SYSTEMIC ANTIBIOTICS IN PERIODONTAL THERAPY

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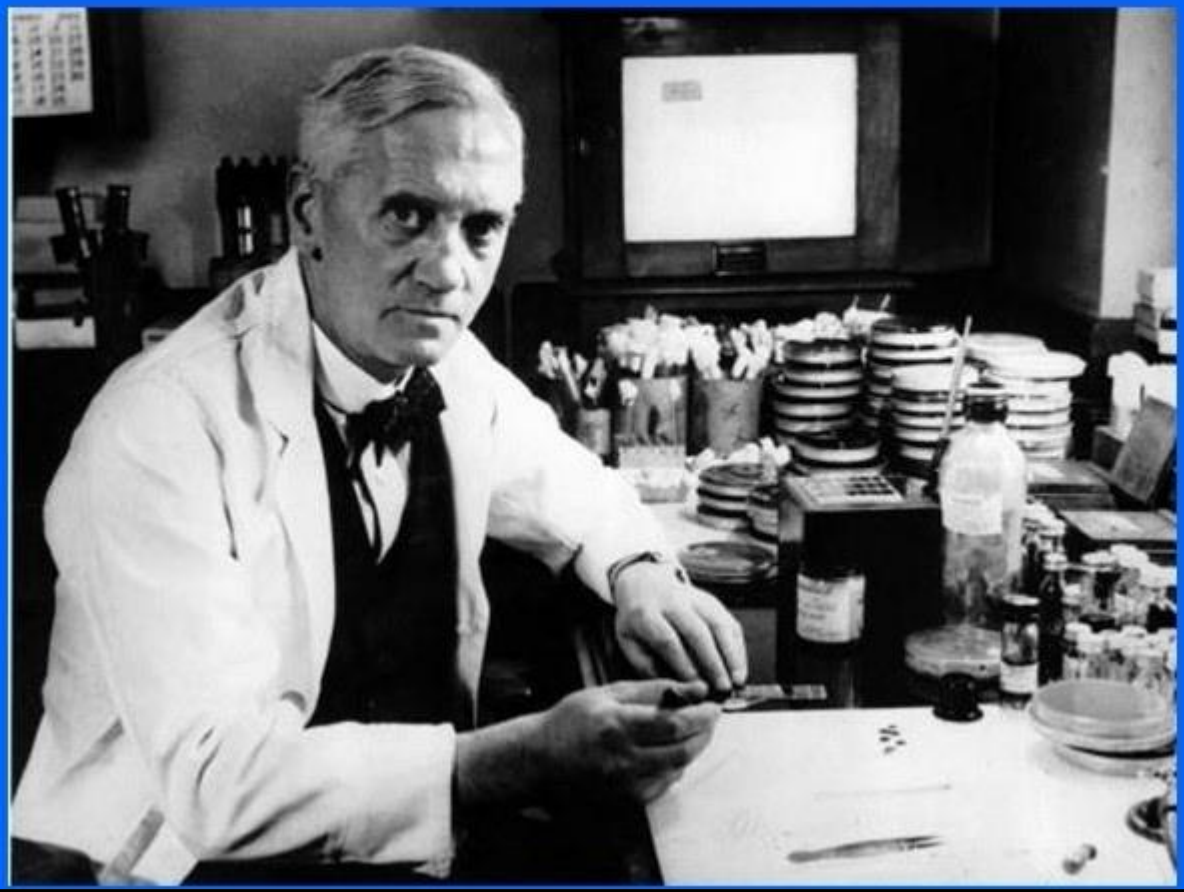
INTRODUCTION

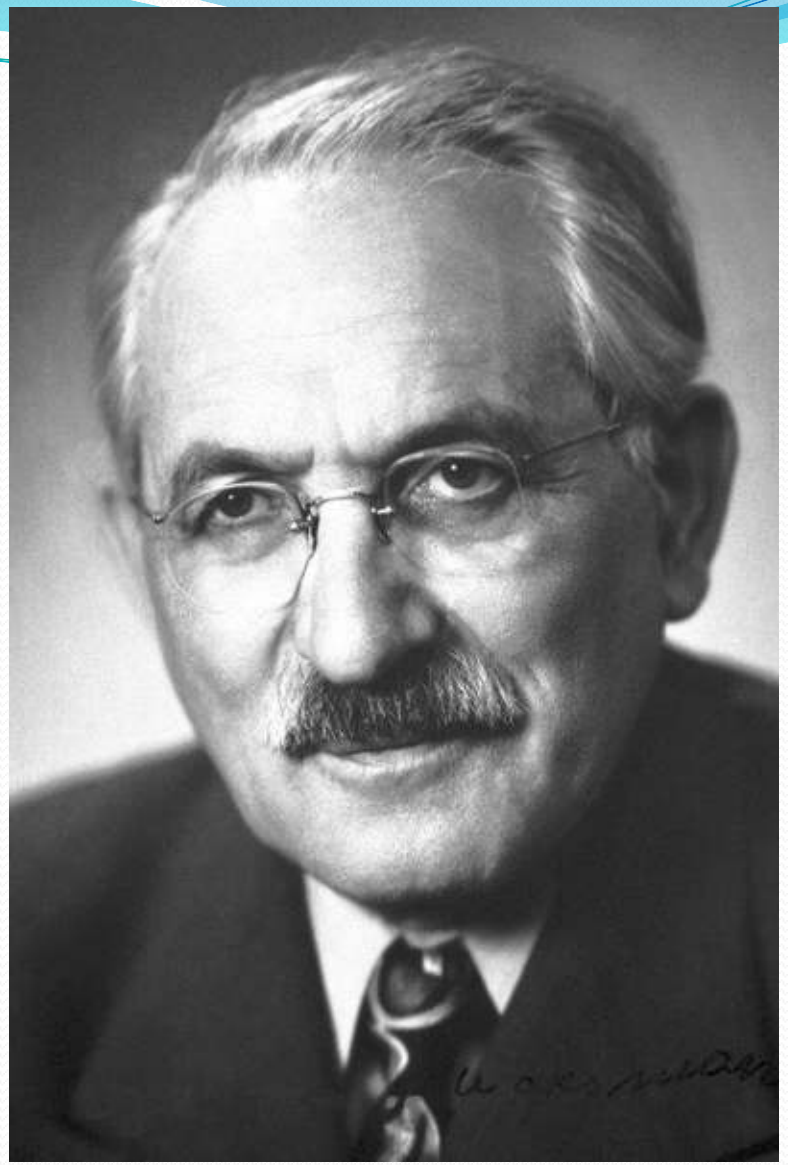
- Antibiotics are used to eliminate infections.
- Recognition of the microbial origin and specificity of periodontal diseases in late 1970s.
- Five daunting problems –
  - Heterogeneous nature of periodontal disease.
  - Clinical diagnosis based on clinical signs not molecular pathology.
  - Actual causal factor not identified.
  - Microbiological sampling not reproducible and inaccurate.
  - Different antibiotic protocols.

Alexander Fleming and Penicillin: The Accidental Discovery?



ANTIBIOTICS

A naturally occurring, semi synthetic ,or synthetic type of anti-infective agent that destroys or inhibits the growth of selective microorganisms generally at low concentration.



Selman Abraham **Waksman**

CLASSIFICATION

BACTERICIDAL

CONC.DEPENDENT

METRONIDAZOLE

QUINOLONES

AMINOGLYCOSIDES

TIME DEPENDENT

β-LACTAM ANTIBIOTICS

PENICILLIN

CEPHALOSPORINS

BACTERIOSTATIC

TETRACYCLINE

ERYTHROMYCIN

CLINDAMYCIN

**Pallasch TJ et al Periodontology2000,Vol.10,1996,5-11*

RATIONALE

Periodontal breakdown despite diligent mechanical therapy.

Mechanical treatment fail to eliminate pathogens that

invade periodontal tissues

reside in anatomic niches that are outside the reach of periodontal instruments

**Van Winkelhoff AJ et al Periodontology 2000, Vol.10,1996,45-78.*

PRIMARY CANDIDATES FOR ADJUNCTIVE ANTIMICROBIAL THERAPY

- Continued attachment loss despite adequate mechanical therapy.
- Aggressive form of Periodontitis.
- Predisposing medical conditions/refractory periodontitis.
- Acute/severe periodontal infection.

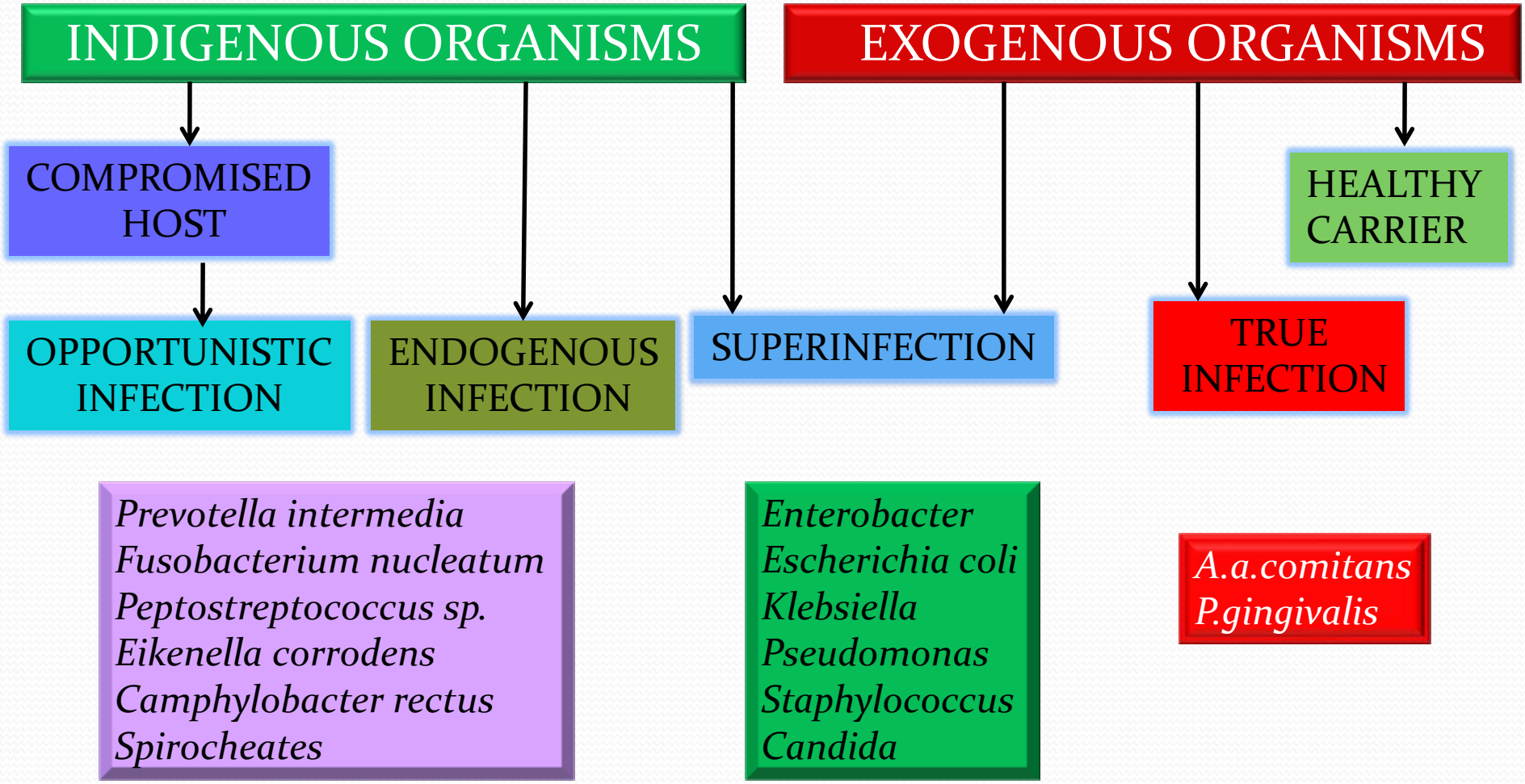
**Van Winkelhoff AJ et al Periodontology 2000, Vol.10,1996,45-78*

SYSTEMIC VS. LOCAL ANTIMICROBIAL THERAPY

ISSUE	SYSTEMIC ADMINISTRATION	LOCAL ADMINISTRATION
Drug distribution	Wide	Narrow
Drug concentration	Variable levels in different body compartments	High level at treated sites
Therapeutic potential	Acts on widely distributed microorganisms	Acts better locally
Problems	Systemic side effects	Re-infection from non treated
Clinical limitations	Requires good patient compliance	Requires infection to be limited

**Jepsen K & Jepsen S Periodontology2000, Vol.71,2016,82-112.*

TYPES OF PERIODONTAL INFECTIONS



*Van Winkelhoff AJ et al Periodontology 2000, Vol.10,1996,45-78

ECOLOGICAL CONCEPT IN THE TREATMENT OF PERIODONTAL DISEASE

HOST COMPATIBLE SPECIES

Veillonella parvula
Actinomyces odontolyticus
Streptococcus oralis
Streptococcus mitis
Streptococcus intermedius
Actinomyces sp.

PATHOGENIC SPECIES

Streptococcus constellatus
Fusobacterium sp.
Campylobacter sp.
Prevotella nigrescens
E.nodatum
P.intermedia

T. forsythia
P.gingivalis
T.denticola

A.actinomycetemcomitans

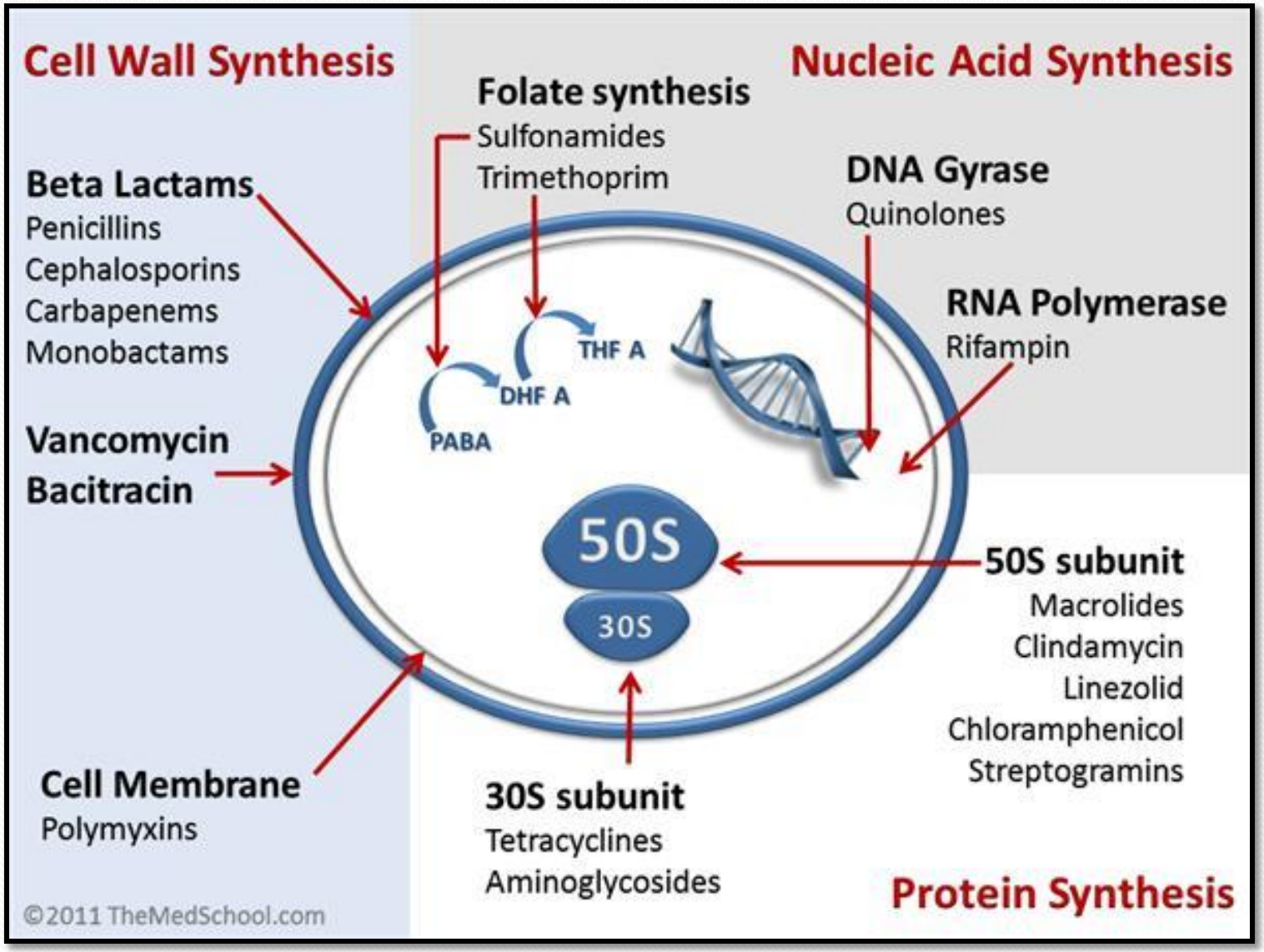
*Important to foster the overgrowth of host compatible bacteria as it is to eliminate periodontal pathogens . *Socransky and Haffajee*

**Feres M et al Periodontology2000,Vol.67,2015,131-186*

SYSTEMIC ANTIBIOTICS USED IN PERIODONTAL DISEASES

Category	Agent	Major feature
Penicillin	Amoxicillin	Extended spectrum of antimicrobial activity
	Amoxicillin+ Clavulanate potassium	Effective against penicillinase-producing microorganisms
Tetracycline	Tetracycline	Effective against broad spectrum of microorganisms, applied locally also.
	Minocycline	
	Doxycycline	SDD for host modulation
Nitroimidazole	Metronidazole	Effective against anaerobic bacteria, applied locally also.
Quinalone	Ciprofloxacin	Effective against gram-negative rods, promotes health associated microflora
Macrolide	Azithromycin	Concentrates at the site of inflammation
Lincomycin	Clindamycin	Effective against anaerobic bacteria, used in penicillin-allergic patients

MECHANISM OF ACTION



CONTRAINDICATIONS AND DRUG INTERACTIONS

ANTIMICROBIAL	CONTRAINDICATION	DRUG INTERACTION
PENICILLINS	Hypersensitivity to penicillin	Efficacy decrease by bacteriostatic agent. Potentiates anticoagulant.
TETRACYCLINE	Pregnancy, children<12yrs, impaired renal function	Potentiates anticoagulant, and lithium toxicity. Oral contraceptives less effective.
METRONIDAZOLE	CNS disorder, severe hepatic disease, 1st trimester of pregnancy, concurrent intake of alcohol.	Potentiates anticoagulants, lithium, phenytoin, phenobarbitone.
CLINDAMYCIN	Impaired hepatic /renal function Patients with colitis.	Decreases effects of erythromycin.
CIPROFLOXACIN	Combined liver & kidney disease. Pregnancy & children<16yrs	Efficacy decrease by bacteriostatic agent. absorption reduced by antacids. Theophyllin and caffeine levels increased.

**Van Winkelhoff AJ et al Periodontology 2000, Vol.10,1996,45-78*

TERMINOLOGIES

- Minimum inhibitory concentration(MIC): The lowest concentration of the agent that prevents visible growth of micro-organism after 18-24 hours of incubation.

- Minimum bactericidal concentration(MBC): The concentration at which subculture from the parent tubes shows no visible growth.

**Tripati KD. Essentials of Medical Pharmacology,5thEdition: 628-640*

ANTIBIOTIC DOSING PRINCIPLES

1. Employ high doses for short duration.
2. Use an oral antibiotic loading dose.
3. Achieve blood levels of antibiotic at 2-8 times the MIC.
4. Use frequent dosing intervals.
5. Determine the duration of therapy by the remission of disease.

**Pallasch TJ et al Periodontology2000,Vol.10,1996,5-11*

FACTORS THAT PLAY A ROLE IN THE EFFICACY OF ANTIBIOTICS

- Drug binding to tissue.
- Protection of key organism through binding of drug by non target micro-organism(*E.faecalis* protect *B.fragilis* from metronidazole).
- Microbial invasion of tissue and root surface.
- Inoculum effect.
- Bacteriostatic drugs suppresses the pathogens but fail to eradicate some key subgingival organisms.
- Microorganisms in biofilm are more resistant than planktonic cells.
- β-lactam antibiotics inactivated by bacteria derived β-lactamase.

**Van Winkelhoff AJ et al Periodontology 2000, Vol.10,1996,45-78.*

CLINICAL REASONS FOR ANTIBIOTIC FAILURE

- Inappropriate choice of antibiotic.
- Emergence of resistant strains.
- Too low blood concentration of drug.
- Slow growth of microorganism.
- Impaired host defences.
- Patient non compliance.
- Antibiotic antagonism.
- Inability of antibiotic to penetrate the site of infection.
- Limited blood supply.
- Unfavourable local factors.
- Failure to eradicate source of infection.

COMMON ANTIBIOTIC THERAPIES IN THE TREATMENT OF PERIODONTITIS

ANTIBIOTIC	ADULT DOSAGE
SINGLE DRUG THERAPY	
Amoxicillin	500mg /tid /8days
Metronidazole	250 or 500mg /tid /8days
Tetracycline	250mg/qid/14days
Doxycycline /Minocycline	100mg-200mg/OD/21days
Ciprofloxacin	500mg /bid /8days
Azithromycin	500mg /OD/4-7days
Clindamycin	300mg /tid /8days
COMBINATION THERAPY	
Metronidazole+Amoxicillin	250/tid /8days of each drug
Metronidazole+Ciprofloxacin	500mg /bid /8days of each drug

**Slots J Systemic antibiotic in periodontics J Periodontol 2004:75:1553-1565.*

ACUTE PERIODONTAL ABSCESS

ANTIBIOTIC	LOADING DOSE	MAINTENANCE DOSE
AMOXICILLIN	1 g	500mg /tid /3days
Allergy to β-lactum drugs		
Azithromycin	1 g	500mg /OD/3days
Clindamycin	600mg	300mg /qid /3days

ACUTE NECROTIZING ULCERATIVE GINGIVITIS

ANTIBIOTIC	DOSAGE
Amoxicillin	500mg/qid/10days
Allergy to Amoxicillin	
Erythromycin	500mg/qid/10days
Metronidazole	500mg/bid/7days

**Slots J Systemic antibiotic in periodontics J Periodontol 2004:75:1553-1565*

CLINICAL STUDIES

SYSTEMIC ANTIBIOTIC AS A MONOTHERAPY	
STUDY	ANTIBIOTIC
Clark et al (1983) Lindhe J et al (1983)	Metronidazole
Lopez NJ (2000) Winkle EG (2001)	Metronidazole+Amoxicillin

•*Herrera D et al J ClinPeriodontol 2002:29(suppl 3):136-159*

INFERENCE

- Inferior results when compared to SRP
- Effect was minimal and short term
- Development of multiple periodontal abscess .(*Topell et al 1990)*
- Increased risk of side effects and antibiotic resistance

CONCLUSION

The use of systemic antimicrobial as a monotherapy in the treatment of periodontitis not recommended.(*Herrera D 2002, Haffajee AD 2003*)

Herrera D et al J ClinPeriodontol 2002:29(suppl 3):136-159

SYSTEMIC ANTIBIOTIC AS AN ADJUCTIVE THERAPY TO SRP

STUDY	DISEASE	ANTIBIOTIC THERAPY	CONCURRENT THERAPY
Listgarten et al Hellden et al	Chronic periodontitis	Tetracycline 250mg/qid/14days	SRP
Haffajee et al	Refractory periodontitis	Tetracycline 250mg/qid/14days	Periodontal surgery
Muller et al	Chronic periodontitis	Minocycline 100mg/bid/21 days	Modified widman flap
Asikainen et al Saxen etal	Aggressive periodontitis	Doxycycline 100mg/OD/14 days	SRP
Mandel et al Socransky et al	Aggressive periodontitis	Doxycycline bid-loading dose 100mg/OD/14 days	Periodontal surgery
Gorden et al Trieger et al	Refractory periodontitis	Clindamycin 150mg/qid/7days	SRP/periodontal surgery

SYSTEMIC ANTIBIOTIC AS AN ADJUCTIVE THERAPY TO SRP

STUDY	DISEASE	ANTIBIOTIC THERAPY	CONCURRENT THERAPY
Sampaio et al Haas etal	Chronic periodontitis	Azithromycin 500mg/OD/5days	SPR
Emingil et al	Aggressive periodontitis		
Sampaio et al Haas et al	Chronic periodontitis	Azithromycin 500mg/OD/5days	SPR
Emingil et al	Aggressive periodontitis		
Carvalho et al	Chronic periodontitis	Metronidazole 400mg/bid/10days	SPR
Gusberti et al	Refractory periodontitis	Metronidazole 250mg/tid/10days	SPR
Akcakanat et al	Aggressive periodontitis	Moxifloxacillin 400mg/OD/7days	SPR
Haffajee et al	Chronic periodontitis	AMOX/CLA 250mg/tid/10days	Surgery
Winkel et al	Chronic periodontitis	AMOX/CLA 500mg/tid/10days	SRP

INFERENCES

- Slight improvement in gingival status, PD reduction & CAL gain.
- No clinical benefits in conjunction with surgery.
- Recurrent disease activity after systemic therapy of tetracyclines.
- May lead to colonisation of super infecting & opportunistic pathogens following tetracycline.
- Systemic doxycycline showed enhanced resolution in localised aggressive periodontitis.

*Feres M et al Periodontology2000,Vol.67,2015,131-186
*Slots J Systemic antibiotic in periodontics J Periodontol 2004:75:1553-1565
*Van Winkelhoff AJ et al Periodontology 2000,Vol.10,1996,45-78

INFERENCES

- Significant reduction in subgingival spirocheates, *P.gingivis, P.intermedia,* but negligible effect on *F.nucleatum, Selenomonas* after systemic therapy of metronidazole.
- Clindamycin/Augmentin in refractory periodontitis with high levels of *P.gingivis ,Peptostreptococcus, β-hemolytic streptococcus was beneficial*.
- Azithromycin not a promising drug for periodontal infection.*(Teles RP et al)*

*Feres M et al Periodontology2000,Vol.67,2015,131-186
*Slots J Systemic antibiotic in periodontics J Periodontol 2004:75:1553-1565
*Van Winkelhoff AJ et al Periodontology 2000,Vol.10,1996,45-78

CONCLUSIONS

- May induce beneficial microbial effects and decrease sites with active breakdown.
- The clinical improvement is due to suppression of the total subgingival bacterial load and change in its composition.
- Unable to predictably eliminate some putative exogenous pathogens.
- May be the choice in many endogenous infections where the major goal is to establish subgingival microbiota with low levels of putative pathogens.

**Van Winkelhoff AJ et al Periodontology 2000, Vol.10,1996,45-78*

COMBINATION ANTIMICROBIAL THERAPY

- Putative periodontal pathogens may differ in antimicrobial susceptibility.
- Broaden the antimicrobial range beyond single antibiotic.
- Prevents emergence of bacterial resistance by using agents with overlapping antimicrobial spectra.
- Lower the dose of individual antibiotic by exploiting synergy.

Disadvantages

- Increased adverse effects.
- Antagonistic drug interactions with improper selection .

**Van Winkelhoff AJ et al Periodontology 2000, Vol.10,1996,45-78*

SERIAL ANTIMICROBIAL THERAPY

- Systemic doxycycline followed by Amox+Clav or metronidazole (*Aitken S, Matisko M*).
- Overcomes the potential risk of antagonism between bacteriostatic and bactericidal antibiotics.

**Van Winkelhoff AJ et al Periodontology 2000, Vol.10,1996,45-78*

COMBINATION ANTIMICROBIAL THERAPY

STUDY	DISEASE	ANTIBIOTIC THERAPY	CONCURRENT THERAPY
Feres et al	Chronic periodontitis	MET400mg+AMOX500mg tid/ 14days	SRP
Varela et al	Aggressive periodontitis	MET 250mg+AMOX500mg tid/ 14days	SRP
Van Winkelhoff Goene et al	Refractory periodontitis	MET 250mg+AMOX375mg tid/ 7days	SRP/Surgery
Fleming et al Berglund et al	Aggressive periodontitis	MET 250mg+AMOX375mg tid/ 7days	SRP
Pavicic et al	Refractory periodontitis	Metronidazole + Ciprofloxain 500mg/bid/ 7days	SRP
Rams et al	Refractory periodontitis	Metronidazole + Ciprofloxain 500mg/bid/ 7days	SRP

CONCLUSIONS

Metronidazole+Amoxicillin, Amox+Clav

- Most promising in treatment of *A.actinomycetemcomitans and P.gingivis* associated *aggressive periodontitis and refractory* periodontitis.
- Lower levels of orange and red complex.
- Higher proportions of *Actinomyces* species and *Streptococcus sanguis*.
- Significantly improved clinical outcomes in patients with Type II Diabetes.
- Refractory periodontitis, apical periodontitis, periodontal destruction in immunocompromised patients may not respond well.

Metronidazole+Ciprofloxacillin

- Mixed infections involving *A.actinomycetemcomitans ,enteric rods, Pseudomonas*.

*Van Winkelhoff AJ et al Periodontology 2000,Vol.10,1996,45-78
*Slots J Systemic antibiotic in periodontics J Periodontol 2004:75:1553-1565
*Feres M et al Periodontology2000,Vol.67,2015,131-186

SUMMARY

- Effect of adjunctive systemic antibiotics more pronounced in

  Aggressive periodontitis than Chronic periodontitis.

  Initially deep(>6mm) than moderately deep(4-6mm) and shallow(<4mm).

- Specific clinical situations like patients with deep pockets, progressive active disease use of antibiotics clinically relevant.

- *S*triking inhibition of keystone pathogens would help reverse the dysbiotic changes in the subgingival microbiota, thus clinical improvements are sustained

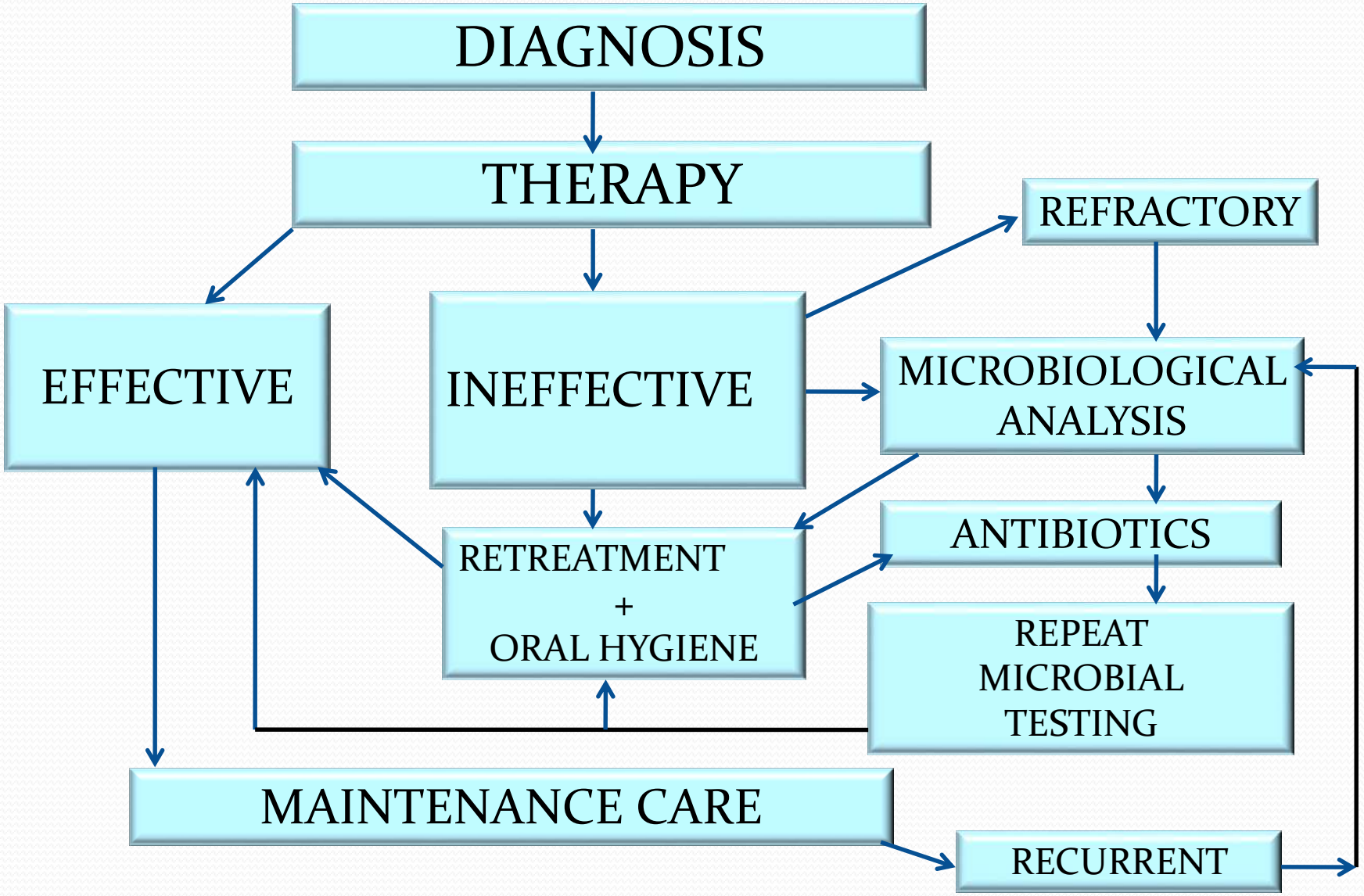
- Antibiotics at the initial therapy showed additional benefits compared to those who received at re-treatment phase(*Griffin).*

SUMMARY

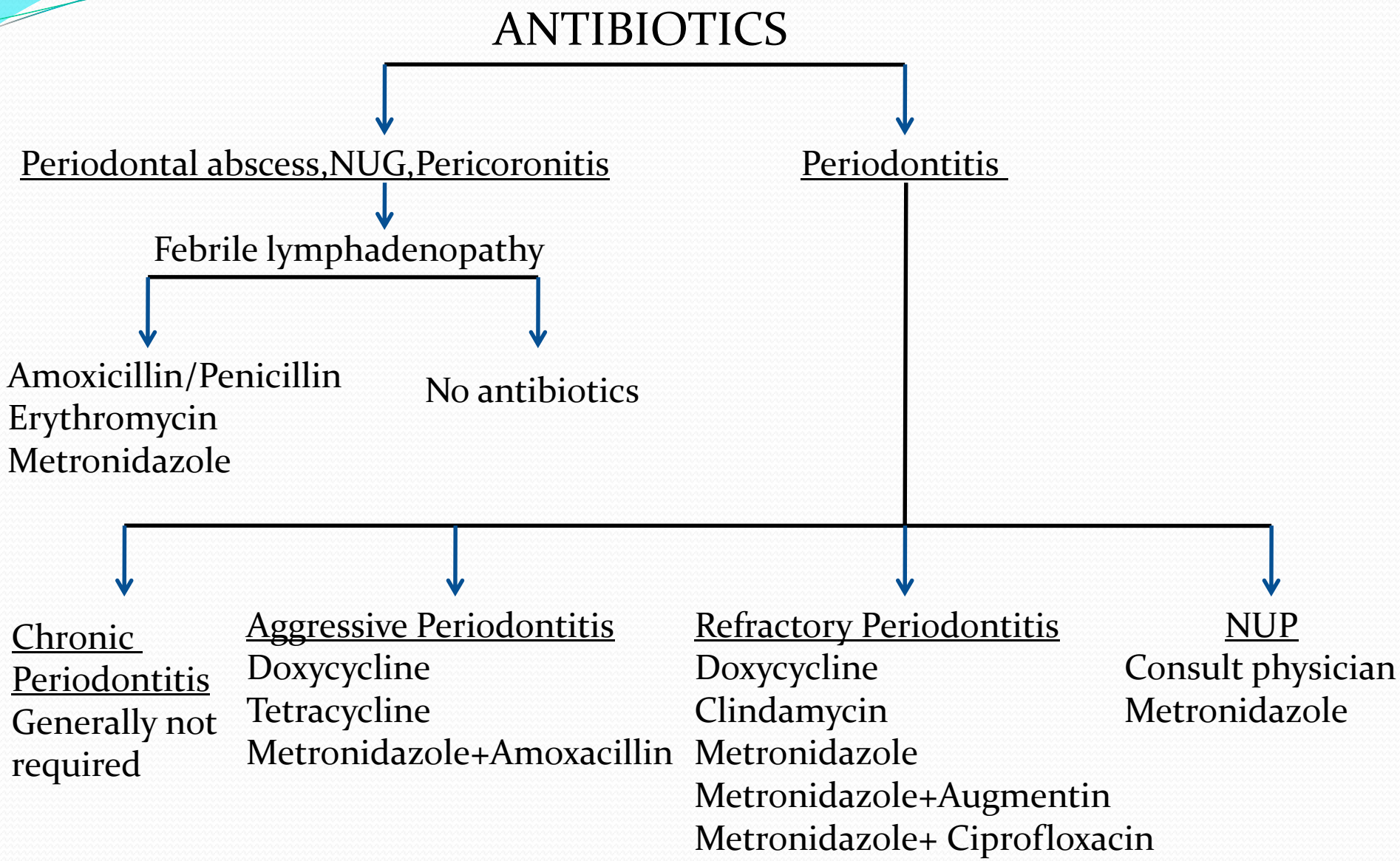
- Prescribe the antibiotic in sufficient dose and for adequate duration.
- Antibiotics should start on the day of debridement completion and be completed with a short period of time.*(Sans M)*
- Adjunctive antibiotics could reduce the need for surgical intervention because of decreased residual pockets. *(Mombelli)*.
- Prevents postsurgical infection following regenerative periodontal therapy. *(Sculean &Loos)*

*Feres M et al Periodontology2000,Vol.67,2015,131-186
*Jepsen K & Jepsen S Periodontology2000,Vol.71,2016,82-112
* Heitz-Mayfield LJA Australian Dental Association2009:54:s96-s101

SEQUENCING OF ANTIMICROBIAL THERAPY



PROTOCOL FOR USAGE OF ANTIBIOTICS



ANTIBIOTIC PROPHYLAXIS

Patients at risk for Infective Endocarditis

1. Prosthetic cardiac valves, including transcatheter-implanted prostheses and homografts.
2. Prosthetic material used for cardiac valve repair, such as annuloplasty rings and chords.
3. Previous IE.
4. Unrepaired cyanotic congenital heart disease or repaired congenital heart disease, with residual shunts or valvular regurgitation at the site of or adjacent to the site of a prosthetic patch or prosthetic device.
5. Cardiac transplant with valve regurgitation due to a structurally abnormal valve.

**AAE Quick Reference Guide on Antibiotic Prophylaxis 2017 Update*

Antibiotic prophylaxis -ADA recommended regimen 2017

Situation	Agent	Adults	Children
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin OR Cefazolin / Ceftriaxone	2 g IM or IV 1 g IM or IV	50 mg/kg IM or IV 50 mg/kg IM or IV
Allergic to penicillins/ ampicillin—oral	Cephalexin ϕδ OR Clindamycin OR Azithromycin / Clarithromycin	2 g 600 mg 500 mg	50 mg/kg 20 mg/kg 15 mg/kg
Allergic to penicillins /ampicillin and unable to take oral medication	Cefazolin / Ceftriaxone δ Clindamycin	1 g IM or IV 600 mg IM or IV	50 mg/kg IM or IV 20 mg/kg IM or IV

ϕ Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosage. δ Cephalosporins should not be used in an individual with a history of anaphylaxis, angiodema, or urticaria with penicillins or ampicillin

Regimen: Single Dose 30 to 60 min. Before Procedure

SIDE EFFECTS OF ANTIBIOTICS

Adverse events
Nausea
Vomiting
Diarrhoea
Rashes
Headache
Drowsiness
Metallic taste
Hypersensitivity

Impact on gastrointestinal microbiome.

Repeated exposure to broad spectrum antibiotics lead to dysbiosis.

Chronic disorders linked to dysbiosis- obesity, under nourished, Diabetes autoimmune disease metabolic syndrome, allergic diseases.

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ANTIBIOTIC RESISTANCE

GENETIC

Mutation

Spontaneous
Hyper mutators
Adaptive mutagenesis

Horizontal gene transfer

Plasmids
Conjugation
Transposition

INTRINSIC

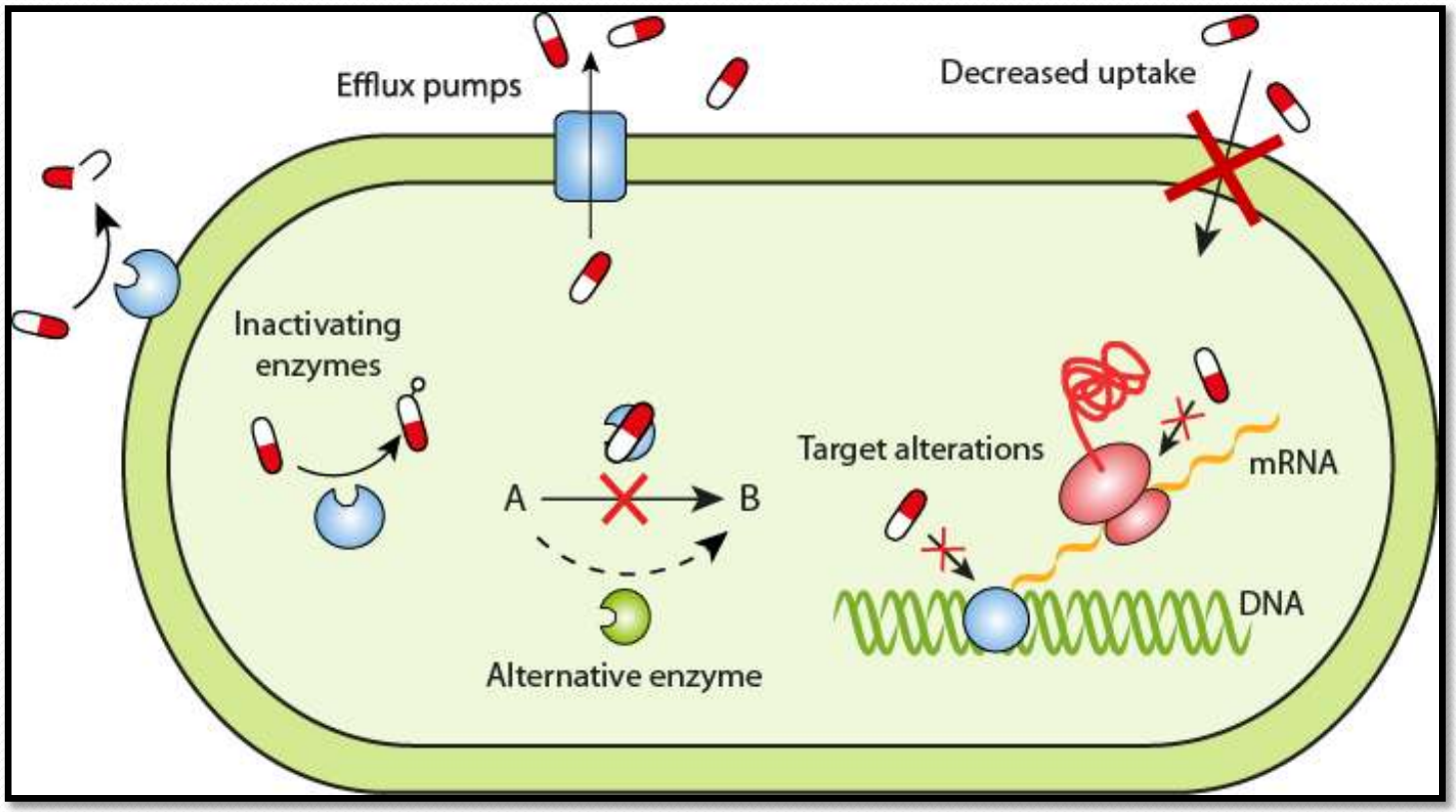
Dismantling enzymes

Antibiotic pump

Inactivating enzymes

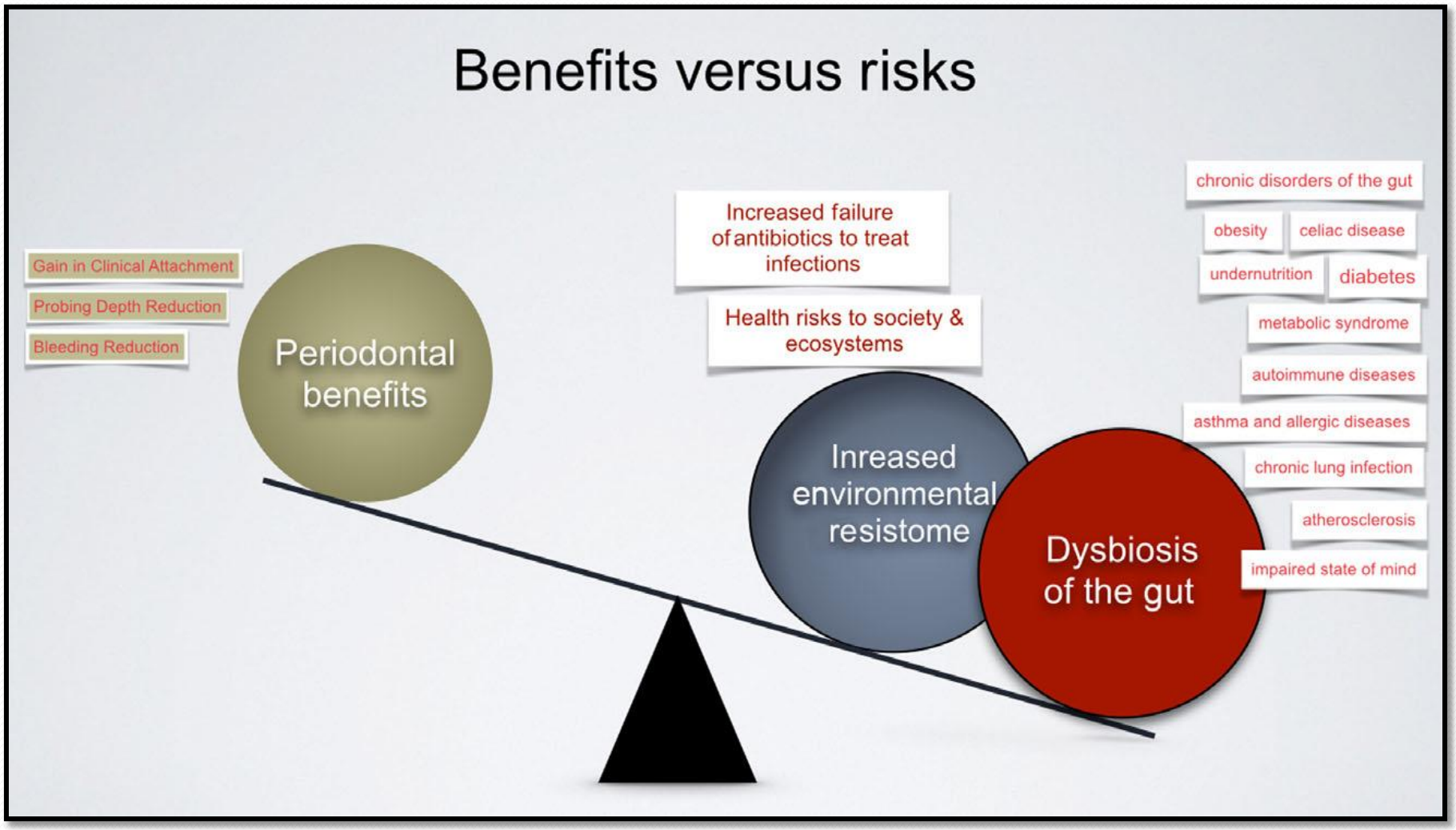
Change in binding molecule

BACTERIAL RESISTANCE



CONCLUSION

- Therapeutic success in periodontal therapy will undoubtedly increase with improved diagnosis, critical host factors, and individually tailored periodontal treatment.
- Antibiotics as a monotherapy are inferior to the time-honoured methods of treatment such as SPR.
- Adjunctive systemic antibiotics, combined with mechanical debridement offer additional clinical improvements.
- Antibiotic prescription should be limited and only used as last resort.



*Jepsen K & Jepsen S Periodontology2000, Vol.71,2016,82-112

Viva voce questions

- What is inoculum effect?
- What is cross resistance?
- What do you mean by MIC & MBC, which is used as a guide for selection of antibiotic?
- What is paradoxical or Eagle effect?
- What do you mean by post antibiotic effect?
- Can systemic antimicrobials used as a monotherapy and why?
- Are adjunctive systemic antibiotics expedient over surgical mechanical therapy alone?
- Which patients would most benefit from systemic antibiotic administration?
- What are the mechanisms of increased antibiotic resistance of organisms in biofilm compared to planktonic cells?
- Adjunctive systemic antimicrobial Vs. LDD?
- Antibiotic prophylaxis for infective endocarditis?

THANK YOU