Association of Diabetes with Meningitis Infection Risk : A Systematic Review and Mete-Analysis

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Identitas Jurnal

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ABSTRAK

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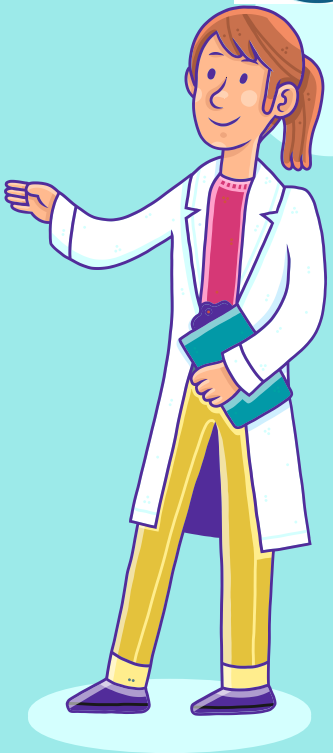


ABSTRAK 1.0

Latar Belakang

- 2016 –> Kasus Global meningitis mencapai 320.000
- Bukti saat ini menunjukkan bahwa diabetes mungkin merupakan faktor risiko utama meningitis di antara individu, termasuk orang dewasa yang lebih tua.

Tujuan

Mensintesis literatur secara kuantitatif tentang risiko meningitis yang terkait dengan diabetes dan membandingkan risiko tersebut di berbagai wilayah global.

Metode

- Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)
- Using relevant MESH terms

ABSTRAK 2.0

Hasil

- Pencarian awal menghasilkan 772 makalah tetapi 756 studi dikeluarkan
- Secara keseluruhan, 16 makalah yang melibatkan 16.847 kasus digunakan
- Efect Size (ES) = 2.240 (OR = 2.240, 95% CI = 1.716–2.924)
- Namun, secara mengejutkan tidak ditemukan penelitian di Afrika atau Amerika Selatan

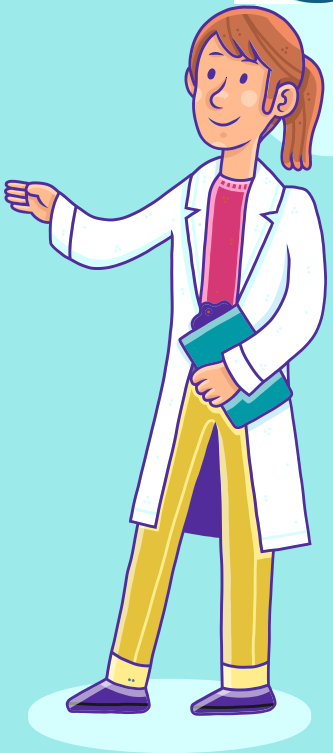
Kesimpulan

- Diabetes adalah faktor risiko untuk mengembangkan meningitis.
- Penelitian tentang topik ini tidak berasal dari Afrika dan Amerika Selatan, temuan kami harus ditafsirkan secara kontekstual.

02

Introduction

Journal Reading Denisa



MENINGITIS

Meningitis is defined as inflammation of the meninges. The meninges are the three membranes (the dura mater, arachnoid mater, and pia mater) that line the vertebral canal and skull enclosing the brain and spinal cord. Encephalitis, on the other hand, is inflammation of the brain itself. – NCBI

Non-Infeksi

- Autoimmune Disorders
- Cancer/Paraneoplastic Syndromes
- Drug Reactions
- Malignant cells
- Inflammatory disease

Infeksi

BAKTERI	VIRUS	FUNGI
Mycobacterium Tuberculosis	Group B Coxsackievirus	Cryptococcus neoformans
Streptococcus pneumoniae	Parechovirus	Coccidioides immitis
group B Streptococcus	Herpesviruses	Aspergillus
Neisseria meningitidis	Influenza	Candida
Haemophilus influenzae	Arboviruses	Mucormycosis
Listeria monocytogenes	Echovirus	
	Mumps	

CIRI KHAS KUMAN

Tabel 2 Perbandingan karakter CSS pada jenis meningitis yang berbeda[1]

	Normal	Bakterial	Viral	TB	Fungal
Makroskopik	Jernih, tak berwarna	Keruh	Jernih/*opalescent*	Jernih/*opalescent*	Jernih
Tekanan	Normal	Meningkat	Normal atau meningkat	Meningkat	Normal atau meningkat
Sel	0-5/mm^3	100-60.000/mm^3	5-100/mm^3	5-1000/mm^3	20-500/mm^3
Neutrofil	Tak ada	>80%	<50%	<50%	<50%
Glukosa	75% glukosa darah	Rendah (<40% glukosa darah)	Normal	Rendah (<50% glukosa darah)	Rendah (<80% glukosa darah)
Protein	<0,4 g/L	1-5 g/L	>0,4-0,9 g/L	1-5 g/L	0,5-5 g/L
Lainnya		Gram positif <90%; kultur positif <80%; kultur darah positif <60%	PCR kultur positif <50%	Kultur positif 50-80%	Gram negatif; kultur positif 25-50%

gejala

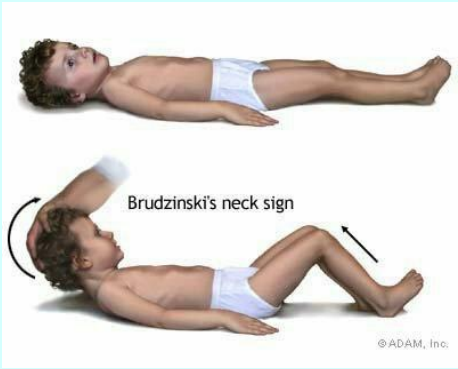
- **Demam**

- **Nyeri kepala hebat**

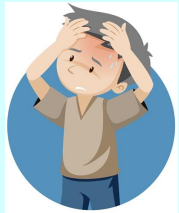
- **Kaku kuduk**

- Tidak jarang disertai kejang umum dan gangguan kesadaran.

- Tanda Brudzinski



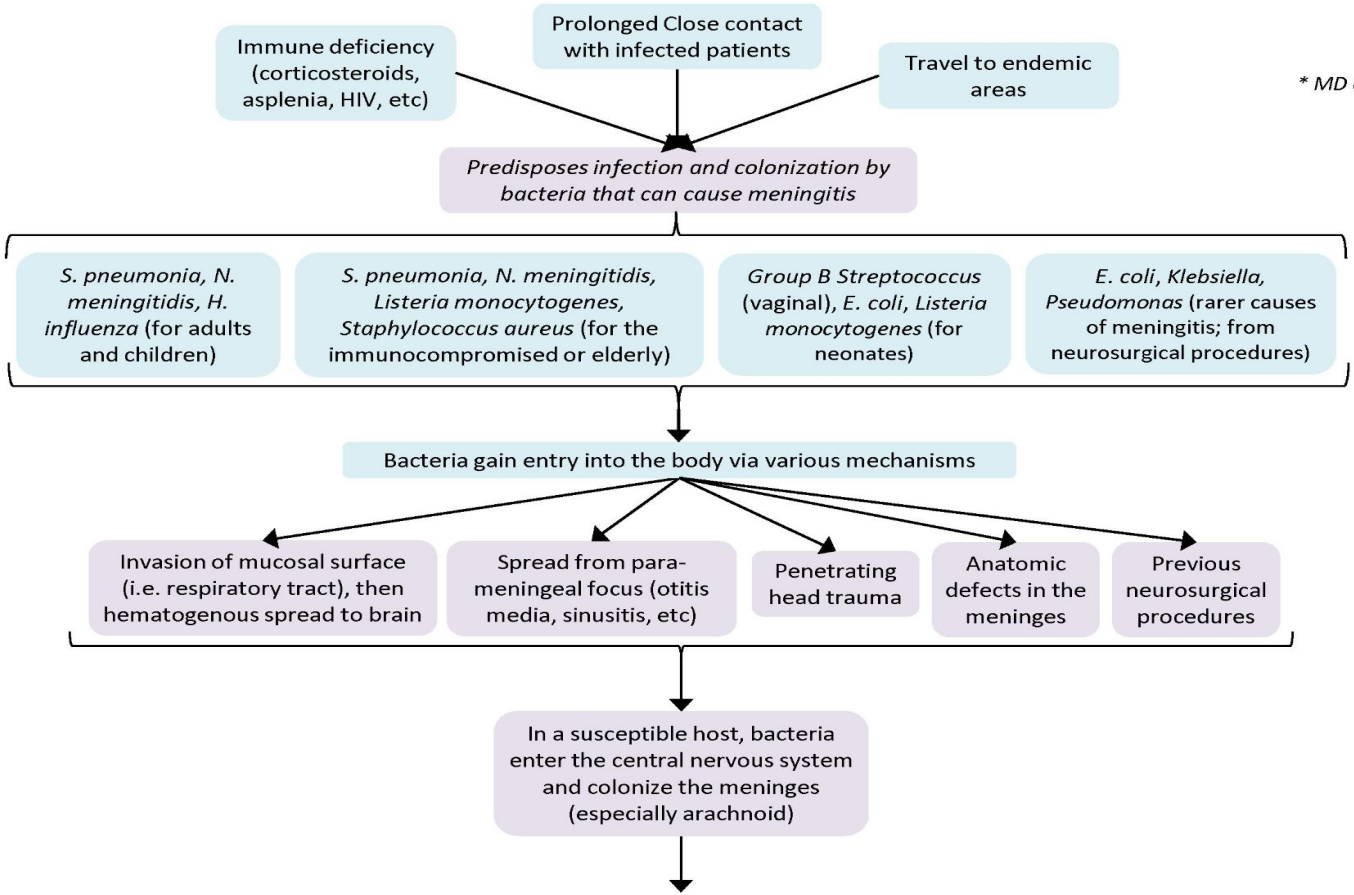
- Tanda Kernig



- Photophobia

Bacterial Meningitis: *Pathogenesis*

Author:
Yan Yu
Reviewers:
Owen Stechishin
Dustin Anderson
Scott Jarvis*
** MD at time of publication*



Published **November 22, 2012** on www.thecalgaryguide.com

Bacterial Meningitis: *Clinical Findings*

Author:
Yan Yu
Reviewers:
Owen Stechishin
Dustin Anderson
Scott Jarvis*
** MD at time of publication*

A Note on Diagnosis:
- Fever, neck stiffness, headache, and altered mental status are the four most common signs that ↑ suspicion for bacterial meningitis

Bacterial meningitis
(bacterial infection of the meninges, especially arachnoid layer)

Infection induces a systemic inflammatory response
- Inflammation ↑ body's basal metabolic rate → **Fever, Tachycardia**
- Inflammation near brain parenchyma interferes with normal CNS function → **Altered mental status; GCS < 14 *(Lethargy, stupor, confusion, delirium, coma)***
  - Visual pathways become sensitized to light, and pain due to inflamed meninges around CN2 is worsened with CN2 stimulation by light → **Photophobia**

Meningeal irritation
- Stimulates dural nociceptors
  - *Around the brain* → **Headache**
  - *Around the brainstem (neck)* → **Stiff neck *(pain worsens when neck is flexed)***
  - *Around the spinal cord* → **Sore back**
- Cranial Nerves exiting the CNS through inflamed meninges can be irritated themselves → **Cranial Nerve Palsies**
- Detected by certain physical exam maneuvers:
  - *Hip flexion while pt is supine* → *Stretches lumbar/sacral meninges → irritates and "excites" nerve roots innervating knee flexors* → *Hamstrings contract, ↓ knee extension* → **Kernig's Sign**
  - *Passive neck flexion* → *Stretches lumbar/sacral meninges → irritates and "excites" nerve roots innervating hip + knee flexors* → *These muscles contract → Spontaneous hip/knee flexion* → **Brudzinski's Sign**

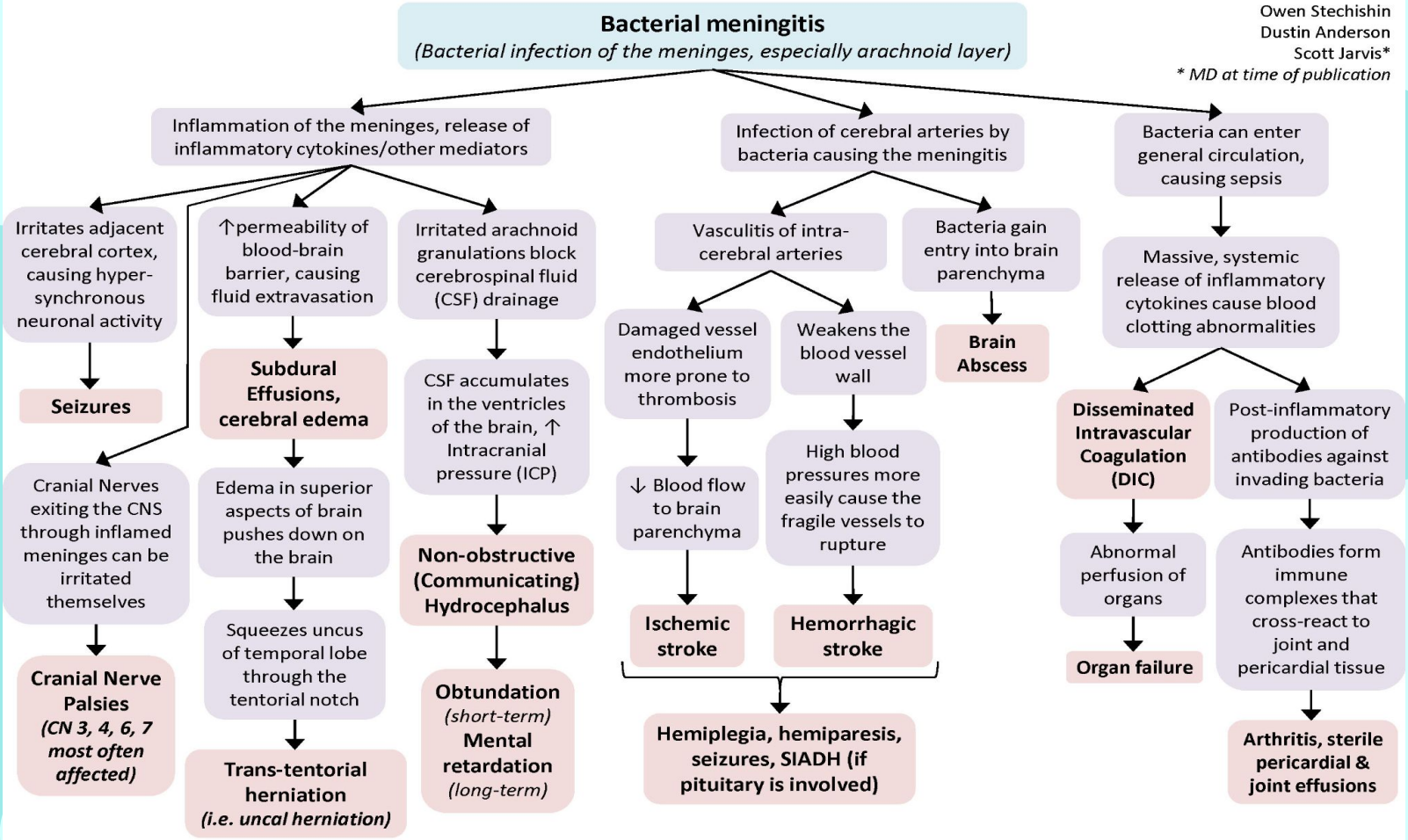
Meningococcus also infects blood vessel endothelium in lower limbs → Resulting immune response creates a vasculitis that causes local clotting abnormalities → **Petechial or Purpuric rash *(especially on lower limbs)*** → Can lead to **Limb Ischemia!**

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

Published **November 22, 2012** on www.thecalgaryguide.com

Bacterial Meningitis: *Complications*

Author:
Yan Yu
Reviewers:
Owen Stechishin
Dustin Anderson
Scott Jarvis*
** MD at time of publication*



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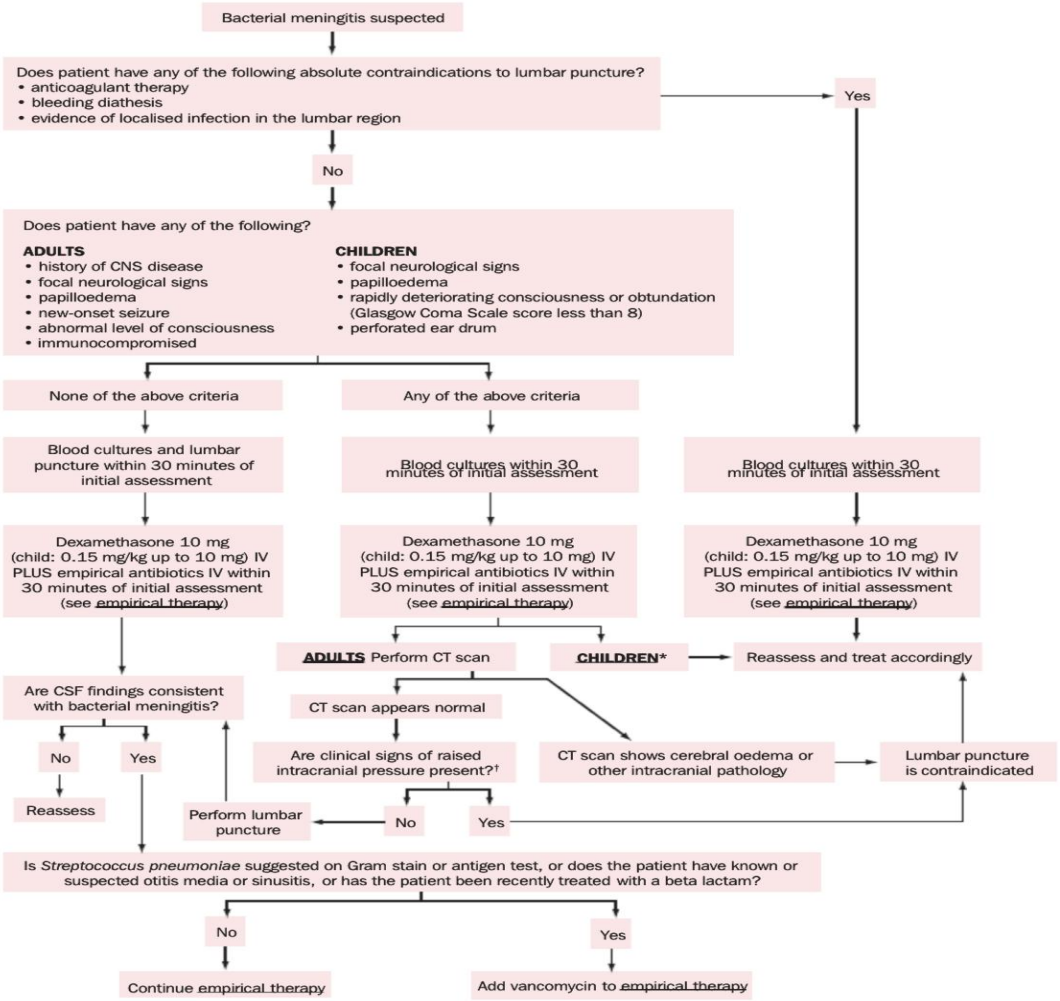

* CT scans are not routinely performed in children. Review daily, and perform lumbar puncture as soon as the contraindication(s) have resolved. If lumbar puncture is still contraindicated, reassess and treat accordingly.

PATHWAY DIABETES

Pathogenesis of Diabetes Mellitus (DM), Type II

Unhealthy Lifestyle: i.e. over-eating, obesity, inactivity

Intraperitoneal cavity accumulates "visceral fat" (aka. "abdominal fat"), which is an endocrine organ that secretes:

- Inflammatory mediators
- Adipokines
- Free fatty acids (FFAs)

Note: "adipokines" are inflammatory mediators released from adipose tissue (e.g. TNFalpha). The more adipose tissue a patient has, the more adipokines are released.

Complex, unclear actions on body tissue

Genetic Susceptibility: Polygenetic or monogenetic factors (i.e. maturity-onset diabetes of the young (MODY)) can predispose insulin resistance

Aging: Beta-cell mass declines with aging, so those predisposed to insulin resistance may develop Type II DM as they age.

Medications: i.e. corticosteroids, anti-psychotics, highly-active anti-retrovirals, progestin-only oral contraceptives

Insulin resistance
(liver, muscle, adipose tissue become less responsive to insulin, and thus less able to use glucose as a fuel source)

Lipotoxicity: FFAs inhibit function of GLUT2 on Beta-cells, ↓ glucose import

Beta-cells do not recognize high blood glucose → ↓ insulin secretion

Initially, beta-cells of the pancreas work overtime to ↑ Insulin secretion

Blood [glucose] is kept normal

Over many years, as insulin resistance worsens, Beta-cells "tire out", ↓ insulin secretion **(relative insulin deficiency)**

Glucotoxicity: hyperglycemia is directly toxic to Beta-cells

Hyperglycemia

Since cells can't use glucose, body perceives a state of "starvation", thus mobilizing triglycerides into FFAs, to be used as fuel by cells.

Over many more years: Beta-cells deteriorate until they finally stop producing insulin, **(absolute insulin deficit)**

Type II Diabetes Mellitus

Note: There is a HUGE genetic basis for Type II DM: high concordance rate between family members (90% for monozygotic twins), and if a first-degree relative is affected, the risk for other family members is 5-10x above baseline.

Author: Yan Yu
Reviewers: Peter Vetere, Gillian Goobie, Doreen Rabi*
** MD at time of publication*

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications
Published **July 11, 2013** on www.thecalgaryguide.com

PATOFISIOLOGI DIABETES MELITUS

- Faktor Genetik
- Kelainan Jaringan Perifer
- Infeksi, Penyakit Imunologi,
- Gaya hidup (merokok)
- Makan makanan bergula tinggi
- Mewarisi gen resesif DM
- Resistensi efek insulin
- Sel Beta pancreas rusak atau terganggu
- Produksi insulin terganggu (defisiensi insulin)
- Gula dalam darah tidak mampu ditransport masuk kedalam sel
- Hiperglikemia
- Anabolisme protein menurun
- Glukosuria
- Viskositas darah meningkat
- Kerusakan pada antibody
- Diuretik osmotik
- Aliran darah lambat
- Kekebalan tubuh menurun
- Poliuria
- Iskemik jaringan
- **Resiko infeksi**
- **Ketidakefektifan perfusi jaringan perifer**
- **Kekurangan volume cairan dan elektrolit**
- Metabolisme menurun
- Luka sukar
- Dehidrasi
- Produksi energi menurun
- Ulkus ,
- **Resiko syok**
- **Kelemahan**
- **Kerusakan integritas**
- **Nyeri akut/kronik**
- **Resiko perlambatan pemulihan pasca bedah**
- Merangsang hipotalamus
- Merangsang hipotalamus
- Rasa lapar dan haus
- **Ketidakseimbangan nutrisi kurang dari kebutuhan tubuh**

02

Methods

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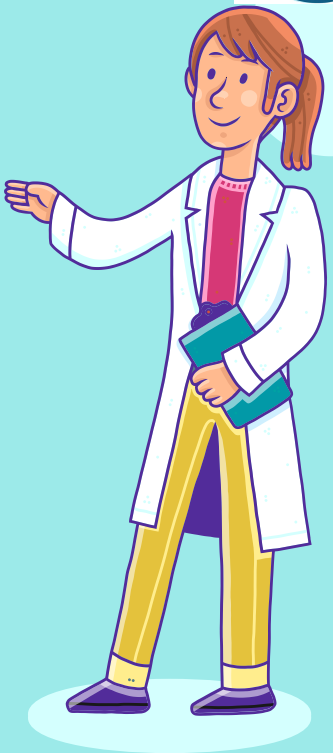

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

1. Databases and Search Criteria.

Table 1: Medical subject headings (MESH) terms used for extracting papers.

The subject	The MESH terms
Meningitis	"Arachnoiditis meningitis," "bacterial meningitis," "*E. coli* meningitis," "listeria meningitis," "meningococcal meningitis," "pneumococcal meningitis," "cryptococcal" "lymphocytic choriomeningitis," "meningoencephalitis"
Diabetes	"Diabetes mellitus," "type 2 diabetes mellitus," "lipoatrophic diabetes," "gestational donohue syndrome," "latent autoimmune diabetes."

2. Inclusion and Exclusion Criteria.

Inkulsi → Semua studi yang melaporkan hubungan antara meningitis dan diabetes (lihat Tabel 1)

Ekskulsi → Studi yang membahas meningitis dan diabetes namun bukan hubungan atara kedua nya.

3. Statistical Analysis

- Studi total dgn statitik Q dan I
- Uji Residual/outlier dgn analisis LOO
- Analisis moderator dgn analisis mata-regresi
- Model efek campuran.

03

Results

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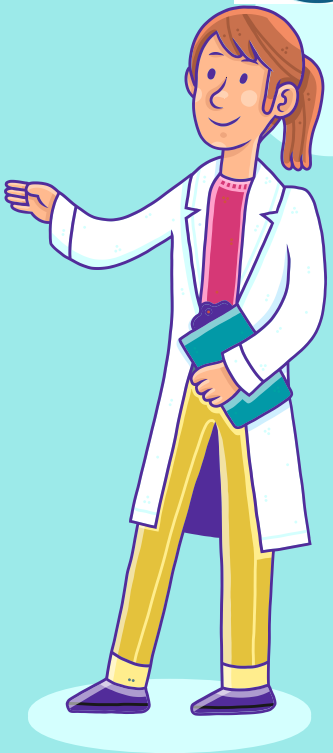


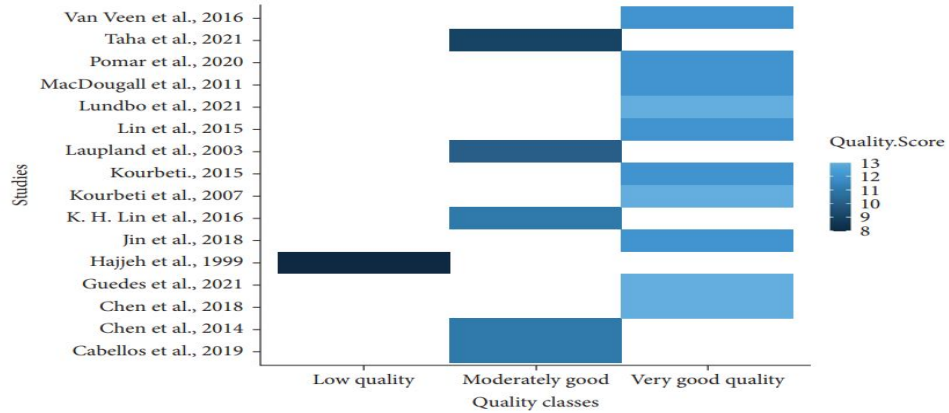


FIGURE 1: A plot indicating the quality score for individual studies.

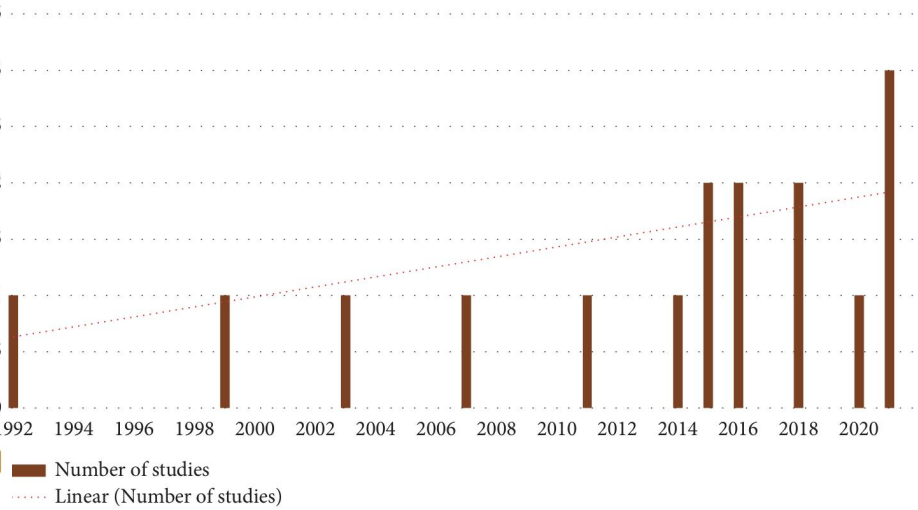


FIGURE 2: Studies conducted from 1997 to 2021.

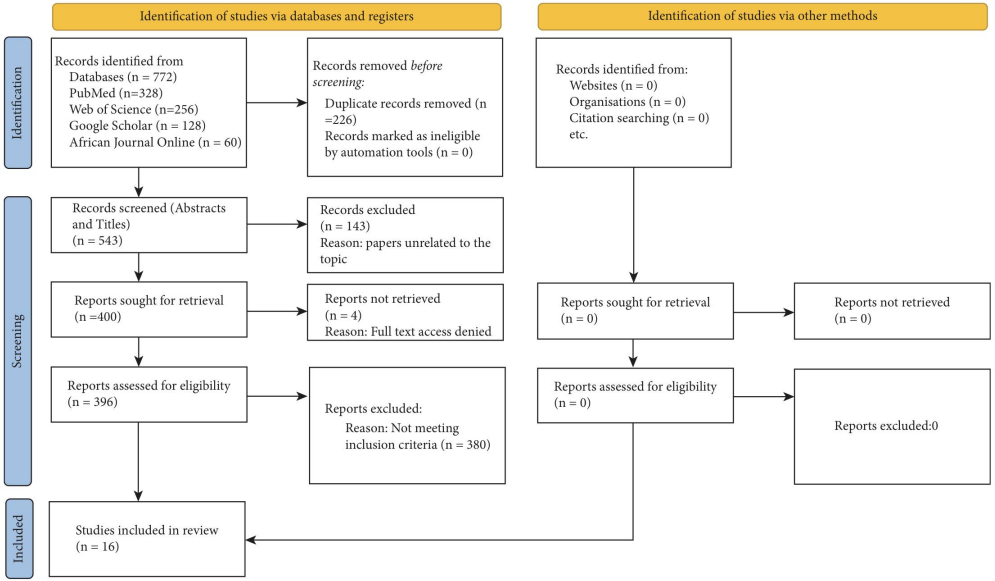


FIGURE 3: PRISMA 2020 flow diagram for new systematic reviews.

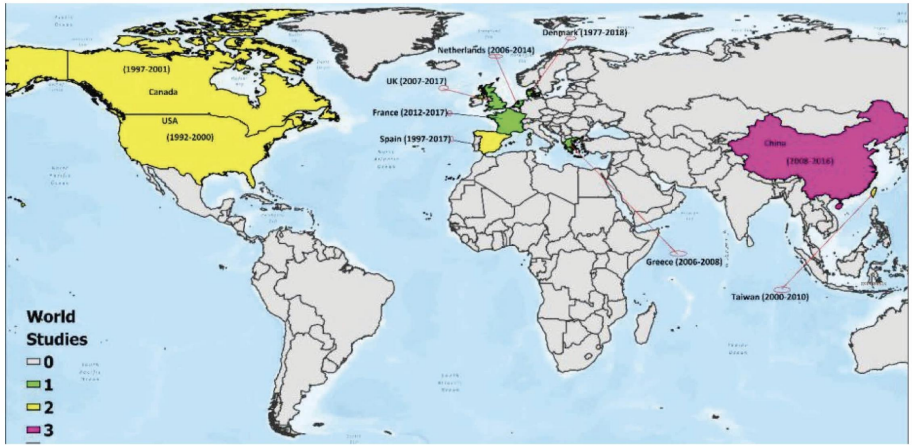


FIGURE 4: A map indicating the spatial distribution of papers conducted in different countries and the period of study.

Karakteristik studi

Table 2: Study characteristics and the quality score assigned. All columns' values under disease etiology indicated as "Multiple" represent studies that reported finding both negative and negative grams but did not specify these pathogens. Same for sections indicated "General".

Study	Country	Study period	Analytic method	Disease etiology	Study design	Quality score	Major etiology	Definition of meningitis
[40]	China	2014-2015	Multivariate and univariate logistic	Multiple	Retrospective	13	General	Meningitis was defined by: (1) organisms cultured from CSF; (2) at least one of these signs without identified cause: Fever (>38°C), headache, stiff neck, meningeal signs, irritability, and if analysis was conducted antemortem, attending physician instituted appropriate antimicrobial therapy, and at least one of the following: (a) Elevated white blood cell count, a rise in protein level in the CSF, and/or attenuated glucose level in CSF, (b) positive antigen test of CSF or blood; and (c) investigative single antibody titer (IgM) or an increase in paired sera (IgG) for pathogen by four-fold
[28]	Taiwan	2002–2010	Conditional logistic regression	*C. neoformans meningitis, C. neoformans fungemia*	Retrospective cas-control	12	Fungal	Cerebrospinal fluid [CSF]or blood culture positive culture n
[29]	USA	1996–2000	Logistic regression	*Coagulase-negative staphylococci, Acinetobacter calcoaceticus, Pseudomonas aeruginosa, Serratia marcescens, Serratia species, Haemophilus influenzae*	Retrospective	13	Bacteria	Meningitis was defined through gram stain, CSF culture or both, CSF leukocytosis with elevated protein concentration and reduced glucose level or both. Fever or nuchal rigidity with unknown cause or patients under antibiotic treatment prescribed by a physician.

Karakteristik studi

Table 2: Continued.

Study	Country	Study period	Analytic method	Disease etiology	Study design	Quality score	Major etiology	Definition of meningitis
[41]	Taiwan	2000–2010	Logistic regression	Cryptococcal meningitis	Prospective case-control	11	Fungal	Definition of meningitis: Cryptococcosis (ICD-9 117.5) or cryptococcal meningitis (ICD-9 321.0)
[42]	France	2012–2017	Logistic regression	Invasive meningococcal disease	Case-control	9	Bacteria	Meningitis was defined according to ICD-10 diagnostic code (A39.0 to A39.9) criteria
[4]	Spain	1977–2013	Simple linear regressions	*Neisseria meningitidis, Streptococcus pneumoniae, Listeria monocytogenes*	Observational cohort study	11	Bacteria	Meningitis was defined through the following means: a Positive CSF culture, the occurrence of negative cultures when Gram negative diplococci was found from the CSF stain or when patients showed incidence of severe bacterial meningitis which is medically confirmed
[43]	Denmark	1977–2018	Logistic regression	Meningococcal serogroups B&C	Case-control	13	Bacteria	Positive CSF culture, positive antigen tests, on Gram's stain of CSF
[44]	Taiwan	2012–2016	Logistic regression	Coagulase-negative*Staphylococcus, Staphylococcus aureus, Streptococcus pneumoniae, Viridans* group, *streptococci, Enterococcus faecalis, Corynebacterium, Micrococcus luteus, Gemella morbillorum, Klebsiella pneumoniae, Enterobacter aerogenes, Pseudomonas aeruginosa, Acinetobacter baumannii, Escherichia coli, Bacteroides fragilis, Citrobacter freundii, Morganella morganii, Enterobacter cloacae, Cryptococcus neoformans*	Retrospective observational	12	Bacteria	Positive organism CSF culture, and at least one of the following signs or symptoms where no other recognized cause was observed: Fever (>38$^{\circ C}$), headache, stiff neck, meningeal signs, cranial nerve signs, or irritability

Table 2: Continued.

Study	Country	Study period	Analytic method	Disease etiology	Study design	Quality score	Major etiology	Definition of meningitis
[31]	Spain	1982–2017	Logistic regression	*Neisseria meningitidis, Streptococcus pneumoniae, Listeria monocytogenes, Gram-negative bacilli*	Prospective observational cohort study	12	Bacteria	Meningitis was defined as a diagnostic outcome of positive CSF culture and positive antigen tests. Any negative culture was further confirmed through CSF neutrophilic pleocytosis (=>100 neutrophils/cu mm or decreased CSF glucose (defined as CSF/blood glucose ratio <0.40) or elevated CSF proteins >0.5 g/l (for unknown etiology)
[30]	China	Jan-December 2008	Logistic regression	*Acinetobacter baumannii, Enterococcus* sp, *Streptococcus intermedius and Klebsiella pneumonia*	Retrospective cohort study	11	Bacteria	Patients had meningitis if they had one of these unknown indications: (Fever >38°c), meningeal signs, elevated white cell count, increased protein, or reduced glucose in the CSF. Organism identified on Gram's stain of CSF, antigen test, positive blood culture, a prognosis of one antibody titer (IgM) or an elevation in paired sera (IgG) for pathogen by four-fold

Table 2: Continued.

Study	Country	Study period	Analytic method	Disease etiology	Study design	Quality score	Major etiology	Definition of meningitis
[27]	Netherlands	2006–2014	Logistic regression	*Streptococcus pneumoniae, Neisseria meningitidis, Listeria monocytogenes*	Prospective cohort	12	Bacteria	Bacterial meningitis was defined as having a positive cerebrospinal fluid culture, or a mix of positive blood culture without a significant pathogen, or a positive PCR result for streptococcus *pneumoniae* or neisseria meningitis with at least one cerebrospinal fluid finding predictive bacterial meningitis of a CSF of leukocyte counts >2000 cells/mm^3, polymorphonuclear leukocyte count >1180 cells/mm3, glucose level <1.9 mmol/L, protein level >2 g/L, or CSF/blood glucose ratio <0.23
[45]	UK	2007–2017	Multivariate cox models	*Neisseria meningitidis*	Retrospective observational cohort study	13	Bacteria	Not reported
[46]	USA	1992–1994	Conditional logistic regression	*Cryptococcus neoformans*	Prospective study	8	Fungal	Positive culture for C. neoformans for any body part; detection of cryptococcal antigen in the blood, cerebrospinal fluid, or urine; or histopathologic findings consistent with cryptococcosis

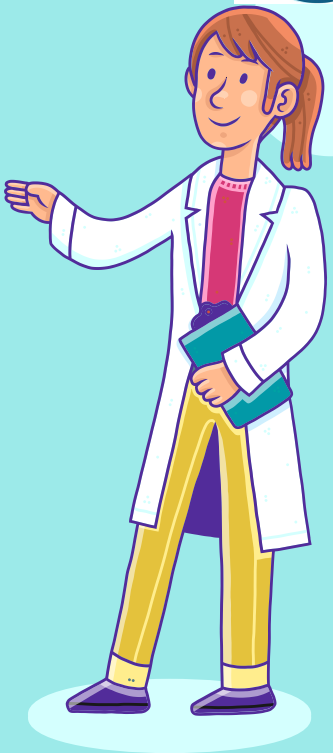
Table 2: Continued.

Study	Country	Study period	Analytic method	Disease etiology	Study design	Quality score	Major etiology	Definition of meningitis
[47]	Canada	1999-2000	Logistic regression	*Staphylococcus aureus, Enterococcus, Streptococcus, Clostridium butyricum, Candida albicans*	A population-basedactive-surveillance cohort design	10	Fungal	CSF and blood culture, pleural or synovial fluid, or aseptically obtained deep-tissue aspirates or surgical-tissue samples
[48]	Greece	2006–2008	Multivariate logistic regression, mantel-haenszel test	*Acinetobacter* spp., *Klebsiella* spp., *Pseudomonas aeruginosa, Enterobacter cloaceae, Proteus mirabilis*	Prospective study design	12	Bacteria	CSF culture, signs of: fever, headache, stiff neck, meningeal and cranial nerves signs or irritability (if diagnosis was made antemortem) antimicrobial therapy, increased WBC counts, increased protein level or increased level of glucose in the CSF, organisms seen on Gram stain of CSF; organisms cultured from blood; positive antigen test of CSF, blood, or urine; diagnostic single antibody titer (IgM) or 4-fold increase in paired sera (IgG) for pathogen
[49]	Canada	1997–2001	Logistic regression	*Cryptococcus gattii, Cryptococcus neoformans*	Case-control study	12	Fungal	CSF and/or blood culture and classification of diseases, 9th revision (ICD-9), code 117.5 (cryptococcosis)

04

Discussion

Journal Reading Denisa



Studi kami mencakup 16.847 kasus meningitis dengan 7 desain studi prospektif dan 9 retrospektif.

Infeksi meningitis merupakan ancaman global bagi kesejahteraan manusia

Di antara penderita meningitis yang selamat, satu dari lima dapat mengalami gejala sisa permanen, termasuk kelumpuhan saraf kranial, hidrosefalus, kejang, hemiparesis, dan gangguan penglihatan dan pendengaran

Dalam sebuah penelitian, diketahui bahwa diabetes melitus meningkatkan risiko S. pneumoniae, diikuti oleh L. monocytogenes.

Diabetes telah dicatat sebagai faktor risiko independen untuk infeksi multipel, termasuk tuberkulosis dan pneumonia dan faktor substansial dalam rawat inap

Tinjauan kami menemukan bahwa diabetes meningkatkan risiko meningitis dua kali lipat

Tingkat risiko yang ditemukan menunjukkan bahwa orang dengan diabetes dua kali lebih mungkin mengalami meningitis bakteri daripada mereka yang tidak menderita diabetes

05

Conclussions

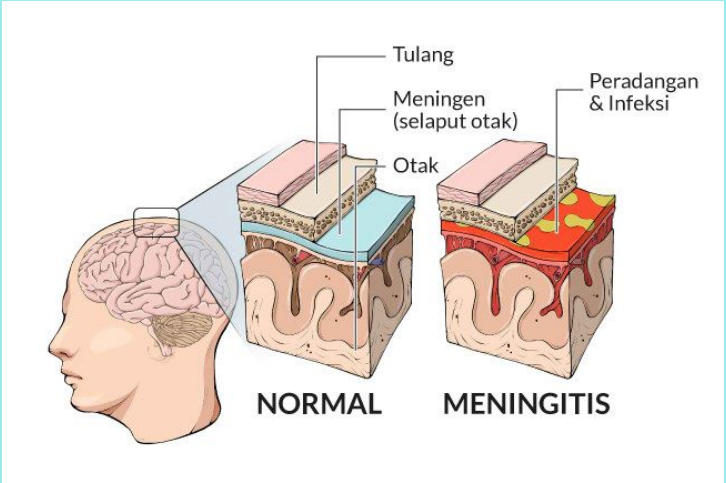
Journal Reading Denisa

Kesimpulan

Diabetes meningkatkan risiko meningitis lebih dari dua kali lipat. Risiko ini sangat signifikan di seluruh wilayah global yang termasuk dalam penelitian ini (Amerika Utara, Eropa, dan Asia).

Saran

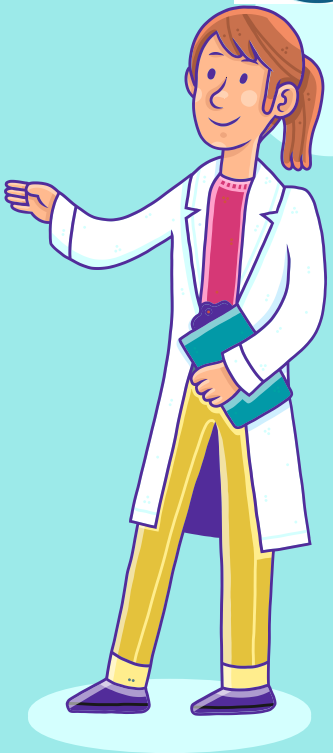
- Perhatian harus diarahkan pada daerah Afrika dan Amerika
- Berfokus pada subtipe meningitis yang terperinci dan hubungannya dengan kelas diabetes yang berbeda akan sangat membantu untuk mengonfirmasi temuan kami dan memberikan bukti komprehensif untuk patologi dan etiologi meningitis.



06

PICO

Journal Reading Denisa



Analisis PICO

Problem

- Masalah Klinik pada jurnal ini adalah untuk mengetahui hubugan antara Diabetes dengan Risiko Infeksi Meningitis
- Digunakan 16 makalah dengan 16.847 kasus pada tahun 2016-2020

Intervention

- Teknik pengambilan data pada penelitian ini dengan data sekunder yang berasal dari 16 makalah selanjut nya menggunakan protokol pencarian literatur dan desain studi mengikuti panduan Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA)
- Pencarian dilakukan di PubMed, Web of Science, African Journal Online, dan Google Scholar menggunakan istilah MESH yang relevan.

Analisis PICO

Comparasion

Kualitas berbagai makalah berdasarkan sistem penilaian dibagi menjadi buruk (0–7,99), baik (8–11,99), dan sangat baik (12–16)

Outcome

- Penelitian ini melakukan meta-analisis yang melibatkan 16.847 kasus untuk menyelidiki hubungan antara diabetes dan risiko berkembangnya meningitis. Menunjukkan bahwa diabetes meningkatkan risiko meningitis lebih dari dua kali lipat. Risiko ini sangat signifikan di seluruh wilayah global yang termasuk dalam penelitian ini (Amerika Utara, Eropa, dan Asia)

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