Instructions for use

eazyplex® CSF direct

Molecular biological rapid test for direct detection of infectious agents in cerebrospinal fluid

for use with Genie® II Mk2 devices

For in vitro diagnostic use

CE

eazyplex® CSF direct	REF: 7630
eazyplex® CSF direct V	REF: 7631
eazyplex® CSF direct B	REF: 7633
eazyplex® CSF direct M	REF: 7634
language: english	valid from: April 2019

Explanation of symbols

IVD		in vitro diagnostic medical device
LOT		Batch code
REF		Catalogue number
		Use by
		Temperature limitation
TESTSTRIP		Teststrip
		Contains sufficient for <n> tests
		Consult instructions for use
		No re-use
		Manufacturer
	H319 P305 + P351 + P338 P337 + P313	Warning

Nature of special risk and safety precautions (H and P codes):

H319	Causes serious eye irritation.
P305 + P351 + P338	IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
P337 + P313	If eye irritation persists: Get medical advice/attention.

Document Revision Information:
Actualization of symbols according to EN ISO 15223-1, page numbers inserted, centrifuge added (4.2), software version actualised (4.2), „select the test manually“ deleted (8.1), Documentation under 9. amended by PDF report and CSV file, Warning messages inserted under 9., 11. Troubleshooting amended, general improvement of phrases.

1. Intended Use

The **eazyplex® CSF direct** test system is a qualitative in vitro diagnostic medical device for the detection of infectious agents (bacteria and viruses) in cerebrospinal fluid which may cause inflammations of the central nervous system (CNS).

eazyplex® CSF direct (Cat. No. 7630) determines HSV-1, HSV-2, VZV, as well as *N. meningitidis*, *S. pneumoniae*, *S. agalactiae* and *L. monocytogenes*.

The following variants are available:
eazyplex® CSF direct V (Cat. No. 7631) determines HSV-1, HSV-2 and VZV.

eazyplex® CSF direct B (Cat. No. 7633) determines *N. meningitidis*, *S. pneumoniae*, *S. agalactiae* and *L. monocytogenes*.

eazyplex® CSF direct M (Cat. No. 7634) determines *E. coli*, *H. influenzae*, *N. meningitidis*, *S. pneumoniae*, *S. agalactiae* and *L. monocytogenes*.

The test can be performed at any time by qualified professional staff in a medical laboratory. The intended use includes aid to diagnosis (providing additional information to assist in the determination or verification of a patient´s clinical status, test is not the sole determinant) of all kind of patients via testing cerebrospinal fluid.

2. Inflammations of CNS in response to infectious agents

The central nervous system consists of cerebrum, cerebellum, pons, brainstem, spinal cord and the meninges. The space in-between contains cerebrospinal fluid. Infections may intrude directly into the CNS (e.g. Otitis media), ascend via cranial or spinal nerves (e.g. VZV, HSV) or reach CNS via blood or lymph streams.
One discriminates:

- meningitis (inflammation of meninges)
  - meningitis: caused by bacteria, fungi, and sometimes protozoa
  - abacterial meningitis: lacking above mentioned microorganisms; mostly of viral origin (but also tumors or bleedings)
- encephalitis (inflammation of brain): mostly of viral etiology (but diseases accompanied by demyelination as well)
- myelitis (inflammation of myelon / spinal cord): subacute or chronical infections. Depending on the dimension an afferent or motoric paraplegia can occur. A meningomyelitis results from direct expansion of an inflammation to the spinal cord. Differential diagnosis is important for differentiation against acute myelopathy, a severe illness requiring prompt action (e.g., compression of myelon by bleeding, herniated disc, tumor).
- meningoencephalitis: inflammation of brain and meninges
- encephalomyelitis: inflammation of brain and myelon

Bacterial meningoencephalitis

Clinical symptoms are headache, high fever and stiffness of neck (may be absent in early stage, in comatose patients, in children or immune deficient persons). About 10% of patients show involvement of cerebral nerves (e.g., facial nerve paresis). Furthermore, sickness, vomiting, photophobia, amentia, loss of vigilance, epileptic seizures or auditory defects can appear.
The main agents of bacterial meningoencephalitis in europe are:

- In adults: *Streptococcus pneumoniae* and *Neisseria meningitidis*, followed by *Listeria monocytogenes* <5% (mostly patients >60 years), staphylococci, gram-negative enterobacteria, *Haemophilus influenzae*
- In children: *S. pneumoniae* and *N. meningitidis*, (*H. influenzae* declined)
- In new-borns: *Streptococcus agalactiae, Escherichia coli* and *L. monocytogenes*

In spite of efficient antibiotics, mortality remains still up to 34% and up to 50% of survivors suffer from late-onset complications.
Early diagnosis and rapid beginning of treatment of bacterial meningitis / meningo-encephalitis is very important. Lethality increases strongly with decelerated therapy start. A delay of therapy start of more than 3 hours has to be avoided.

Neisseria meningitidis

The gram-negative bacteria (diplococci) of the species *N. meningitidis* are transmitted via close contact or droplet infection from person to person. About 10% of healthy population shows colonization of mucous membranes of nasopharyngeal area. Invasive illnesses can be favored by unspecific damages of the nasopharyngeal mucous membranes. Headache, fever, ague, dizziness and severe sense of illness can evolve to a severe life-threatening clinical picture. In the case of meningitis, vomiting and stiffness of neck appear additionally. Complications arise in 10-20% of all persons concerned. Coma, epileptic seizures or cerebral nerve paralysis may occur. Lethality of an isolated infection with *N. meningitidis* is in Germany about 1%.

Streptococcus pneumoniae

Bacteria of the species *S. pneumoniae* are world-wide spread gram-positive diplococci. They are transmitted via droplet infection from person to person and colonize nasopharyngeal area of 50-60% of children and 2-10% of adults, normally without causing illnesses. But in the case of newborns, small children, older people and persons with chronic underlying disease, several diseases can be induced. One is afraid of meningitis in newborns (high fever, vomiting and epileptic seizures) and small children (typical stiffness of neck, headache and unconsciousness). Even if the child survives, brain damages can remain. In the group of children under 5 years, *S. pneumonia* is the second frequent cause of acute bacterial meningitis.

Listeria monocytogenes

Bacteria of the species *L. monocytogenes* are gram-positive, motile, non-spore-forming, catalase-positive and facultative anaerobe rods, which are wide-spread in the environment. Persons with good immune system show no symptoms or it takes only a light course with symptoms of fever or diarrhoea, possibly due to solely local colonization of intestinal region. Mainly in immune deficient persons (e.g., pregnant women, new-borns,

older people, persons with chronic diseases or unborn children) exists the risk of manifestation of disease. Besides flu-like symptoms, encephalitis, meningitis (about one third) and / or septic disease can occur, as well as neurological deficiencies and reduced consciousness. Lethality of Listeria-meningitis is about 13 % in Germany.
The clinical picture of listeriosis is very variable and therefore difficult to diagnose (amount of cells and proteins in CSF are not elevated). Cultivated strains show similar morphology to group-B-streptococci on sheep blood agar. Adequate treatment with effective antibiotics often takes place too late. Problematically, cephalosporins do not have any effect on *L. monocytogenes.*

Streptococcus agalactiae
S. agalactiae are gram-positive bacteria (group-B-streptococci) and belong to the normal flora of gastro-intestinal and genital region. They can lead to invasive illnesses in children, pregnant women, women in childbed and older adults.
Particularly in new-borns and young infants severe courses of disease like sepsis, pneumonia and meningitis can occur. Without intervention (prophylactic antenatal treatment with penicillin) 1-2% of children from colonized mothers could be infected during birth. 10-30% of pregnant women are colonized with *S. agalactiae* in vagina or rectum. Illness incidence is about 0,3 / 1000 life births in Italy, thereof 36% were meningitis cases.

Escherichia coli
Besides GBS (59%), *E.coli* (28%) was shown to be the main cause for neonatal bacterial meningitis in France. Among preterm infants, *E. coli* was more commonly isolated (45%), especially in very preterm infants (54%). Infection in babies may occur during delivery, or from bacteria acquired in hospital, or in the home.
Haemophilus influenzae
Haemophilus influenzae type b (Hib) is a Gram-negative bacterium that causes meningitis and acute respiratory infections, mainly in children. *Haemophilus influenzae* infection is transmitted by droplets from infected (but not necessarily symptomatic) people. The introduction of the Hib vaccination program led to a dramatic reduction in the incidence of Hib meningitis. However, the burden of Hib in developing countries without adequate vaccination programs still remains significant.

Viral meningitis
Viral meningitis is accompanied by headache, fever, sickness, stiffness of neck, photophobia and sensitivity to noise (not: reduced consciousness and/or focal-neurological deficiency). Acute symptoms decay even without therapy (normally after 7-10 days).

Viral (meningo-) encephalitis
In addition, acute viral (meningo-)encephalitis is characterized by reduced consciousness, eventually focal-neurological deficiency and palsies. A general disease often preceeded. Virus encephalitis is a medical emergency, patients have to be housed in intensive care units. Prognosis depends on the infectious agent and the patient´s immune status. Correct immediate diagnosis and start of a specific therapy have dramatic influence on survival of the patient and reduce the extent of remaining damages.
Viral encephalitis in immune competent people is mainly caused by HSV-1, VZV, EBV, mumps-, measles- and enteroviruses with regionally different incidences.

HSV-encephalitis is the prevailing sporadic encephalitis in Western Europe (about 5 cases per year and 1 million inhabitants). If viral encephalitis is suspected, therapy has to be initiated immediately.

Herpes-simplex-virus (HSV)
Human herpes virus 1 (HHV-1) (simplexvirus – herpesviridae) is mainly caused by saliva contact and smear infection (mouth-pharynx), HSV-2 by close contact of mucous membranes (mainly genital region). In adults and older children, encephalitis is mostly caused by HSV-1, HSV-2 solely induces meningitis. Flu-like symptoms (headache, high fever) are followed by focal encephalitic phase. Lethality can be lowered from 70% (without therapy) to 20% by therapy start on time.

Varizella-Zoster-Virus (VZV)
VZV are double stranded DNA viruses (Varicellovirus – Herpesviridae). VZV is capable to induce two different diseases: chickenpox by exogenic infection and herpes zoster by endogenic reactivation. Transmission happens via droplet or smear infection, incubation time is 8-28 days.
In about 0,1% of chickenpox disease, involvement of CNS arises some days after skin leasons and fever; rarely even with herpes zoster.

3. Principle of the test

A single **eazyplex®** test strip contains six oligonucleotide primers in each filled cap and these provide the means for simultaneous, specific amplification of different genes in a single isothermal amplification reaction. In the presence of relevant DNA sequences, specific amplification products are generated and visualised by real-time fluorescence measurement of a fluorescence dye bound to double-stranded DNA. Thus, positive signals indicate the presence of one of the corresponding genes or species in the sample to be investigated.
Data interpretation is based on an algorithm in the eazyReport™ software.

The following protective mechanisms prevent the use of false results:
Performance of “inhibition control” with each sample prevents the use of false negative test results due to inhibition of the amplification reaction and simultaneously serves as reagent control.
As required, a test strip can be processed as negative / contamination control by testing **LA-RS** without addition of sample material. In this case, only the inhibition control is allowed to create a positive signal.

eazyplex® CSF direct:

tube-n°	Assay parameter (abbreviation in result display)	Specificity	Colour of curve
1	HSV-1	HSV-1	**red**
2	HSV-2	HSV-2	**orange**
3	VZV	VZV	**yellow**
4	N. meningitidis	*Neisseria meningitidis*	**light green**
5	S. pneumoniae	*Streptococcus pneumoniae*	**dark green**
6	Inhibition control	Inhibition control	**turquois**
7	S. agalactiae	*Streptococcus agalactiae*	**purple**
8	L. monocytogenes	*Listeria monocytogenes*	**pink**

eazyplex® CSF direct V:

tube-n°	Assay parameter (abbreviation in result display)	Specificity	Colour of curve
1	HSV-1	HSV-1	**red**
2	HSV-2	HSV-2	**orange**
3	VZV	VZV	**yellow**
4	Inhibition control	Inhibition control	**light green**
5-8	-	-	

eazyplex® CSF direct B:

tube-n°	Assay parameter (abbreviation in result display)	Specificity	Colour of curve
1	N. meningitidis	*Neisseria meningitidis*	**red**
2	S. pneumoniae	*Streptococcus pneumoniae*	**orange**
3	S. agalactiae	*Streptococcus agalactiae*	**yellow**
4	L. monocytogenes	*Listeria monocytogenes*	**light green**
5	Inhibition control	Inhibition control	**dark green**
6-8	-	-	

eazyplex® CSF direct M:

tube-n°	Assay parameter (abbreviation in result display)	Specificity	Colour of curve
1	E. coli	*Escherichia coli*	**red**
2	H. influenzae	*Haemophilus influenzae*	**orange**
3	Inhibition control	Inhibition control	**yellow**
4	N. meningitidis	*Neisseria meningitidis*	**light green**
5	S. pneumoniae	*Streptococcus pneumoniae*	**dark green**
6	S. agalactiae	*Streptococcus agalactiae*	**turquois**
7	L. monocytogenes	*Listeria monocytogenes*	**purple**
8	-	-	**-**

4. Reagents

4.1 Content

The reagents contained in one kit are sufficient for 12 determinations.
Each kit contains:

TESTSTRIP	Test strips with 8* filled tubes, each containing lyophilized, ready-to-use mix for isothermal amplification. The mix contains DNA-polymerase, buffer components, Mg_2SO_4, dNTPs, oligonucleotide primers and a fluorescence dye.	12 strips
LA	2 ml –tube with 600µl „LA - Lysis Agent“ (blue cap)	1 x 600 µl
RS	reddish 2 ml –tubes with 125 µl „RS - Resuspension Solution”	12 x 125 µl

*in the variants 4 (eazyplex® CSF direct V), 5 (eazyplex® CSF direct B) or 7 (eazyplex® CSF direct M).

4.2 Additional accessories required

- GENIE® II Mk 2 with eazyReport™ - software version 2.34 or higher (including Instructions for Use in PDF format)
- Heating block for 2 ml tubes
- If necessary: Centrifuge for 2 ml tubes
- 2 ml Safe-Lock reaction tubes (e.g. Eppendorf)
- Pipettes with sterile disposable filter tips
- optional: USB bar code scanner
- optional: printer DYMO® Labelwriter 450 (Dymo) with labels 54x101mm

5. Warnings and precautions

- All reagents and materials which come into contact with potentially infectious samples must be treated with suitable disinfectant or autoclaved.

- Suitable disposable gloves must be worn during the entire test.

- **Never** open a test strip after use! Autoclave used test strips!

- Lysis Agent “LA”: H319: Causes serious eye irritation.
  P305 + P351 + P338: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
  P337 + P313: If eye irritation persists: Get medical advice/attention.

6. Handling notes – preparation of assay realization

The components of **eazyplex® CSF direct** have to be stored from 15°C to 30°C.
The kits have an expiry date. Quality cannot be guaranteed after this date.
Before beginning the test, remove a test strip from the bag. The test strip may only be used if the white pellets in the filled tubes are visible.

As with any test procedure, good laboratory practice is essential to the proper performance of this assay.

7. Sample material

The sample material has to be cerebrospinal fluid. Optimally, the sample is not older than 6 hours.

Any swabs, culture, blood or stool samples **CANNOT** be used.

8. Test procedure

8.1 Preparation of the system

- Turn on GENIE® II Mk2
- Touch the Screen
- Enter user name and password
- Select „Run“
- Scan test barcode via barcode scanner or enter test barcode manually
- Check display if the right test profile is selected
- Enter patient´s / sample ID (via barcode scanner or keyboard)
- Confirm the selection with “Enter”

8.2 Preparing the amplification reaction

Mix 125 µl of cerebrospinal fluid with 25 µl LA (in a 2 ml Safe-Lock reaction tube).

☝ **Caution! Too much cell material may considerably reduce the effectiveness of the reaction and may lead to invalid test runs.**

Incubate this LA-suspension at 99°C for 3 min for cell lysis.

If CSF is strongly turbid or contains large (suppurative) particles, the LA-suspension should be centrifuged at 1000 x g for 1 minute.

Afterwards, transfer 125 µl of the lysed LA-suspension into 125 µl RS (reddish 2 ml “Safe-Lock” tube) and mix it gently (please do not vortex).

Carefully remove the protective foil from the test strip.

Pipette 25 µl of the **LA-RS**-suspension onto the ready-to-use mix in each filled tube of the test strip, taking care not to allow the pipette tip to make contact with the pellet. Do not vortex, shake heavily or pipette up and down. Remove any air bubbles by tapping the test strip gently.

Once the pellets have dissolved, place the test strip immediately into the GENIE® II Mk2 device and start the run (8.3).

8.3 Realization of the amplification reaction

- Select „Start“
- Select block A or B
- Place the test strip into the selected block
- Close the lid
- Start test run by selecting „Yes“.
- If the second block is not in use, a second test run can be initiated by the button “start test run” (see 8.1)
- Note: the directory path and number of test run data file can be seen on the display
- Once the run is complete, open the lid and remove the test strip, taking care as the block could still be hot!
- **Never** open a test strip after use! Danger of contamination!

9. Evaluation

The test run can be monitored in real time mode (choose „Amplification“). Positive results are indicated by a strong rise in fluorescence signal (in the form of a typical amplification curve). Unambiguous assignment of the curves to the test parameters takes place by coloring.

After completion of the test run select „Results“:

Valid test run:
Positive results are colored red.

Invalid test run:
The result of „Inhibition Control“ is colored red (invalid). In this case, data interpretation of the eazyReport™ software is displayed above the result table as follows:
„Invalid control” (colored red)

Warning messages:
„WARNING! Kit expired!“:
A kit has been used which is out of date (see 6.).

„WARNING! Too much sample material!“:
Too much sample material was used; this could have been the reason for an invalid test run (see 11.)

Documentation:

- Result printout via Dymo® Labelwriter 450 printer: select „print“
  or
- create a PDF result report: select „PDF“; the generated PDF file is stored in the folder „Report“ on the device and can be exported via USB stick (according to Instructions for Use Genie® II Mk2).
  or
- create a result file in CSV format: select „CSV“; the generated CSV file is stored in the folder „Report“ on the device.

The stored run file can be reviewed at any time:

- select symbol „Folder“
- select „LOG“ and confirm with „✓ “
- the data files are numbered consecutively and archived according to creation date

10. Interpretation of the test results

The **eazyplex® CSF direct** is a rapid test for the specific detection of several different infectious agents directly from CSF(depending on the test variant).
Positive results of the **eazyplex® CSF direct** system demonstrate the presence of the respective infectious agents in a sample.

The **eazyplex® CSF direct** system is neither intended to diagnose an infection with infectious agents nor to guide or monitor medical treatment.
The test solely generates a test result. The attending doctor is responsible for achieving a decision about diagnosis or treatment of a patient or taking hygienic measures.

The **eazyplex® CSF direct** system is able to detect some few genome copies within 30 minutes under optimal conditions. But it is not possible to detect one single copy of the infectious agent. Therefore, a negative test result can be generated despite a weak colonization of the patient´s CSF.

During amplification of HSV-1 DNA, an additional amplification curve in the HSV-2 well may occur because of high homology of both target gene sequences. In this case, it is most likely that only an infection with HSV-1 is present.

Comparison to molecular biological methods showed that a positive result for HSV-1 with $T_t > 25$ minutes can only be taken as a hint for the presence of HSV-1. The result should be checked in addition.

11. Troubleshooting

All signals negative (incl. inhibition control):

- Reaction is inhibited due to inhibitory substances in the sample and must not be interpreted (invalid test).

All signals positive (incl. inhibition control):

Very occasionally cell lysis in a sample will not complete within the first 3 minutes of the test run (signals are not displayed at the beginning of the run). If cell lysis occurs later on during the amplification reaction, newly appearing dsDNA will lead to unspecific amplification signals. This phenomenon can be identified easily because it will happen simultaneously in all wells (but the IC curve or correct positive amplification curves could appear earlier). ➔It is recommended to repeat the test run with fresh sample material with an extended incubation time of 10 minutes for complete cell lysis.
➔If the phenomenon reoccurs, the sample should be interpreted as "invalid“ or "not valid".

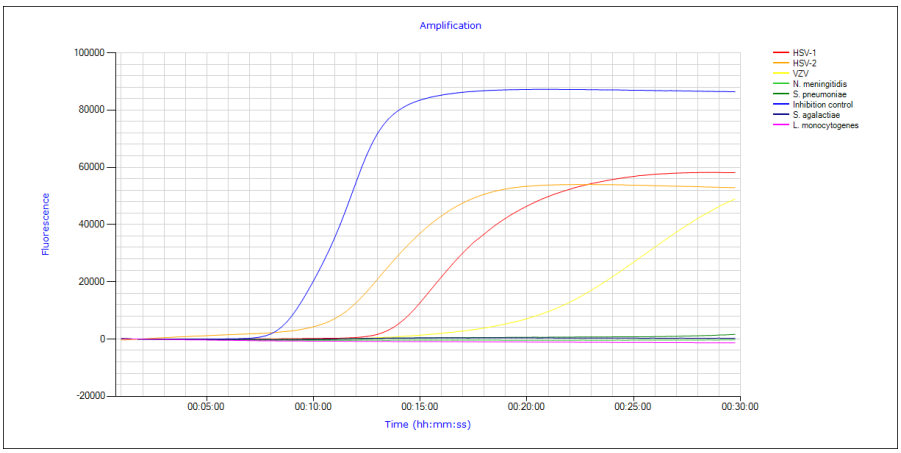
12. Performance data

A) As part of a prospective evaluation study at the „Institut für medizinische Mikrobiologie des Universitätsklinikum Jena" (Head of Department: Prof. Dr. Pfister; study coordinator: PD Dr. Rödel) in the period 2014-07 to 2015-10, 39 CSF samples were tested in comparison to microbiological and molecular biological routine methods:
One sample was invalid (inhibition rate 2,6%)

		microbiology positive								microbiology complete negative
		HSV	VZV	N.m	S.pn	S.ag	L.mo	E.coli	H.infl.	
eayzplex positive	HSV	2	0	0	0	0	1**	0	0	0
	VZV	0	0	0	0	0	0	0	0	0
	N.m	0	0	4	0	0	1**	0	0	0
	S.pn	0	0	0	3	0	0	0	0	0
	S.ag	0	0	0	0	0	0	0	0	0
	L.mo	0	0	0	0	0	2	0	0	0
eayzplex negative		-	-	-	-	-	-	2*	1*	24

* 3 samples were microbiologically positive. They contained *E. coli* (n=2) and *H. influenzae* (n=1), which are not included as test parameter in eazyplex® CSF direct.
** In a L. monocytogenes positive sample *N. meningitidis* (T_t=28 min) and HSV-1 (T_t=23 min) were detected with eazyplex® CSF direct. The microbiological and molecular biological routine methods did not proof evidence.

B) As part of our internal evaluation study, reference material from NIBSC „Clinical Virology Multiplex I NIBSC code 15/130-XXX" was tested. NIBSC have determined that the C_t values are approximately 30 for HSV-1, HSV-2 and VZV (manufacturer information, chapter3) using their in-house RT-PCR assays.



Results of eazyplex® CSF direct:

HSV-1	positive	T_t = 14:45 min
HSV-2	positive	T_t = 11:45 min
VZV	positive	T_t = 21:15 min

C) As part of pro- as well as retrospective evaluation studies at three universal hospitals in Germany, France and Italy in the period 2016-07 to 2017-05, 44 CSF samples were tested with eazyplex® CSF direct M in comparison to microbiological (culture, blood culture) and molecular biological routine (in-house PCR) methods:

		Comparison diagnostics positive						Comparison diagnostics negative
		N.m	S.pn	S.ag	L.mo	E.coli	H.infl	
eayzplex positive	N.m	6	0	0	0	0	0	0
	S.pn	0	4	0	0	0	0	0
	S.ag	0	0	0	0	0	0	1*
	L.mo	0	0	0	1	0	0	0
	E.coli	0	0	0	0	7	0	0
	H. infl	0	0	0	0	0	4	0
eayzplex negative		0	0	0	0	0	0	21**

*This sample contained *Enterococcus faecalis* en masse, as determined by culture; The T_t for *S. agalactiae* was 27:00 minutes.

** In 4 out of 21 samples other pathogens (not included in eazyplex CSF direct M) have been detected: 1 x *Staphylococcus aureus*; 1 x *Staphylococcus epidermidis*; 1 x *Streptococcus pyogenes*; 1 x *Cryptococcus* spec.

13. References

1. Imöhl, M., van der Linden, M. Epidemiologie invasiver Streptokokkenerkrankungen in Deutschland. Der Mikrobiologe 3, Sept. 2013
2. Nationale Referenzzentrale für Pneumokokken (AGES, Graz, Austria), Jahresbericht 2012.
3. Nationale Referenzzentrale für Meningokokken (AGES, Graz, Austria), Jahresbericht 2012.
4. Nationale Referenzzentrale für Listeriose (AGES, Wien, Austria), Jahresbericht 2012.
5. Berardi, A., Rossi, C., Lugli, L., Creti, R., Reggiani, M.L., Lanari, M., Memo, L., Pedna, M.F., Venturelli, C., Perrone, E., Ciccia, M., Tridapalli, E., Piepoli, M., Contiero, R., Ferrari, F., Group B Streptococcus Late-onset disease: 2003-2010. Pediatrics, 2013; Vol. 131, no. 2, Feb 2013.
6. Chaiwarith, R., Jullaket, W., Bunchoo, M., Nuntachit, N., Sirisanthana, T. and Supparatpinyo, K., Streptococcus agalactiae in adults at chiang mai university hospital: a retrospective study. BMC Infectious Diseases 2011, 11:149
7. Tacon, C.L. and Flower, O. Diagnosis and Management of Bacterial Meningitis in the Pediatric Population: A Review. Emergency Medicine International 2012, ID 320309
8. Verani, J.R., McGee, L., Schrag, S.J., Prevention of Perinatal Group B Streptococcal Disease, Revised Guidelines from CDC, CDC Morbidity ans Mortality Weekly Report, Nov. 2010 Vol. 59 / No. RR-10.
9. Hoffman and Weber, Pathophysiology and treatment of bacterial meningitis. Ther Adv Neurol Disord, 2009, 2[6] 401-412.
10. Adelmann M, Bamborschke S, Becker D, Blaes F, Gerritzen A, Hobusch D, Kaiser R, Kleine TO, Kölmel HW, Kühn H-J, Lehmitz R, Linke E, Ludewig R, Meyer-Rienecker H, Mix E, Oschmann P, Otto M, Petereit H-F, Regeniter A, Rieckmann P, Rolfs A, Scharein S, Sindern E, Tumani H, Uhr M, Voltz R, Weber T, Wick M, Wildemann B, Wurster U, Zimmermann K. Leitlinien der Liquordiagnostik der DGLN.
11. Meyding-Lamade, U., Virale Meningoenzephalitis. Aus: Diener, H-C. Weimar, C., Leitlinien für Diagnostik und Therapie in der Neurologie. Deutsche Gesellschaft für Neurologie. Thieme Verlag, Stuttgart, September 2012.
12. Pfister, H-W., Ambulant erworbene bakterielle (eitrige) Meningoenzephalitis. Aus: Diener, H-C. Weimar, C., Leitlinien für Diagnostik und Therapie in der Neurologie. Deutsche Gesellschaft für Neurologie. Thieme Verlag, Stuttgart, September 2012.
13. www.rki.de: Meningokokken-Erkrankungen, Listeriose
14. Gaschignard J, Levy C, Romain O, Cohen R, Bingen E, Aujard Y, Boileau P. Neonatal Bacterial Meningitis: 444 Cases in 7 Years. Pediatr Infect Dis J., 2011, 30(3):212-7.
15. van de Beek D, Cabellos C, Dzupova O, Esposito S, Klein M, Kloek AT, Leib SL, Mourvillier B, Ostergaard C, Pagliano P, Pfister HW, Read RC, Resat Sipahi O and Brouwer MC, for the ESCMID Study Group for Infections of the Brain (ESGIB). Clin Microbiol Infect 2016: 22: S37-S62.

AmplexDiagnostics GmbH
Werkstraße 2
83555 Gars-Bahnhof
Germany

Support:
Tel.: +49 (0) 8073 / 9 16 93-50
Fax: +49 (0) 8073 / 9 16 93-55
support@eazyplex.com