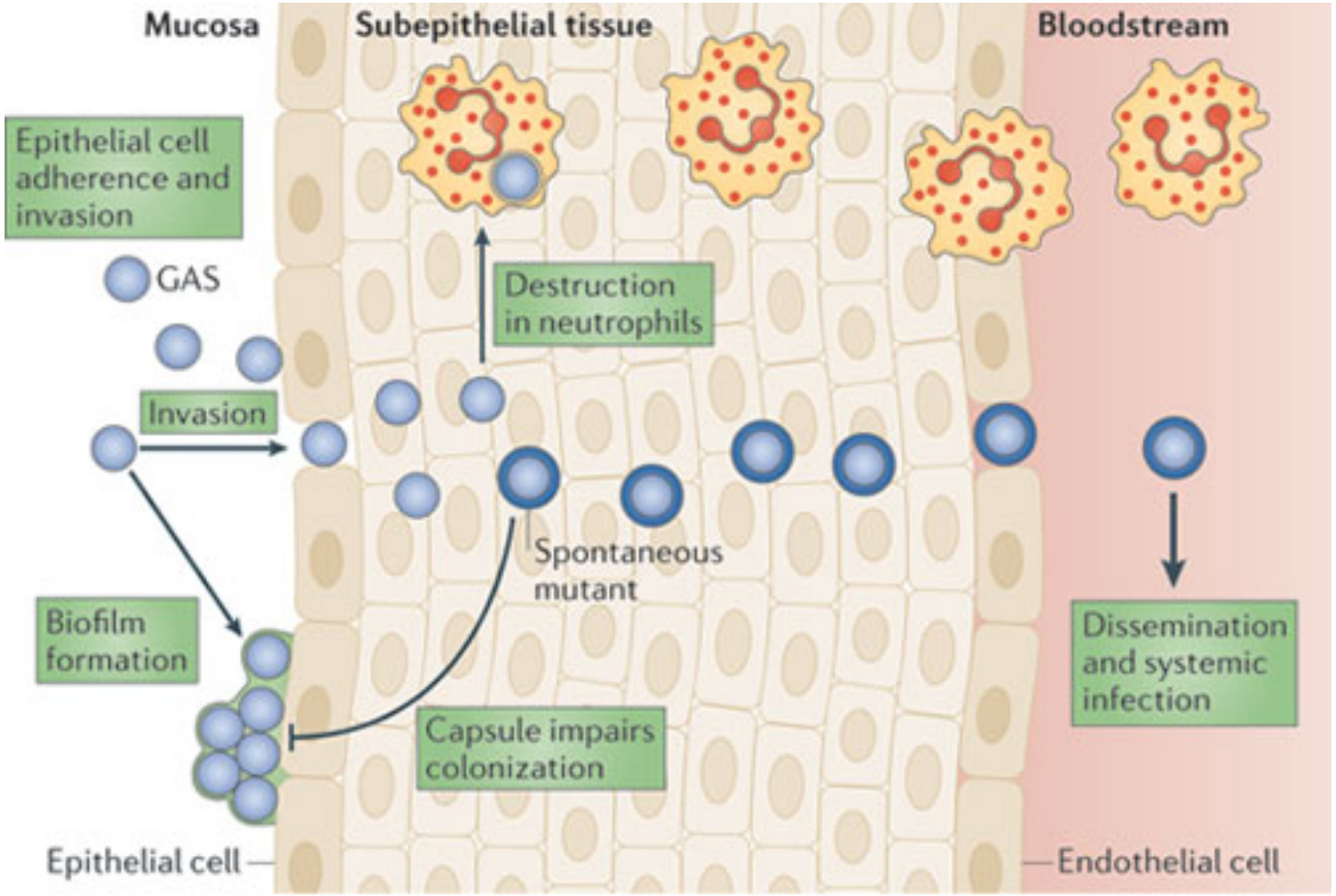

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Gene	Protein and function	Gene expression levels relative to wild-type controls‡				
		covRS-mutant isolates from humans (ITP)§	*covRS*-mutant isolates from mice‖	*covS* 877::A mutant *in vitro*¶	*covS* 877::A mutant during *in vivo* colonization#	Δ*covS* mutant**
Antiphagocytic factors						
sic	Streptococcal inhibitor of complement	+	+	++	+	++
scpA	C5a peptidase	+	+	+	No change	+
hasA	Hyaluronase, involved in production of the hyaluronic acid capsule	++	++	+	+	++
hasB	Production of the hyaluronic acid capsule	++	++	+	+	+
hasC	Production of the hyaluronic acid capsule	++	++	NR	+	++
ideS	Imunoglubulin G endopeptidase, a CD11b homologue	++	++	No change	No change	NR
spyCEP	Interleukin-8 protease, a CXC chemokine protease	++	++	–	No change	+
sda1	Extracellular streptodornase D, a DNase	+	+	No change	+	++
emm	M protein	No change	No change	+	No change	++
Adhesins						
fbaA	A fibronectin-binding protein	+	+	+	No change	NR
sclA	Collagen-like surface protein	++	++	+	+	+
Toxins						
sagA	Streptolysin S precursor	–	–	–	–	+
sagB	Production of streptolysin S	–	–	NR	–	NR
sagC	Production of streptolysin S	–	–	NR	–	NR
speA	Exotoxin type A, a GAS superantigen	+	+	+	+	++
speJ	Exotoxin type J	+	+	No change	No change	+
spyA	C3 family ADP-ribosyltransferase	+	+	No change	No change	++
slo	Streptolysin O	++	+	No change	No change	+
nga	NAD glycohydrolase	++	+	No change	No change	+
Other genes						
spd	DNase	–	–	–	–	NR
grab	G protein-related α2-macroglobulin-binding protein	–	–	–	–	NR
speB	Streptococcal pyrogenic exotoxin B, a cysteine protease	–	–	– –	– –	– –
ska	Streptokinase	+	+	+	+	++

GAS, group A *Streptococcus*; ITP, invasive transcriptome profile; NR, not reported. *Genes that have altered transcriptional profiles following perturbation of *covRS* in GAS serotype M1T1 isolates. ‡++, upregulated more than tenfold; +, upregulated between twofold and tenfold; –, downregulated between twofold and tenfold; – –, downregulated more than tenfold. §Data from REF. 11. Human ITP isolates are *covRS* mutants that were isolated from human invasive disease. ‖Data from REF. 11. Isolates with mutations in the *covRS* locus were obtained by passage of M1 GAS strain MGAS2221 through a mouse model of invasive disease. ¶Data from REF. 114. *In vitro* expression data are from strains that were grown to exponential phase in broth cultures. #Data from REF. 114. *In vivo* expression data were obtained by incubating each strain in a mouse subcutaneous chamber. **Data from REF. 113. Expression data are from 18 h broth cultures of each strain.

- Exotoxins may bind to T-cell receptors, causing an overwhelming production of TNF, IL-1, and IL-6, setting in motion a destructive process that may lead to subsequent organ failure and toxic shock syndrome.

- TNF has been clearly associated with streptococcal toxic shock syndrome.

Subacute NVE

- Typically affects only abnormal valves
- Its course, even in untreated patients, is usually more indolent than that of the acute form and may extend over many months
- Due to
  - Alpha-hemolytic streptococci
  - Enterococci

PVE

- 10-20% of cases of IE (MV>AV)
  - 5% of mechanical and bioprosthetic valves become infected
- Mechanical valves are more likely to be infected within the first 3 months of implantation
- Bioprosthetic valves are more likely to be infected after 1 year

Early PVE

- Occurs within 60 days of valve implantation
- Common causative agents
  - Coagulase-negative staphylococci
  - Gram-negative bacilli
  - Candida species

Late PVE

- 60 days or more after valve implantation, due to
  - Staphylococci
  - Alpha-hemolytic streptococci
  - Enterococci

- Recent data suggest that S aureus may now be the most common infecting organism in both early and late PVE

Infections of Implantable Pacemakers and Cardioverter-Defibrillators

- Infected within few months from implantation (0.5% of implanted pacemakers)
- Most challenging to treat
- 75% of pacemaker infections are produced by
  - Staphylococci (both coagulase-negative and coagulase-positive)

S. aureus

- Overall, S aureus infection is the most common cause of IE, including PVE, acute IE, and IVDA IE.
- Approximately 35-60.5% of staphylococcal bacteremias are complicated by IE. More than half the cases are not associated with underlying valvular disease.
- The mortality rate of S aureus IE is 40-50%.
- The primary risk factor for S aureus BSI is the presence of intravascular lines. Other risk factors include cancer, diabetes, corticosteroid use, IVDA, alcoholism, and renal failure.
- S. aureus bacteremia cases in the United States, 7.8% (200,000) per year are associated with intravascular catheters.

NVE caused by penicillin-susceptible S viridans, S bovis, and other streptococci (MIC of penicillin of ≤0.1 mcg/mL)

- Penicillin G at 12-18 million U/d IV by continuous pump or in 6 equally divided doses for 4 weeks
- Ceftriaxone at 2 g/d IV for 4 weeks
- Short-course therapy with ceftriaxone and gentamicin for 2 weeks is a cost-effective regimen and is effective in selected patients (uncomplicated NVE caused by sensitive S viridans and of less than 3 months' duration)
- For pts Allergic to penicillin, use vancomycin at 30 mg/kg/d IV in 2 equally divided doses for 4 weeks); peak vancomycin level of 30-45 mcg/mL 1 hour after completion of the intravenous infusion of vancomycin

NVE caused by relatively resistant streptococci (MICs of penicillin of 0.1-0.5 mcg/mL)

- Penicillin G at 18 million U/d IV, either by continuous pump or in 6 equally divided doses, for 4 weeks
- Cefazolin at 6 g/d IV in 3 equally divided doses for 4 weeks
- Both of the above regimens are combined with gentamicin at 1 mg/kg every 8 hours for the first 2 weeks of therapy

IE caused by nonresistant enterococci, resistant S viridans (MICs of penicillin G of >0.5 mcg/mL)*

- IE caused by nonresistant enterococci, resistant S viridans (MICs of penicillin G of >0.5 mcg/mL), or should be treated as follows:
- Penicillin G at 18-30 million U/d IV, combined with gentamicin at 1 mg/kg every 8 hours for 4-6 weeks
- Ampicillin at 12 g/d by continuous infusion or in 6 equally divided doses daily, combined with gentamicin at 1 mg/kg for 4-6 weeks
- Vancomycine +- gentamicin if allergy

* Also for nutritionally variant S viridans and PVE caused by penicillin-G–susceptible S viridans or S bovis

NVE caused by methicillin-sensitive S aureus (MSSA)

- Oxacillin at 2 g IV every 4 hours for 4-6 weeks
- Cefazolin at 2 g IV every 8 hours for 4-6 weeks

PVE caused by MSSA

- Oxacillin at 2 g IV every 4 hours for 6 weeks or longer
- Cefazolin at 2 g IV every 8 hours for 6 weeks or longer
- Each of these options should be combined with rifampin at 300 mg orally every 8 hours for 6 weeks or longer and with gentamicin at 1 mg/Kg IV every 8 hours for the first 2 weeks

Treatment of other microorganisms

- For P. aeruginosa
  - ceftazidime, cefepime, or imipenem, combined with gentamicin for 6 weeks
- Enteric gram-negative rods (eg, E coli, Proteus mirabilis)
  - ampicillin, ticarcillin-clavulanic acid, piperacillin, piperacillin-tazobactam, ceftriaxone, or cefepime combined with gentamicin or amikacin for 4-6 weeks
- For Streptococcus pneumoniae
  - ceftriaxone at 2 g/d IV or vancomycin (if penicillin allergy or high-level penicillin G resistance [MIC of 2 mcg/mL or more]) for 4 weeks
- For diphtheroids
  - penicillin G at 18-24 million U/d in 6 divided doses or vancomycin combined with gentamicin for 4 weeks
- For Q fever (C burnetii infection)
  - doxycycline combined with rifampin, trimethoprim-sulfamethoxazole, or a fluoroquinolone for 3-4 years

Enterococcal PVE therapy

- Complicated by the multiple types of enterococcal antimicrobial resistance, including beta-lactamase production (rare), different types of aminoglycoside-inactivating enzymes (more common), and VRE (increasingly common).
- If the enterococci are highly resistant to both gentamicin and streptomycin, ampicillin should be administered for 8-12 weeks by continuous infusion.

PVE cure rates

- Rates are 10-15% lower for each of the above categories, for both early and late PVE.
- Surgery is required far more frequently
- 60% of early CoNS PVE cases and 70% of late CoNS PVE cases are curable
- The fatality rate of pacemaker IE ranges up to 34%.

Cure rates for appropriately managed NVE

- S viridans and S bovis infection 98%.
- For enterococci and S aureus infection in individuals who abuse intravenous drugs 90%.
- For community-acquired S aureus infection in individuals who do not abuse intravenous drugs 60-70%.
- For infection with aerobic gram-negative organisms 40-60%.
- For infection with fungal organisms, the rate is lower than 50%.

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CURRENT OPINION

Fungal endocarditis

Candida spp EI: echinocandine o L-AMB per 6-8 settimane

- NVE: intervento chirurgico entro 7 gg dall'inizio del trattamento
- PVE: intervento chirurgico in urgenza

Se chirurgia non attuabile, considerare trattamento soppressivo permanente con fluconazolo

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CURRENT OPINION

Fungal endocarditis

Aspergillus spp EI: voriconazolo o L-AMB per 6-8 settimane

- Intervento chirurgico in urgenza per il rischio aumentato di SC e complicanze emboliche

Profilassi con triazoli orali fortemente raccomandata per l'incidenza di infezioni ricorrenti

Therapy

- Effective therapy progressively more difficult to achieve due to increased use of implantable devices and because of the rise in the number of multiresistant microorganisms.

- Understanding the genetic basis of intrinsic bacterial resistance, and hence the spectrum of activity of an antibiotic, can therefore guide the development of new combinations of agents with improved or expanded activity against target species

- Various studies have identified *in vitro* synergies between unconventional combinations of antibiotics that can be used to target particularly problematic pathogens

FUTURE ISSUES

- To develop inhibitors of multidrug efflux pumps or to inhibitors of the R plasmid transfer process.
- To prevent the further increase in multidrug resistant bacteria minimizing antibiotic usage.
- Simultaneous administration of more than one agent (as is done with tuberculosis) may be considered.
  - For example, an inhibitor of multidrug efflux pumps lowers the MICs of various drugs strongly in gram-negative bacteria and may prevent the emergence of resistant organisms.

Piddock LJV. Multidrug-resistance efflux pumps—not just for resistance. Nat. Rev. Microbiol. 2006;4:629–36.

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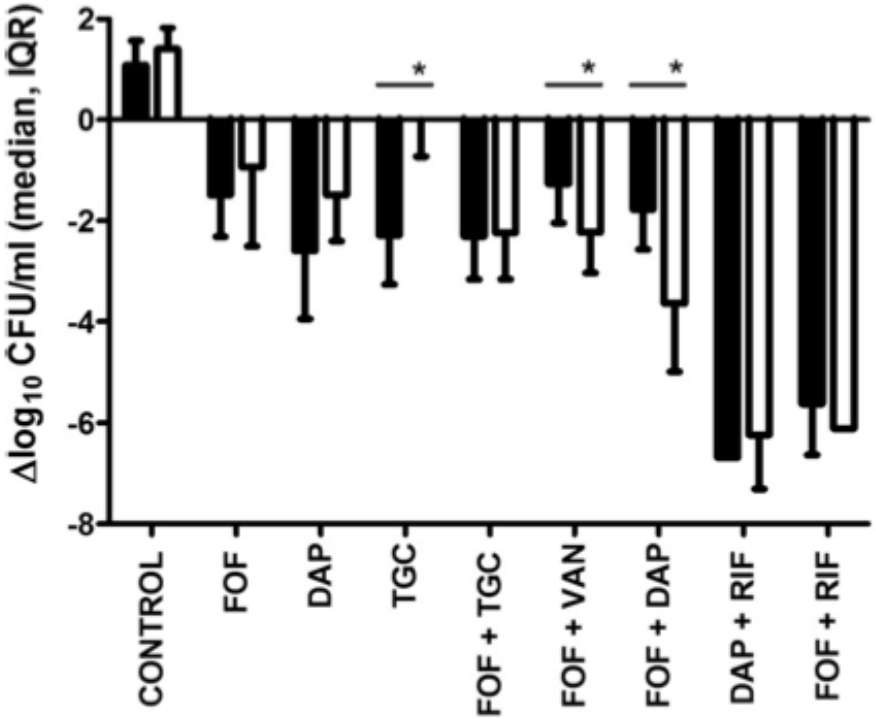
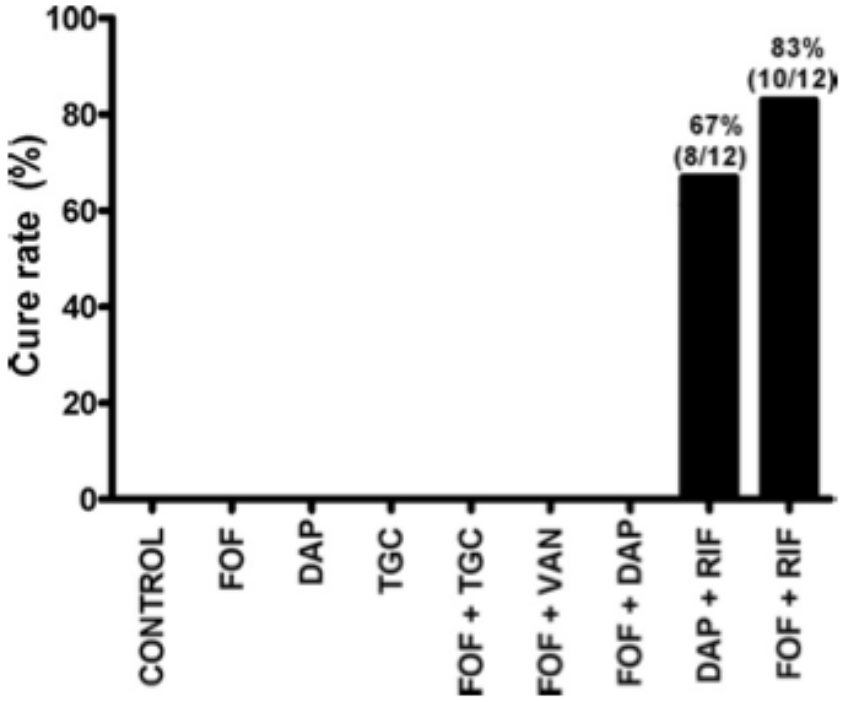
May 2014 Volume 58 Number 5

High Activity of Fosfomycin and Rifampin against Methicillin-Resistant *Staphylococcus aureus* Biofilm *In Vitro* and in an Experimental Foreign-Body Infection Model





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High-Dose Daptomycin Therapy for Left-Sided Infective Endocarditis: a Prospective Study from the International Collaboration on Endocarditis

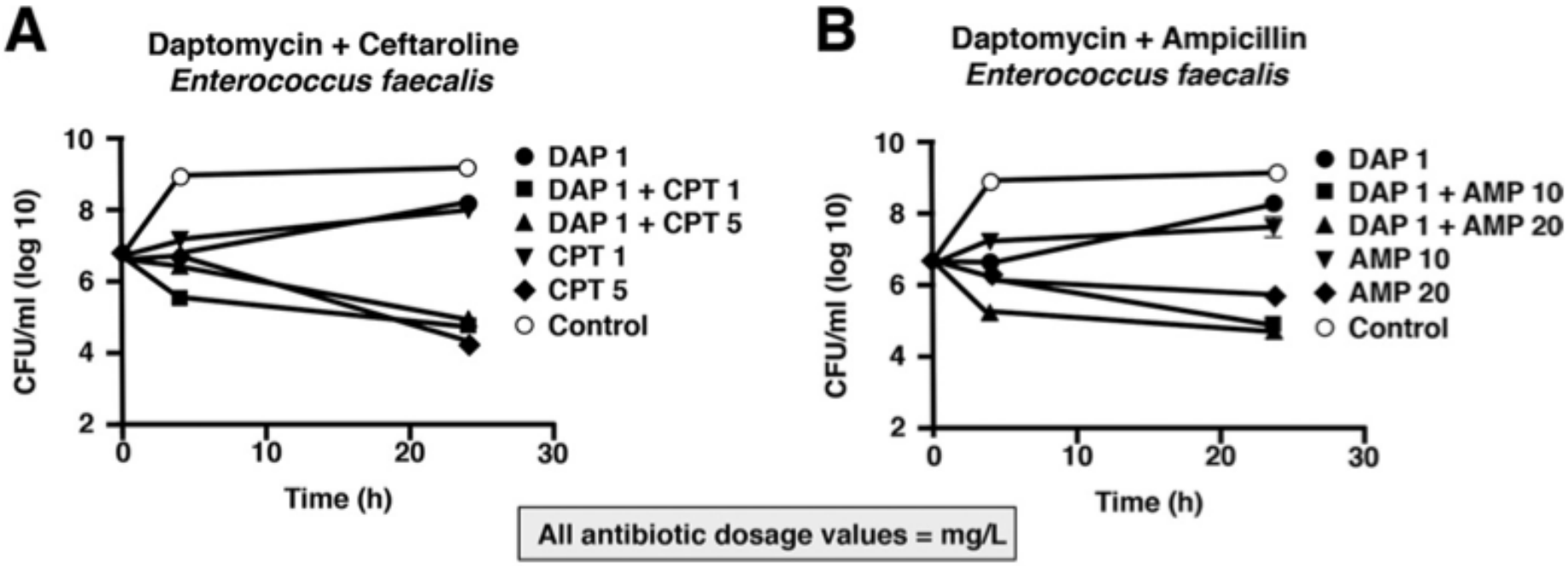
In this study, in-hospital and 6-month mortality rates were similar among patients treated with daptomycin and SOC antibiotics in the setting of *S. aureus* (both MSSA and MRSA), CoNS, and *E. faecalis* IE. The outcomes observed with the use of daptomycin are also notable because patients in cohort A (daptomycin cohort) were characterized by higher rates of comorbidities (i.e., diabetes), and daptomycin was the second-line treatment for two-thirds of the subjects in cohort A. Furthermore, over 20% of the patients receiving daptomycin had discontinued a previous antibiotic regimen because of either clinical or microbiological failure. In contrast, no patients discontinued daptomycin because of persistently positive blood cultures or other evidence of clinical or microbiological failure.

Antimicrobial Agents and Chemotherapy

Combination Therapy with Ampicillin and Daptomycin for Treatment of Enterococcus faecalis Endocarditis

Antimicrobial Agents and Chemotherapy

Treatment of High-Level Gentamicin-Resistant Enterococcus faecalis Endocarditis with Daptomycin plus Ceftaroline



March 2014 Volume 58 Number 3

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Ceftaroline Restores Daptomycin Activity against Daptomycin-Nonsusceptible Vancomycin-Resistant *Enterococcus faecium*

Characteristic	Result[a] DAP-susceptible VRE	DAP-nonsusceptible VRE
Synergy with DAP		
AMP	+	−
CPT	+	+
Effect on cell wall thickness		
AMP	↓ ↓	↑
CPT	↓	↑
Effect on membrane fluidity		
AMP	−	−
CPT	−	↑
Poly-L-lysine binding		
AMP	−	↑
CPT	↑	↑
Bodipy-DAP binding		
AMP	−	↑
CPT	↑	↑
LL37 binding and activity		
AMP	↑	↑
CPT	↑ ↑	↑ ↑

Therapy for Enterobacteriaceae MDR

- Tigecyclin + gentamicin

- Meropenem + Colistin + Tigecyclin

- Or combination of
  - Colistin: 9MU, then 4.5 x 2
  - Tige: 200, then 100 x 2
  - Gentamicin 240 mg
  - Meropenem 2 g x 3

Conclusion

- Therapy duration is between 2 to 6 weeks
  - Longer for PVE, MDR microorganisms and fungi
  - Shorter for right sided endecarditis due to Streptococcus (viridans and alfa haemolytics)
  - Duration is not quite clear in available guide lines, it should be discussed between team members case by case