VANC3

cobas®

ONLINE TDM Vancomycin Gen.3

Order information

REF		CONTENT		Analyzer(s) on which **cobas c** pack(s) can be used
08445605190	08445605500	ONLINE TDM Vancomycin Gen.3 (100 tests)	System-ID 2121 002	**cobas c** 303, **cobas c** 503
08058849190	08445605500	ONLINE TDM Vancomycin Gen.3 (200 tests)	System-ID 2121 003	**cobas c** 303, **cobas c** 503

Materials required (but not provided):

03375790190	Preciset TDM I CAL A-F (1 × 5 mL) Diluent (1 × 10 mL)	Codes 20691-20696	
04521536190	TDM Control Set Level I (2 × 5 mL) Level II (2 × 5 mL) Level III (2 × 5 mL)	Code 20310 Code 20311 Code 20312	

English

System information

VANC3: ACN 21210 (100 tests; System ID 2121 002)

VANC3O: ACN 21211 (200 tests; System ID 2121 003)

Intended use

In vitro test for the quantitative determination of vancomycin in serum and plasma on **cobas c** systems.

Summary

Vancomycin measurements performed with this assay, in human serum and plasma, are used for monitoring vancomycin treatment to ensure appropriate therapy.

Vancomycin is a tricyclic glycopeptide isolated from *Streptomyces orientalis* that inhibits the synthesis of the cell wall in sensitive bacteria (mainly gram-positive bacteria and some gram-negative cocci).[1,2] It displays concentration-independent activity[2] and is used because of its efficacy against methicillin-resistant staphylococci and corynebacteria.[3,4]

Vancomycin is available as intravenous and oral formulations and is indicated in the treatment of infections such as complicated skin and soft tissue infections, community and hospital acquired pneumonia and *Clostridium difficile* infection, and for the perioperative antibacterial prophylaxis in patients that are at high risk of developing bacterial endocarditis.[2,3,4]

Monitoring of vancomycin serum or plasma levels is used to ascertain clinical efficacy and to limit potentially dose-dependent serious side effects, such as nephro- and ototoxicity[1,2,4] and is recommended by guidelines and clinical societies.[5,6,7,8,9,10,11]

Test principle

The assay is based on the kinetic interaction of microparticles in a solution (KIMS). Vancomycin antibody is covalently coupled to microparticles and the drug derivative is linked to a macromolecule. The kinetic interaction of microparticles in solutions, photometrically detected by turbidity measurements is induced by binding of drug-conjugate to the antibody on the microparticles and is inhibited by the presence of vancomycin in the sample. A competitive reaction takes place between the drug conjugate and vancomycin in the serum sample for binding to the vancomycin antibody on the microparticles. The resulting turbidity is indirectly proportional to the amount of drug present in the sample.

Reagents - working solutions

R1 Vancomycin conjugate; piperazine-N,N'-bis(2-ethanesulfonic acid) (PIPES) buffer, pH 7.2; preservative; stabilizer

R3 Anti-vancomycin antibody (mouse monoclonal); latex microparticle; 3-(N-morpholino)propane sulfonic acid (MOPS) buffer, pH 7.2; stabilizer

R1 is in position B and R3 is in position C.

Precautions and warnings

For in vitro diagnostic use for health care professionals. Exercise the normal precautions required for handling all laboratory reagents.

Infectious or microbial waste:
Warning: handle waste as potentially biohazardous material. Dispose of waste according to accepted laboratory instructions and procedures.

Environmental hazards:
Apply all relevant local disposal regulations to determine the safe disposal.

Safety data sheet available for professional user on request.

Reagent handling

Ready for use

Carefully invert reagent container several times prior to use to ensure that the reagent components are mixed.

Storage and stability

Shelf life at 2-8 °C:	See expiration date on **cobas c** pack label
On-board in use and refrigerated on the analyzer:	12 weeks

Do not freeze.

Specimen collection and preparation

For specimen collection and preparation only use suitable tubes or collection containers.

Only the specimens listed below were tested and found acceptable.
Serum
Plasma: K_2- or K_3-EDTA, lithium heparin.
Sample collection tubes containing separating gel have not been verified for use.

Stability:	48 hours capped at 15-25 °C
	14 days capped at 2-8 °C
	12 months capped at -20 °C (± 5 °C)

The sample types listed were tested with a selection of sample collection tubes that were commercially available at the time of testing, i.e. not all available tubes of all manufacturers were tested. Sample collection systems from various manufacturers may contain differing materials which could affect the test results in some cases. When processing samples in primary tubes (sample collection systems), follow the instructions of the tube manufacturer.

Centrifuge samples containing precipitates before performing the assay.

See the limitations and interferences section for details about possible sample interferences.

Do not induce foaming of specimens. Specimens can be repeatedly frozen and thawed up to 5 times.

Invert thawed specimens several times prior to testing.

Usual sampling time varies dependent upon desired measurement of peak or trough values.[12]

Materials provided

See “Reagents – working solutions” section for reagents.

Materials required (but not provided)

See “Order information” section

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General laboratory equipment

Assay

For optimum performance of the assay follow the directions given in this document for the analyzer concerned. Refer to the appropriate operator's manual for analyzer-specific assay instructions.

The performance of applications not validated by Roche is not warranted and must be defined by the user.

Application for serum and plasma

Test definition

Reporting time	10 min		
Wavelength (sub/main)	800/600 nm		
Reagent pipetting		Diluent (H_2O)	
R1	65 µL	–	
R3	46 µL	–	
Sample volumes	*Sample*	*Sample dilution*	
		Sample	Diluent (H_2O)
Normal	1.3 µL	–	–
Decreased	1.3 µL	–	–
Increased	1.3 µL	–	–

For further information about the assay test definitions refer to the application parameters setting screen of the corresponding analyzer and assay.

Calibration

Calibrators	S1-6: Preciset TDM I calibrators
Calibration mode	Non-linear
Calibration frequency	Full calibration - after reagent lot change - every 2 weeks on-board - as required following quality control procedures

Calibration interval may be extended based on acceptable verification of calibration by the laboratory.

Traceability: This method has been standardized against USP reference standards.[13] The calibrators are prepared to contain known quantities of vancomycin in normal human serum.

Quality control

For quality control, use control materials as listed in the "Order information" section.

In addition, other suitable control material can be used.

The control intervals and limits should be adapted to each laboratory's individual requirements. It is recommended to perform quality control always after lot calibration and subsequently at least every 12 weeks.

Values obtained should fall within the defined limits. Each laboratory should establish corrective measures to be taken if values fall outside the defined limits.

Follow the applicable government regulations and local guidelines for quality control.

Calculation

cobas c systems automatically calculate the analyte concentration of each sample in the unit µg/mL (µmol/L, mg/L).

Conversion factors:[14]	µg/mL x 0.690 = µmol/L
	µg/mL x 1.0 = mg/L

Limitations - interference

Criterion: Recovery within ± 1 µg/mL (0.690 µmol/L) of initial values of samples ≤ 10 µg/mL (5.18 µmol/L) and within ± 10 % for samples > 10 µg/mL (5.18 µmol/L).

Serum/Plasma

Icterus:[15] No significant interference up to an I index of 60 for conjugated bilirubin and unconjugated bilirubin (approximate conjugated and unconjugated bilirubin concentration: 60 mg/dL or 1026 µmol/L).

Hemolysis:[15] No significant interference up to an H index of 1000 (approximate hemoglobin concentration: 1000 mg/dL or 622 µmol/L).

Lipemia (Intralipid):[15] No significant interference up to an L index of 1000. There is poor correlation between the L index (corresponds to turbidity) and triglycerides concentration.

Triglycerides: No significant interference from triglycerides up to a concentration of 1000 mg/dL (11.4 mmol/L).

Rheumatoid factors: No significant interference from rheumatoid factors up to a concentration of 1200 IU/mL.

Total protein: No significant interference from total protein in the concentration range of 2-12 g/dL.

As with any assay employing mouse antibodies, the possibility exists for interference by human anti-mouse antibodies (HAMA) in the sample, which could cause falsely lowered results.

In very rare cases, gammopathy, in particular type IgM (Waldenström's macroglobulinemia), may cause unreliable results.[16]

In very rare cases (less than 1 reported case per 1000000 tests) certain immunoglobulins can unspecifically interfere with the agglutination reaction leading to unreliable results.

Note: A test result flagged with ">Kin3" indicates unusual reaction kinetics. There is a high possibility that the sample contains an interfering substance which accelerates the reaction kinetics. For such samples it is not possible to report a reliable analyte concentration with this assay.

For diagnostic purposes, the results should always be assessed in conjunction with the patient's medical history, clinical examination and other findings.

ACTION REQUIRED

Special Wash Programming: The use of special wash steps is mandatory when certain test combinations are run together on **cobas c** systems. All special wash programming necessary for avoiding carry-over is available via the **cobas** link. The latest version of the carry-over evasion list can be found with the NaOHD/SMS/SCCS Method Sheet. For further instructions, refer to the operator's manual.

Limits and ranges

Measuring range

4.0-80.0 µg/mL (2.76-55.2 µmol/L)

Manually dilute samples above the measuring range 1 + 1 with the Preciset TDM I diluent (0 µg/mL) and reassay. Multiply the result by 2 to obtain the specimen value.

Lower limits of measurement

Limit of Blank, Limit of Detection and Limit of Quantitation

Limit of Blank	= 1.0 µg/mL (0.69 µmol/L)
Limit of Detection	= 1.5 µg/mL (1.04 µmol/L)
Limit of Quantitation	= 4.0 µg/mL (2.76 µmol/L)

The Limit of Blank, Limit of Detection and Limit of Quantitation were determined in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP17-A2 requirements.

The Limit of Blank is the 95th percentile value from n ≥ 60 measurements of analyte-free samples over several independent series. The Limit of Blank corresponds to the concentration below which analyte-free samples are found with a probability of 95 %.

The Limit of Detection is determined based on the Limit of Blank and the standard deviation of low concentration samples.

The Limit of Detection corresponds to the lowest analyte concentration which can be detected (value above the Limit of Blank with a probability of 95 %).

The Limit of Quantitation is the lowest analyte concentration that can be reproducibly measured with a total error of 20 %. It has been determined using low concentration vancomycin samples.

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Expected values

The practice of routine monitoring and adjustment of serum vancomycin concentrations has been the subject of intense debate for many years.[17] Historically trough concentrations between 5 to 10 µg/mL and peak concentrations between 20 to 40 µg/mL were generally accepted for therapeutic effectiveness.[17,18,14] The increased prevalence of resistant organisms, increasing vancomycin minimum inhibitory concentrations in target pathogens (particularly MRSA) and vancomycin failures have prompted more aggressive vancomycin dosing practices and recommendations.[17,19] Therefore, current guidelines recommend higher trough concentrations in the range of 10-15 µg/mL for uncomplicated MRSA bacteremia and even 15-20 µg/mL in cases of sustained MRSA bacteremia or endocarditis and other severe invasive MRSA infections (i.e. prosthetic joint infections, hospital-acquired pneumonia or central nervous system infections).[7,17] However, higher doses of vancomycin used have been associated with significantly higher vancomycin trough levels, acute renal failure and ototoxicity.[19,20,21,22] The decision to target increased vancomycin trough concentrations should be based on an assessment of the severity of the infection and must consider the risk associated with increased vancomycin levels.

Expected values reflect the data and information provided in the reference and do not necessarily represent therapeutic recommendations and/or dosage instructions. For therapeutic recommendations and dosage instructions refer to applicable guidelines and the full prescription information of the drug.

Each laboratory should investigate the transferability of the expected values to its own patient population and if necessary determine its own reference ranges.

Specific performance data

Representative performance data on the analyzers are given below. These data represent the performance of the analytical procedure itself.

Results obtained in individual laboratories may differ due to heterogenous sample materials, aging of analyzer components and mixture of reagents running on the analyzer.

Precision

Precision was determined using human samples and controls in accordance with the CLSI (Clinical and Laboratory Standards Institute) EP05-A3 requirements with repeatability (n = 84) and intermediate precision (2 aliquots per run, 2 runs per day, 21 days). Results for repeatability and intermediate precision were obtained on the **cobas c** 503 analyzer.

Serum/Plasma

Repeatability	*Mean*	*SD*	*CV*
	µg/mL	*µg/mL*	*%*
TDMC1[a)]	7.49	0.129	1.7
TDMC2[b)]	21.7	0.210	1.0
TDMC3[c)]	34.6	0.304	0.9
Human serum 1	5.18	0.120	2.3
Human serum 2	8.29	0.135	1.6
Human serum 3	27.9	0.263	0.9
Human serum 4	43.1	0.472	1.1
Human serum 5	74.1	0.763	1.0
Intermediate precision	*Mean*	*SD*	*CV*
	µg/mL	*µg/mL*	*%*
TDMC1[a)]	7.49	0.197	2.6
TDMC2[b)]	21.7	0.318	1.5
TDMC3[c)]	34.6	0.447	1.3
Human serum 1	5.18	0.191	3.7
Human serum 2	8.29	0.229	2.8
Human serum 3	27.9	0.414	1.5
Human serum 4	43.1	0.617	1.4
Human serum 5	72.7	1.41	1.9

a) TDM Control Set Level I

b) TDM Control Set Level II

c) TDM Control Set Level III

The data obtained on **cobas c** 503 analyzer(s) are representative for **cobas c** 303 analyzer(s).

Method comparison

Serum/plasma

Vancomycin values for human serum samples obtained on a **cobas c** 503 analyzer (y) were compared with those determined using the corresponding reagent on a **cobas c** 501 analyzer (x).

Sample size (n) = 119

Passing/Bablok[23]	Linear regression
y = 1.004x - 0.345 µg/mL	y = 1.005x - 0.437 µg/mL
τ = 0.966	r = 0.996

The sample concentrations were between 4.29 and 79.8 µg/mL.

Serum/plasma

Vancomycin values for human serum samples obtained on a **cobas c** 303 analyzer (y) were compared with those determined using the corresponding reagent on a **cobas c** 501 analyzer (x).

Sample size (n) = 113

Passing/Bablok[23]	Linear regression
y = 1.007x - 0.427 µg/mL	y = 1.022x - 0.829 µg/mL
τ = 0.977	r = 0.999

The sample concentrations were between 4.90 and 76.6 µg/mL.

Analytical specificity

The following compounds were tested for cross-reactivity.

Compound	Concentration Tested (µg/mL)	% Cross-reactivity
Acyclovir	50	ND
Amikacin	100	ND
Amphotericin B	10	ND
Aztreonam	450	ND
Caffeine	60	ND
CDP-1	20	ND
Cefazoline	500	ND
Cefotaxine	300	ND
Chloramphenicol	60	ND
Ciprofloxicin	12	ND
Cisplatin	15	ND
Clindamycin	50	ND
Cyclosporine	3	ND
Digoxin	0.009	ND
Epinephrine	1	ND
Erythromycin	60	ND
Ethacrynic acid	1.5	ND
Flucytosine	300	ND
Furosemide	60	ND
Fusidic acid	600	ND
Gentamicin	30	ND
Imipenem	250	ND
Methicillin	250	ND

Methotrexate	455	ND
Metronidazole	150	ND
Netilmicin	30	ND
Nitroprusside	90	ND
Penicillin G	36	ND
Pentamidine	1.5	ND
Phenobarbital	150	ND
Rifampin	60	ND
Salicylate	750	ND
Sulphamethoxazole	400	ND
Theophylline	60	ND
Tobramycin	30	ND
Trimethoprim	40	ND

ND = Not detectable

Tests were performed on 16 drugs. No significant interference with the assay was found.

Acetaminophen	Heparin
Acetyl cysteine	Ibuprofen
Acetylsalicylic acid	Levodopa
Ampicillin-Na	Methyldopa + 1.5 H_2O
Ascorbic acid	Metronidazole
Cefoxitin	Phenylbutazone
Cyclosporine	Rifampicin
Doxycycline (Tetracycline)	Theophylline

References

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A point (period/stop) is always used in this Method Sheet as the decimal separator to mark the border between the integral and the fractional parts of a decimal numeral. Separators for thousands are not used.

Any serious incident that has occurred in relation to the device shall be reported to the manufacturer and the competent authority of the Member State in which the user and/or the patient is established.

The Summary of Safety & Performance Report can be found here: https://ec.europa.eu/tools/eudamed

Symbols

Roche Diagnostics uses the following symbols and signs in addition to those listed in the ISO 15223-1 standard (for USA: see navifyportal.roche.com for definition of symbols used):

CONTENT	Contents of kit

VANC3

ONLINE TDM Vancomycin Gen.3

→	Volume for reconstitution
GTIN	Global Trade Item Number
Rx only	For USA: Caution: Federal law restricts this device to sale by or on the order of a physician.

CE 0123

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