Evaluation of the CarbaR+ Novodiag® system for the detection of carbapenemase-producing bacteria

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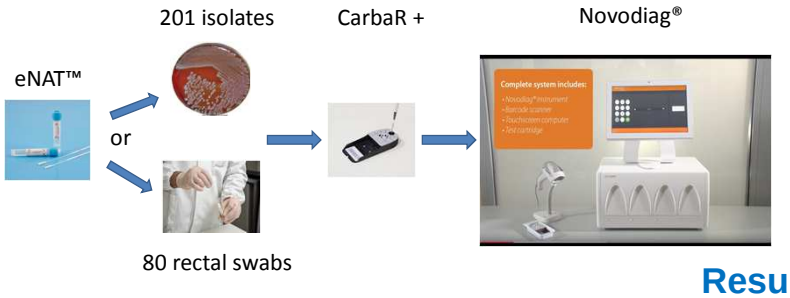
Introduction

Carbapenemase-producing Gram-negatives represent a global concern for public health. The rapid implementation of infection control measures at the hospital requires easy, efficient and reliable detection tools of carbapenemase production .

Recently, Novodiag® CarbaR+ (Mobidiag Ltd, Espoo, Finland), a simple "sample in-answer out" qualitative multiplexed nucleic acid-based *in vitro* diagnostic test, was launched on the market for the simultaneous detection of 9 major carbapenemases and MCR-1 producing strains. This assay was evaluated on collection isolates and clinical fecal swabs.



Material and methods

The NOVOdiag® CarbaR+ is a fully automated random access, multiplex nucleic acid based diagnostic test for the detection carbapenemases genes of on bacterial culture or fecal swabs in eNAT™ tubes (Copan Italia). The principle of the test is based on real-time PCR and microarray hybridization with detection by contact fluorescence imaging and evanescent excitation all performed within a single cartridge.

The test targets 9 carbapenemase encoding genes **including *bla*$_{KPC}$, *bla*$_{NDM}$, *bla*$_{VIM}$, *bla*$_{IMP}$, *bla*$_{OXA-48-like}$;** the ***Acinetobacter* OXA-carbapenemase genes including *bla*$_{OXA-23-like}$, *bla*$_{OXA-24-like}$, *bla*$_{OXA-58-like}$, the chromosomal *bla*$_{OXA-51-like}$ with upstream promoter IS*Aba*1** and the major plasmid-mediated colistin resistance gene **mcr-1**.

Samples :

- **201 cultured colonies** of non fermenters and enterobacterial collection isolates (61 *Pseudomonas*, 60 *Acinetobacter* and 80 Enterobacterales) with characterized β-lactamase content
- **and 80 clinical rectal swabs** collected from hospitalized patients.
- Ss and Sp calculated on the number of targets after reconciliation of the discrepancies

Results

- **Globally, 98.8 % Sensitivity (Ss) and 99.7 % of Specificity (Sp) for the detection of the carbapenemase and MCR-1 coding genes on the entire collection isolates**
  - **100% Ss and Sp for *Pseudomonas* spp.**
  - **96.7 % Ss and 99.4 % Sp for *Acinetobacter sp.***
  - **100 % Ss and 99.7 % Sp for Enterobacterales**
- **97,8 % Ss and 98,6 % Sp on clinical fecal swabs for the detection of the different targets**
- **1 False positive (FP) and 1 False negative (FN) clinical swabs for the detection of the carbapenemase-producing status**
  - **1 FN *E. coli* OXA-181 not detected**
  - **1 FP NDM/OXA-48 detected for a culture negative swabs from a patient formerly known as OXA-48 carrier**
- **2.3 % of invalid results**

Species (n)[a]	β-lactam-, or colistin- resistance mechanism	Novodiag CarbaR+ discordant result KPC, NDM, VIM, IMP, OXA-48-like, OXA-23, OXA-40, OXA-58, IS*Aba1*-OXA-51
Non-carbapenemase and not targeted carbapenemase (53)		
P. aeruginosa (22), A. baumannii (9), A. pittii (3), E. cloacae (7), C. freundii (3), other (9)	Efflux, overexpressed AmpC, Porin deficiency, overexpressed K1, TEM, SHV, CTX-M, BEL, VEB, PER, GES, PME-1, OXA-1, 2, -10, -20, -163, -405, Carb, RTG-4, SCO-1; DIM, FIM, GIM, LMB, NmcA, Sme, SIM, SPM, TMB, FRI, OXA-143, OXA-198, OXA-372	1 FP OXA-163 and 1 FP OXA-405
Single targeted carbapenemase (117)		
P. aeruginosa (30), A. baumannii (23), E. coli (25), K. pneumoniae (11), P. putida (5), other (23)	KPC, VIM, IMP, NDM, OXA-48, IS*Aba* -1-OXA-51, OXA-23, OXA-24 /40, OXA-58	1 FP OXA-23 for *A. baumannii* OXA-72 + OXA-24; 1 FP OXA-24 for OXA-97 (OXA-58-like) and FN OXA-58
Multiple carbapenemase or colistin targeted resistance (26)		
A. baumannii (10), E. coli (5), E. cloacae (3), K. pneumoniae (3), other (5)	KPC + OXA-48, IMP + OXA-58, NDM + IS*Aba* 1-OXA-51 or OXA-48 or VIM or OXA-23 or KPC, VIM + OXA-48 or OXA-23; OXA-23 + IS*Aba* -51 or OXA-58; MCR-1 + NDM-1 or OXA-48	1 FN OXA-23 in *A. haemolyticus* OXA-23 + OXA-58; 1 FP OXA-58 for *A. baumannii* VIM-4 + OXA-23; 1 FN IS*Aba* -1 OXA-51 for *A. baumannii* OXA-23 + IS*Aba1* -OXA-69
Colistin resistance (5)		
E. coli (4), K. pneumoniae (1)	MCR-1, MCR-2, -4, -5, PmrB mutation	

Table 1 Collection of clinical isolates (n=201) FP: false positive result; FN: false negative result

Patients swabs

Species on CHROMID® CARBA SMART and PCR-Seq Resistance identification

	Discordant results CarbaR+
KPC-like (5)	
K. pneumoniae (5)	1 FP NDM
Multiple R (8): OXA-23+VIM; VIM + OXA-48; NDM + OXA-181 or 48; OXA-23 + OXA-48 + IS*Aba*1-OXA-51	
C. freundii (1)	
E. coli (2)	
P. aeruginosa + A. baumannii (2)	
P. aeruginosa + K. pneumoniae (1)	1 FP NDM + FN VIM; OXA-48 OK
E. coli + R. ornithinolytica (1)	
E. coli + A. baumannii (1)	
NDM-like (12)	
E. coli (5)	1 FN VIM, NDM OK
E. coli + K. pneumoniae (3)	1 FP OXA-23; NDM OK
E. cloacae (2)	
K. pneumoniae (2)	
Neg (6)	
Neg (6)	**1 FP NDM + OXA-48**
OXA-23 (1)	
E. coli + A baumannii (1)	
OXA-48-like (48)	
E. coli (20)	**1 FN OXA-48**
E. coli + K. pneumoniae (12)	
K. pneumoniae (8)	1 FP NDM; OXA-48 OK
C. freundii (2)	1 FP OXA-23 + OXA-58; OXA-48 OK
E. coli + R. ornithinolytica (2)	
E. coli + C. freundii (1)	1 FP NDM; OXA-48 OK
E. coli + K. oxytoca (1)	
E. coli + K. pneumoniae+ E. cloacae (1)	
R. ornithinolytica (1)	

Table 2 Clinical rectal swabs (n=80) FP: false positive; FN: false negative

Conclusions

- **The Novodiag® CarbaR+ is an easy to use sample in-answer out technology**
- **The instrument is random access with results obtained in 80 minutes**
- **The test allows the detection of the most frequently encountered carbapenemases among Enterobacterales AND non-fermenters including multiple variants but excluding GES carbapenemases.**
- **Performance directly on faecal swab are very good but deserves further evaluation on a large number of consecutive clinical samples**