



UNIVERSITY HOSPITAL OF NORTH NORWAY  
UNIVERSITETSSYKEHUSET NORD-NORGE

# Grunnleggende resistensmekanismer

## Gram-negative: Aminoglykosider

***NordicAST Workshop***  
***Gøteborg 27.05.2014***

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# AMINOGLYKOSIDER

## Streptomyces spp.

Streptomycin

Neomycin

**Tobramycin**

Paromomycin

Kanamycin

**Amikacin**

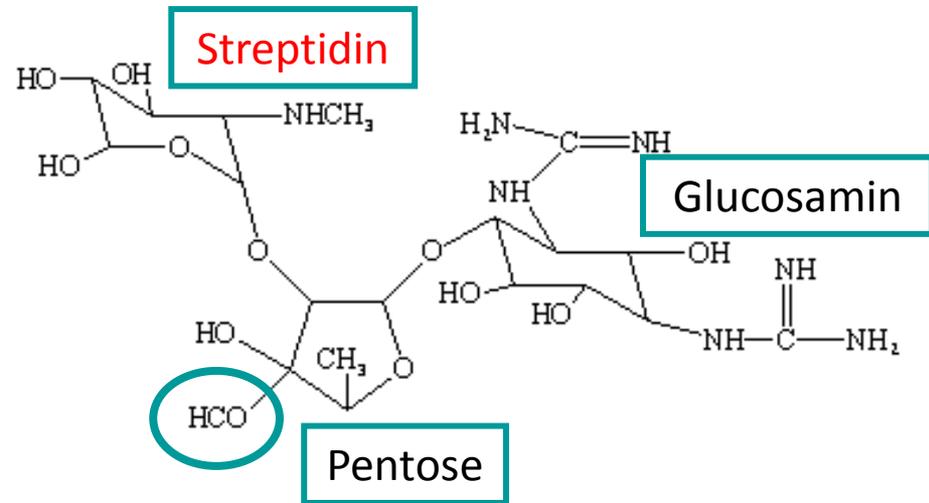
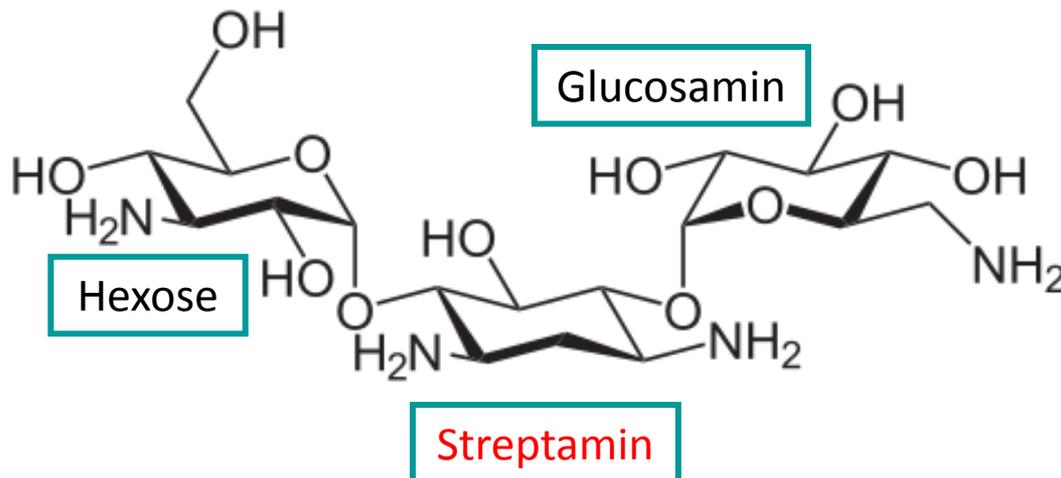
Arbekacin

Spectinomycin

## Micromonospora spp.

**Gentamicin**

Netilmicin



- Aminocyclitolkjerne
- Amino sukker molekyler



# VIRKNINGSMEKANISME

## ➤ Yttermembranen

Erstatter  $Mg^{2+}$  and  $Ca^{2+}$  som kryssbinder lipopolysakkarid molekylene

⇒ økt permeabilitet

## ➤ Proteinsyntesen

Binder til 16S rRNA på 30S subenheten av ribosomet

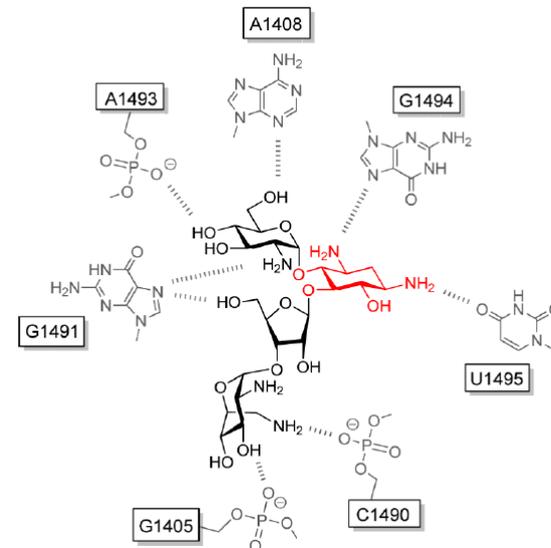
⇒ feil i avlesning av mRNA

⇒ feil i proteinsyntesen

Bactericid, konsentrasjonsavhengig drap

Post-antibiotisk effekt

Synergistisk effekt med celleveggs antibiotika ( $\beta$ -laktamer)



Becker B, Cooper MA ACS Chem. Biol. 2013



# RESISTENSMEKANISMER

- Nedsatt opptak (porintap)
- Efflux (membran pumper)
- Endring i målsetet:
  - ✓ Mutasjoner i målmolekylet 16S rRNA
  - ✓ **Metylering av 16S rRNA (A-setet) – 16S rRNA metylaser\***
- **Aminoglykosidmodifiserende enzymer (AME)\***

**\*Assosiert med mobile genetiske elementer**



# AMINOGLYKOSIDMODIFISERENDE ENZYMER (AME)

- 3 AME familier:
  - ✓ AAC: aminoglykosid N-acetyltransferaser
  - ✓ APH: aminoglykosid O-fosfotransferaser
  - ✓ ANT: aminoglykosid O-nukelotidtransferaser
- Enormt antall AME beskrevet
- Stor diversitet i aktivitetsspektrum



# NOMENKLATUR AME

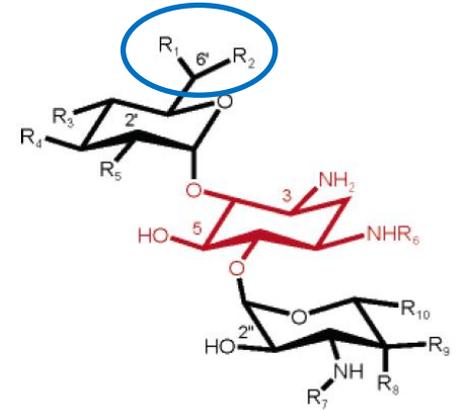
➤ eks. AAC(6')-Ia

✓ **AAC**: mekanisme

✓ AAC(**6'**): posisjon modifisert på AMG

✓ AAC(6')-**I**: fenotype/substratprofil

✓ AAC(6')-I**a**: genotype



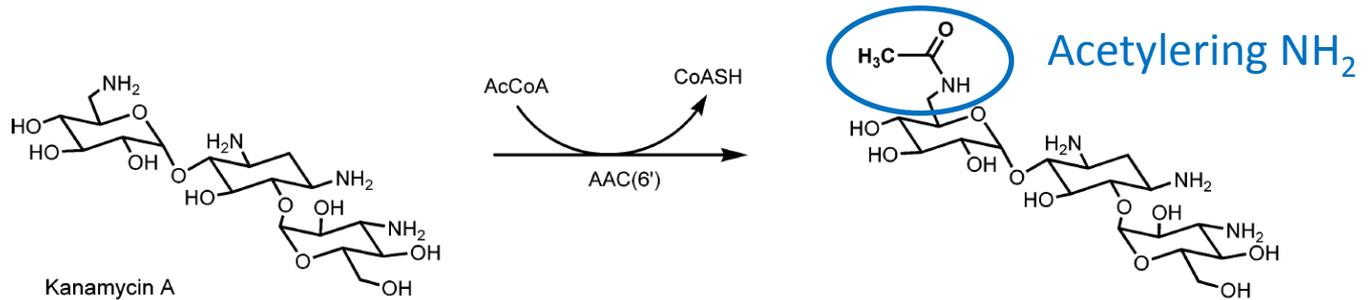
➤ AAC(6')-Ia }  
➤ AAC(6')-Ib }

- Identisk mekanisme
- Modifiserer AMG på samme posisjon
- Identisk substratprofil
- Kodet av forskjellig gen (*aac(6')-Ia* vs. *aac(6')-Ib*)

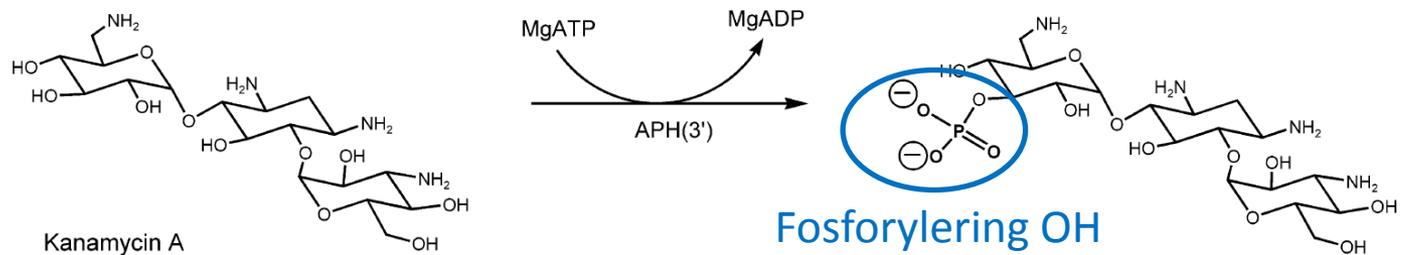


# MEKANISMER AME

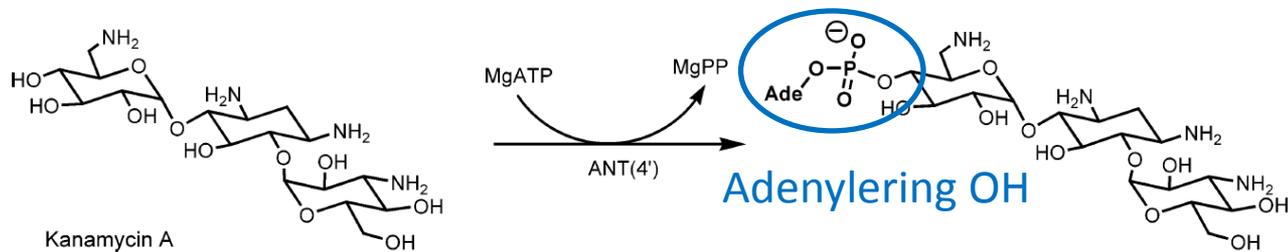
## ➤ AAC



## ➤ APH:



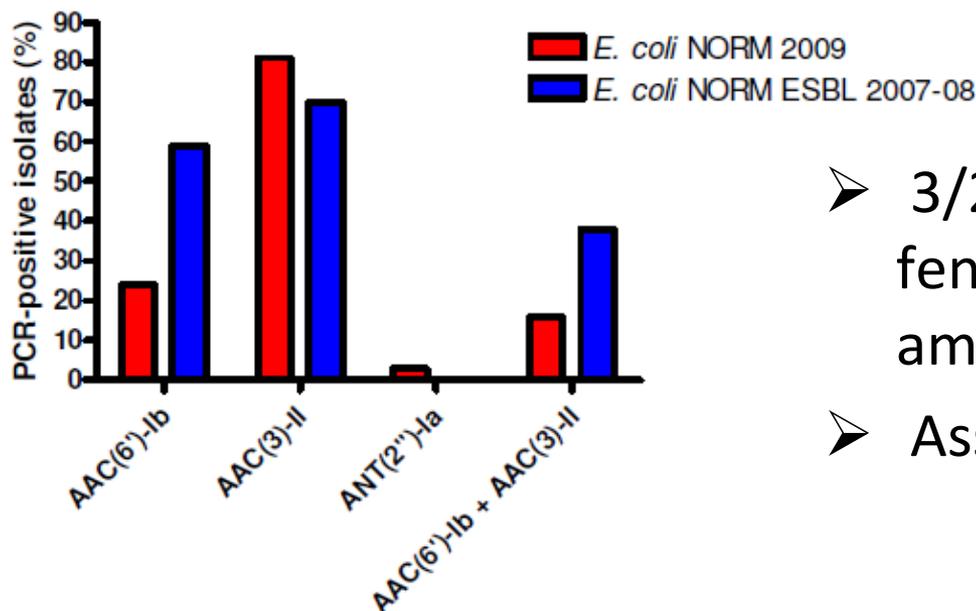
## ➤ ANT:



# AME GRAM-NEGATIVE

| Klasse           | Eks.                        | Substratprofil   |
|------------------|-----------------------------|--|
| <b>AAC(6')</b>   | AAC(6')-Ib/-Ib-cr           | <b>Gentamicin C1a, Gentamicin C2, Amikacin, Ciprofloxacin, Norfloxacin</b> |
| AAC(3)-I         | AAC(3)-Ia, AAC(3)-Ib        | <b>Gentamicin, Sisomycin, Fortimicin</b>                                   |
| <b>AAC(3)-II</b> | AAC(3)-IIb/c                | <b>Gentamicin, Tobramycin, Netilimicin, Sisomicin, Dibekacin</b>           |
| ANT(2'')         | ANT(2'')-Ia ( <i>aadB</i> ) | <b>Gentamicin, Tobramycin, Dibekacin, Sisomycin, Kanamycin</b>             |
| ANT(4')          | ANT(4')-II                  | <b>Tobramycin, Amikacin, Isepamycin</b>                                    |

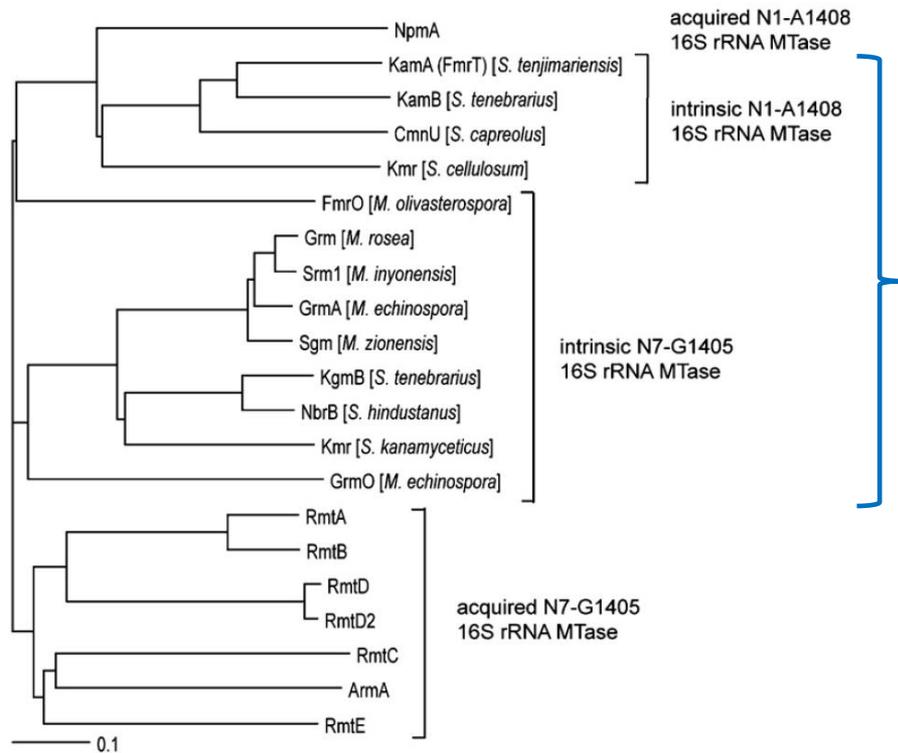
Ramirez MS, Tolmasky ME *Drug Resist. Updates* 2010



- 3/22 AAC(6')-Ib positive isolater fenotypisk resistent mot amikacin
- Assosiasjon med ESBL?



# 16S rRNA METYLASER



Aminoglykosid-produserende  
*Streptomyces* og *Micromonospora*

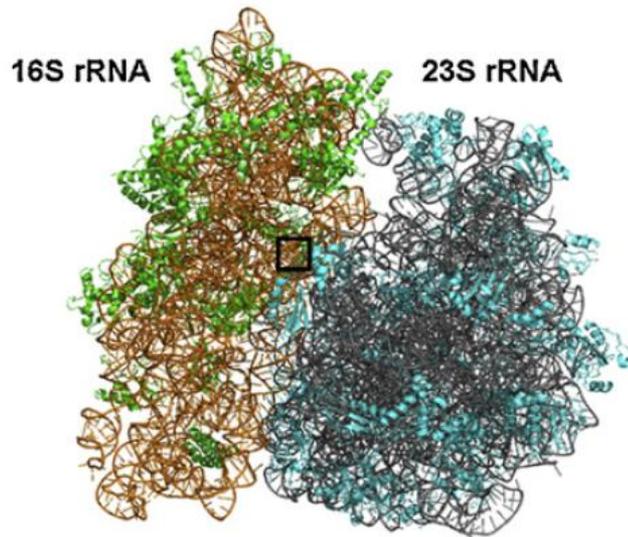
## ➤ Mobile 16S rRNA metylaser:

- ✓ N7-G1405: **ArmA**, RmtA, **RmtB**, **RmtC**, RmtD, RmtE, RmtF, RmtG
- ✓ N1-A1408: NpmA

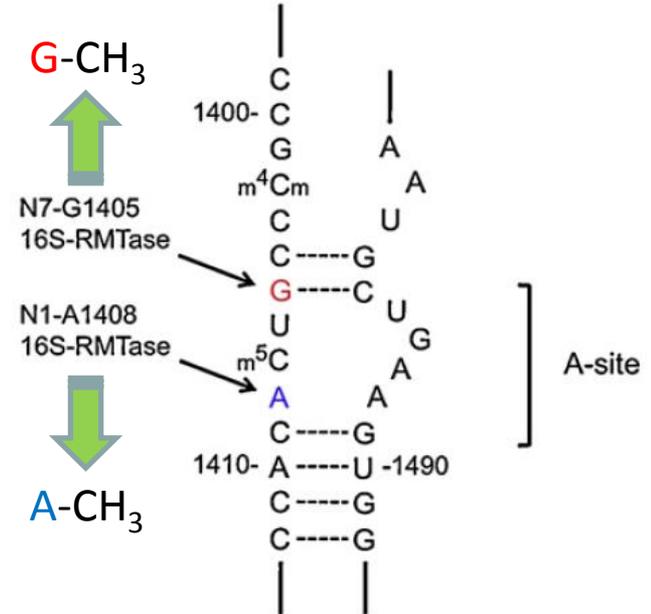


# RESISTENSMEKANISME 16S rRNA METYLASER

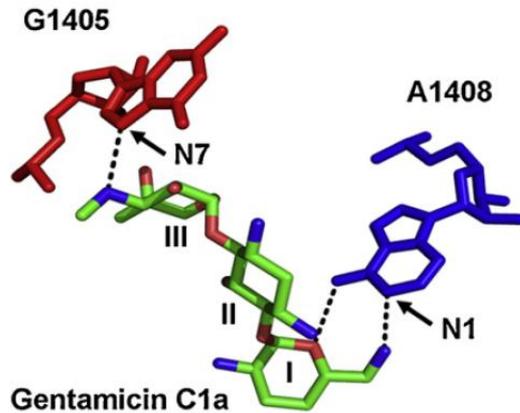
(A)



(B)



(C)



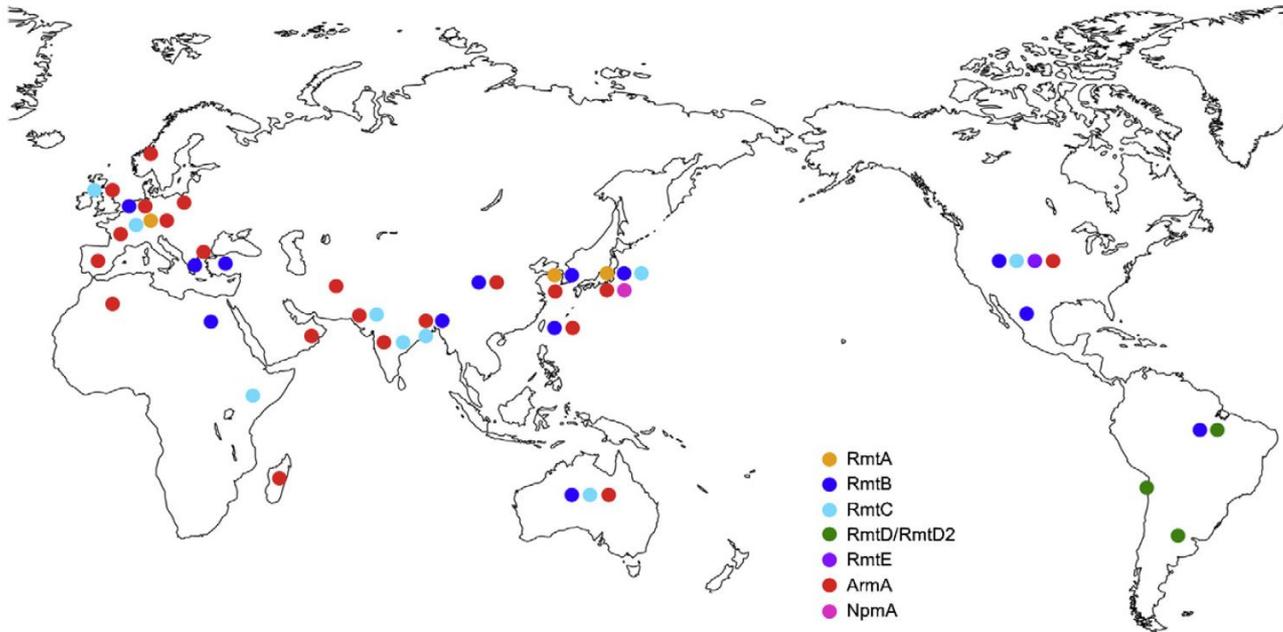
# RESISTENSPROFIL 16S rRNA METYLASER

## ➤ Bredspektret høygradig resistens

| Aminoglykosid | N7-G1405<br>(ArmA, RmtA-G) | N1-A1408<br>(NpmA) |
|---------------|----------------------------|--------------------|
| Gentamicin    | R+ (MIC ≥ 128mg/L)         | R                  |
| Amikacin      | R+ (MIC ≥ 128mg/L)         | R                  |
| Tobramycin    | R+ (MIC ≥ 128mg/L)         | R+                 |
| Neomycin      | S                          | R+                 |
| Apramycin     | S                          | R+                 |
| Streptomycin  | S                          | S                  |



# GLOBAL SPREDNING



- NDM-1:
  - ✓ ArmA/RmtB/RmtC
- SPM-1:
  - ✓ RmtB
- OXA-23:
  - ✓ ArmA
- KPC:
  - ✓ ArmA/RmtB
- CTX-M :
  - ✓ ArmA/RmtB

Wachino J-i, Arakawa Y *Drug Resist. Updates* 2012

|                             | MIC (mg/L) |      |      |      |     |     |     |       |      |       |
|-----------------------------|------------|------|------|------|-----|-----|-----|-------|------|-------|
|                             | AMC        | TZP  | CTX  | CAZ  | MEM | IPM | ETP | GEN   | AMK  | TOB   |
| <i>E. coli</i> NDM-1 + RmtC | >256       | >256 | >256 | >256 | 16  | 32  | 16  | >1024 | >256 | >1024 |



# OPPSUMMERING

## ➤ Aminoglykosidmodifiserende enzymer (AME):

- ✓ AAC; APH; ANT
- ✓ Modifiserer AMG molekylet
- ✓ Diversitet i spektrum
- ✓ AAC(3)-II, AAC(6)-Ib(-cr)

## ➤ 16S rRNA metylaser:

- ✓ Bredspektret høygradig AMG-resistens
- ✓ Modifiserer målmolekylet
- ✓ Assosiert med  $ESBL_{CARBA}$  &  $ESBL_A$



**TAKK FOR OPPMERKSOMHETEN**

