CRP measurement in general practice – Influence on antibiotic prescribing in patients with respiratory tract infections:

Upper RTI: Lars Bjerrum Lower RTI: Rogier Hopstaken

Bojnice, Slovakia 2009 Lars Bjerrum University of Southern Denmark



CRP Point-of-care tests in patients with upper respiratory tract infections – Why?

- 1. Is CRP a valid test in patients with URTI?
- 2. Is there an optimal cut-point for CRP?
- **3.** Is there a need for CRP in patients with URTI?
- 4. Does CRP influence antibiotic prescribing in patients with RTI?
- 5. Did CRP influence antibiotic prescribing in patients participating in HAPPY AUDIT?
- 6. Conclusion





General Practice University of Southern Denmark, Odense



Svendborg: My consultation





DENMARK

- 5 million inhabitants
- 7.300 Km. Coastline
- 500 harbours
- 406 islands









New Harbour, Copenhagen



Antibiotic treatment in general practice

- GPs are responsible for >90% of all prescriptions of antibiotics
- The majority of prescriptions are for patients with respiratory tract infections
 - Most respiratory tract infections are caused by virus
 - Overuse of antibiotics may lead to increased number of resistant bacteria





Why are antibiotics prescribed for non-bacterial infections ?



- Doctors may be too busy to perform a thorough examination
- Doctors have no access to valid point of care tests
- A prescription can be used to terminate the consultation - if the GP is busy
- If doubt you may prescribe "just to be safe"

Diagnostic methods for upper respiratory infections in general practice

- Acute Tonsillitis/pharyngitis
 - Strep A
 - Acute Sinusitis
 - C-Reactive Protein (CRP)
- Acute Otitis media
 - No appropriate point of care test is available











Validity of CRP in patients with acute sinusitis

Acute sinusitis -One of the most difficult diagnoses in daily practice

Uncertain diagnosis results in a considerable overuse of

Diagnosis of acute sinusitis

Daily practice

- Unspecific symptoms:
 - Pain in teeth
 - Unilateral maxillary pain
 - Purulent nasal secretion,
 - Pain at bending forward,
 - Transillumination of sinus
- Lab test:
 - Increased CRPIncreased ESR

- Gold standard
 - CT-scan
 - Sinus puncture with aspiration of purulent secretion
 - culture of secretion with growth of bacteria



Diagnosis of acute sinusitis

The aim is to

- Identify patients who would benefit from antibiotics
- Avoid unnecessary antibiotic treatments



CRP testing in sinusitis in general practice

- CRP and erythrocyte sedimentation rate (ESR) are of value to distinguish between virus and bacteria in patients with sinusitis*
- Validity
 - CRP (>10 mg/l):
 - Likelihood ratio: 1.8 (Hansen et al 1995)
 - ESR (male>10, women>20):
 - Likelihood ratio: 1.7 (Lindbaek et al, 1996)
 - Likelihood ratio: 2.9 (Hansen et al 1995)

*Dahler-Eriksen: The use of CRP, clinical organizational and economical aspects (dissertation, University of Aarhus, 1999) *Hansen JG et al Predicting acute maxillary sinusitis in a general practice population. BMJ 1995; 311: 233-236

Is there an optimal cut-point for CRP in patients with Acute Sinusitis?



Cut point for CRP, true and false values







Validity of CRP in patients with Sinusitis

- Sensitivity and specificity:
 - Cut-point 10mg/l
 - Sensitivity 73%
 - Specificity 60%
 - Cut point 25mg/l
 - Sensitivity 52%
 - Specificity 77%
 - Cut point 50mg/l
 - Sensitivity 33%
 - Specificity 89%

- Predictive values:
 - Cut-point 10mg/l
 - PV pos 0.68
 - PV neg 0.66
 - Cut point 25mg/l
 - PV pos 0.73
 - PV neg 0.59
 - Cut point 50mg/l
 - PV pos 0.79
 - PV neg 0.54

Jens Georg Hansen et al:

Predicting acute maxillary sinusitis in a general practice population

BMJ 1995;311:233-236 (22 July)

• **Objective**: To evaluate the diagnostic value of symptoms, signs, erythrocyte sedimentation rate, and C reactive protein for acute maxillary sinusitis.

Design: Prospective cohort study.

Setting: Danish general practice in cooperation with the otorhinolaryngology and neuroradiology department at Aalborg County Hospital.

Subjects: 174 patients aged 18-65 years who were suspected by the general practitioner of having acute maxillary sinusitis.

Main outcome measure: The independent association of symptoms, signs, erythrocyte sedimentation rate, and concentration of C reactive protein in patients with acute maxillary sinusitis defined as purulent or mucopurulent antral aspirate.

Results: Only raised erythrocyte sedimentation rate (P=0.01) and raised C reactive protein (P=0.007) were found to be independently associated with a diagnosis of acute maxillary sinusitis. The combination of the two variables had a sensitivity of 0.82 and a specificity of 0.57.

Conclusion:

- Low diagnostic value of symptoms and signs
- A raised value of CRP is a better basis for deciding to give antibiotics than a clinical examination

APMIS 117: 724-729

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Symptoms and signs in culture-proven acute maxillary sinusitis in a general practice population

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Hansen JG et al: APMIS 2009

a general practice population. APMIS 2009; 117: 724-9.

The objective of this study was to assess symptoms and signs in patients with ma bacteriological diagnosis obtained by sinus aspiration or lavage. Designed as study in general practice, the study included 174 patients, aged 18-65 years, susp maxillary sinusitis by their general practitioner. The main outcome measures association of symptoms, signs, erythrocyte sedimentation rate (ESR), and C-r concentration and confirmed infection with the predominant bacterial pathoger moniae and Haemophilus influenzae. The predominant organisms found in patient sinusitis were S. pneumoniae and H. influenzae. Body temperature > 38 °C and were significantly associated with the presence of S. pneumoniae and H. influen. logical culture results were significantly associated with increasing ESR and CR symptoms and signs, with the exception of body temperature > 38 °C and max particularly sensitive indicators of the specific aetiology in patients with acu (mElevated ESR and CRP values were significantly associated with positive b results. On the other hand, absence of these symptoms and signs did not exclude maxillary sinusitis.

Key words: Acute maxillary sinusitis; symptoms; signs; microbiology; general pra Jens Georg Hansen, Lindenborgvej 93, DK-9200 Aalborg SV, Denmark. e-mail: j

Hansen JG, Højbjerg T, Rosborg J. Symptoms and signs in culture-proven acute **Table 5**. Association between the concentration of C reactive protein (CRP) and the results of culture for Streptococcus pneumoniae or Haemophilus influenzae from either one or both maxillary sinuses in 45 patients with acute maxillary sinusitis compared with 82 patients with an absence of acute sinusitis

RP	Acute maxillary sinusitis (n)			OR
ng∕l)	Unilateral	Bilateral	Absent	(95% CI)
11	8	4	63	
-49	10	7	10	8.9 (4–22)
49	11	5	8	10.5 (4-27)

Consequence of CRP testing in patients with Acute Sinusitis

- CRP < 10: Most probably Virus</p>
- CRP > 50: Most probably Bacteria
- 0-10 mg/l
 - Low probability of a bacterial infection
 - Follow the patient without antibiotics
 - New CRP within 1-2 days
 - 10-50 mg/l
 - Grey zone, the consequence depends on the clinical condition
 - Expectation without antibiotics
 - New CRP after 1-2 days
 - Antibiotic prescription if increased CRP
- >50 mg/l
 - High probability of a bacterial infection
 - Antibiotic prescription
 - Control the patient after a few days
 - New CRP to control the effect of treatment



Receiver Operating Curve (ROC) and test validity

- Classification of the accuracy of a diagnostic test:
- Area under the curve:
 - 0.9-1.0 = excellent (A)
 - □ 0.8-0.9 = good (B)
 - 0.7-0.8 = fair (C)
 - 0.6-0.7 = poor (D)
 - □ 0.5-0.6 = fail (F)



Is there really a need for CRP measurement in patients with upper respiratory tract infections? General practitioners a busy people that need valid tests to distinguish between viral and bacterial infections



What do patients with respiratory infections want from the GP?



- Doctors are highly influenced by patients demand.
- Testing and Prescribing are ways of showing the patient that the GP understands the patient's problem and is willing to help
- Do patients with RTI expect the doctor to prescribe antibiotics?
 - Nordic countries: Infrequently
 - Southern European countries: Frequently
 - Slovakia?
 - Do patients with RTI expect the doctor to perform a point of care test?
 - Nordic countries: Frequently too frequently?
 - Southern Europe: Generally, no access to POC tests
 - Slovakia?



Antibiotics: "one of the most uncomfortable prescribing decisions general practitioners make"

Use of point of care tests in patients with respiratory tract infections in DK.



CRP in general practice in Denmark

- CRP was introduced in general practice in Denmark about 10 years ago
- Today more than 3/4 of GPs have implemented the test in practice



Diagnostic tests according to focus



Use of CRP in Danish general practice

NycoCard CRP

Axis-Shield Afinion Orion QuikRead CRP















QuikRead

Dispense 1 ml of buffer int the cuvette.

Add 20 µl of whole bloo

(not u cuvette into t









Orion Diagnostica

4 Blank measurement max. 40 seconds. Add the CRPreagent by pressing down the inner di

Take out the cuvette and mix vigorcusly (back and forth) to dissolve the reagent.

6 Put the cuvette back into the measurement well. The CRP result is displayed within 2 minutes.

Measurement of CRP in general practice -Does it influence the use of antibiotics?

British Journal of General Practice, august 2004

Original papers

C-reactive protein measurement in general practice may lead to lower antibiotic prescribing for sinusitis

Lars Bjerrum, Bente Gahrn-Hansen and Anders P Munck

SUMMARY

Background: Symptoms of bacterial sinusitis overlap with viral sinusitis, and it is difficult to distinguish between the two conditions based only on a clinical examination. Uncertain diagnosis results in the significant overuse of antibiotics, which is considered to be one of the most important reasons for development of bacterial resistance to antibiotics. Raised C-reactive protein (CRP) level is an indicator of bacterial infection and the CRP rapid test has been shown to be useful for

Introduction

ACUTE sinusitis is an inflammation of the paranasal sinuses lasting for up to 4 weeks, and is caused by either bacterial (purulent sinusitis) or viral (serous sinusitis) infection.¹ Acute sinusitis is a frequently occurring problem in general practice, and it is challenging for the general practitioner (GP) to diagnose. The 'gold standard' to assess the etiology is a sinus puncture followed by aspiration and bacterial cul-

Treatment of sinusitis in relation to performing of CRP


Choice of antibiotics for sinusitis in relation to practice use of CRP



Treatment of sinusitis in relation to the result of CRP



HOW THIS FITS IN

What do we know?

Symptoms of bacterial sinusitis overlap with viral sinusitis, and it is difficult to distinguish between the two conditions based on a clinical examination. Uncertain diagnosis may result in the overuse of antibiotics and so contribute to the development of bacterial resistance to antibiotics. Raised C-reactive protein (CRP) level is an indicator of bacterial infection, and the CRP rapid test has been shown to be useful for the diagnosis of bacterial sinusitis in general practic

What does this paper add?

Implementing the CRP rapid test in general practice may lead to a reduction in antibiotic prescribing to patients with sinusitis. Logistic regression relating practice characteristics to prescribing of antibiotics for patients with sinusitis

	Odds ratio	Confidence interval
Patient age	1.01	1.00-1.02
Patient sex	1.02	0.80-1.30
Practice with access to CRP	0.43*	0.33-0.58
Number of listed patients	1.00	0.99-1.01
Number of years working in practice	1.0	1.00-1.00
Type of practice (solo/group)	1.41*	1.12-1.77
Workload in practice	0.92	0.81-1.11

Lesson learnt

- Implementing CRP test in general practice may lead to a reduction in antibiotic prescribing for patients with sinusitis
- The chance of avoiding antibiotics in a practice with access to CRP is double as high as the chance in a practice without access to CRP



Eur J Clin Pharmacol DOI 10.1007/s00228-006-0187-y

PHARMACOGENETICS

Effect of intervention promoting a reduction in antibiotic prescribing by improvement of diagnostic procedures: a prospective, before and after study in general practice

Lars Bjerrum • Josep M. Cots • Carl Llor • Núria Molist • Anders Munck

Received: 1 May 2006 /Accepted: 18 July 2006 © Springer-Verlag 2006

Abstract

Objective To investigate if an intervention aimed at improving the quality of the diagnostic procedures in Spanish general practice could lower antibiotic prescribing in patients with respiratory tract infections (RTIs).

Methods GPs in the intervention group (n=17) registered all patients with RTIs during a 3-week period before and after the intervention. The intervention was aimed at reducing prescribing of inappropriate antibiotics for RTIs by improving the diagnostic procedures and thereby belping the GPs to distinguish between bacterial and viral infections. It consisted of courses in management of RTI according to local clinical guidelines, and included implementation of two rapid diagnostic tests (StrepA and CRP measurement). Diagnoses and prescribing of antibiotics were assessed before and after the intervention, and compared to a control group not exposed to intervention (35 GPs).

Results The intervention led to a significant reduction in antibiotic prescribing. Before the intervention 36% (29%–44%) of consultations were followed by antibiotic prescribing, after the intervention 24% (20%–29%). Antibiotic prescribing in the control group not exposed to intervention was 32% (27%–38%). The reduction was most pronounced in patients with sinusitis and lower RTIs.

Conclusion Quality improvement of diagnostic procedures may lead to a reduction of antibiotic prescribing in primary health care in Spain.

Keywords Antibiotics · General practice · Intervention · Diagnostic procedures · Respiratory tract infections





Global perspectives by implementing laboratory test for patients with RTI in general practice

- Will GPs be better to distinguish between bacterial and viral infections?
- Will inappropriate antibiotic prescriptions be reduced?



AMERICA'S HOTTEST NEW THEME PARK

Littleton Remembers

The Long Air War Ahead



ler Bacteria

Because of overuse, many antibiotics are powerless against deadly microbes. This boy survived—but many others may not

Digital TV Comes of Age

A New Plan for Social Security

Pat Buchanan **Punches Away**

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Total Outpatient Antibiotic Use (ATC J01) in 27 European Countries, 2006



* Total use, i.e. including inpatients, for Bulgaria, Cyprus, Greece and Lithuania.

** 2005 data for Estonia, Germany, Latvia, Poland and United Kingdom.

*** Reimbursement data, which do not include over-the-counter sales without a prescription for Spain.

www.happyaudit.org

Health Alliance for Prudent Prescribing, Yield And Use of anti-microbial Drugs In the Treatment of Respiratory Tract Infections

HAPP

6



- Project summary
- Project activities
- Contacts
- Links
- Intranet
- Site Map

Welcome

Kickoff meeting 12-13.4. Programme and registration

FP6 programme: Scientific Support to Policies (SSP) **Project title:** <u>H</u>ealth <u>Alliance for <u>P</u>rudent <u>P</u>rescribing, <u>Y</u>ield <u>And U</u>se of Anti-microbial <u>D</u>rugs <u>In the <u>T</u>reatment of Respiratory Tract Infections **Acronym:** HAPPY AUDIT</u></u>

Project number: 044154 EC contribution: 1.492.300 € Duration: 36 months Starting date: 01/04/2007 Instrument: Specific Targeted Research Project (STREP)

Facts about the use of antibiotics for patients with respiratory tract infections:

- Most respiratory tract infections are caused by virus
- Most respiratory infections are not dangerous
- Very few respiratory infections are serious or lifethreatening
- Only few respiratory infections need acute treatment
- Most prescriptions are issued for fear of serious infections –



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HAPPY AUDIT Objective

- to reduce the occurrence of bacterial resistance
 - by reducing prescribing of unnecessary antibiotics for respiratory tract infections
 - by improving the use of appropriate antibiotics in suspected bacterial infections
 - by improving the quality of diagnostic procedures for RTIs in general practice





Аудит: острые респираторные заболевания в общей врачебной практике



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Kaliningrad



Intervention material for professionals

- Reports with aggregated and individual results based on 1. registration
- Happy Audit Guidelines
- Laboratory tests and instructions





Respiratory infections in general practice Results from 6 countries



Reports in national language including individual results were sent to all paticipating GPs









Reports: Individual results



Antibiotika Antibiotics



Reports: Individual results





Guidelines

VEJLEDNING I DIAGNOSTIK OG BEHANDLING AF LUFTVEJSINFEKTIONER I ALMEN PRAKSIS



GUÍAS PARA EL DIAGNÓSTICO Y TRATAMIENTO DE LAS INFECCIONES DEL TRACTO RESPIRATORIO EN ATENCIÓN PRIMARIA





Guidelines

Akut tonsillitis

Definition

Infektion i tonsiller forårsaget af virus eller bakterier.

Symptomer og fund

Symptomerne er karakteriseret ved ondt i halsen, synkesmerter og almen sygdomsfølelse. Der kan desuden være feber. De objektive fund er meget varierende, fra næsten ingen synlige forandringer til udtalt forstørrelse af tonsiller, hyperæmisk slimhinde, belægninger på tonsiller og hævede lymfeknuder på halsen.

Diagnose

Omkring 2/3 af tilfældene er forårsaget af virus og 1/3 af bakterier.

Målet med diagnostikken er at identificere og behandle patienter med en bakterieinfektion. I de fleste lande er det kun gruppe A streptokokker (Streptococcus pyogenes, S.p.), der kræver behandling. I lande med endemisk forekomst af difteri er en bakteriedyrkning obligatorisk.

Patienter over 4 år

For patienter over 4 år bør den kliniske undersøgelse fokusere på forekomsten af 4 diagnostiske kriterier (Centor kriterier):

- Feber > 38.5 grader
- Hævede og ømme lymfeknuder på halsen
- Belægninger på tonsilller
- Fravær af hoste

Mulig virusinfektion

Patienter med halssmerter ledsaget af symptomer på en virusinfektion (f.eks. hoste, snue, hæshed, universel glandelsvulst, blister i ganen) og/eller forekomsten af maximalt et Centor-kriterie har højst sandsynligt en virusinfektion. Hos disse patienter bør der ikke foretages Strep A test på grund af den øgede risiko for falsk positive resultater.





Intervention material for Patients

Brochures about Respiratory Tract InfectionsPosters in doctors waiting rooms

Brochures

FARINGITIS

Si Usted tiene dolor de garganta y además tos o congestión nasal, presenta entonces una infección causada por un virus y, por tanto, debe tratarse como un resfriado. Los antibióticos no serán por tanto eficaces.

Si su garganta está afectada, tiene fiebre y se siente enfermo, pero no tiene tos ni le gotea la nariz, entonces su infección podría estar causada por una bacteria. Es difícil probar si la infección es causada por una bacteria (estreptococo) o por un virus. Una manera de ayudar al médico es haciendo una prueba rápida en la consulta y si ésta indica una infección bacteriana causada por bacterias, entonces le podría ser útil la penicilina.

Debido a que la mayoría de las infecciones bacterianas son curadas por su propio sistema inmunitario tan rápidamente como lo hace la penicilina, solamente aquéllos que realmente estén enfermos se podrían beneficiar usándola.



Usted debería visitar a su médico si tiene: dolor de garganta, problemas p boca, no es capaz de tragar saliva o tiene fiebre alta y siente malestar gen

CATARRO

Un catarro o resfriado común comienza con una congestión nasal y algunas veces fiebre. Pueden aparecer dolor de garganta y tos después de unos pocos días.

El color del moco (amarillo o verde) que aparece después de unos días es causado por su sistema inmune y no es un signo de infección bacteriana que debiera ser tratado con antibióticos. La mayoría de los resfriados se curan a los 7-10 días.

Centenares de virus distintos causan el "catarro común". Los niños tienen entre 6 y 8 catarros anuales y los adultos, aproximadamente cuatro al año.

Habitualmente no es necesario utilizar pruebas de laboratorio para confirmar el diagnóstico de un resfriado.

Los antibióticos no sólo no son eficaces sino que pueden ser perjudiciales y tener efectos secundarios.

No es necesario que acuda a su médico ni tampoco debe tomar antibióticos cuando tiene un resfriado. En caso de necesidad puede usar analgésicos o antitérmicos.



Información para pacientes

El Proyecto Happy Audit Un Proyecto Europeo de Médicos de Familia





Posters

INFECCIÓNES

¿VIRUS O BACTERIAS? ¿CUÁL ES LA DIFERENCIA?

Los virus causan infecciones virales y las bacterias causan infecciones bacterianas. Los virus son mucho más pequeños que las bacterias y frecuentemente se diseminan con facilidad en el aire. Los antibióticos no tienen ningún efecto sobre los virus.

¿CUÁNDO PUEDEN SER ÚTILES LOS ANTIBIÓTICOS?

La mayoría de las infecciones, incluyendo las bacterianas, se curan gracias a nuestro sistema inmunitario. Es un sistema altamente eficiente y cura la mayoría de las infecciones. Sólo cuando estamos afectos por infecciones bacterianas, los antibióticos pueden ser de utilidad.

ANTIBIÓTICOS- ¡UNA CLASE IMPORTANTE DE MEDICAMENTOS!

Cuando se utilizan correctamente, los antibióticos pueden curar enfermedades infecciosas y salvar vidas. Sin embargo, utilizados incorrectamente pueden ser perjudiciales. Debido a que muchos antibióticos son prescritos a niños de corta edad, es de suma importancia que los padres los utilicen con prudencia.

> ASÍ, ¿NO SIEMPRE CURARÁN LOS ANTIBIÓTICOS TODAS LAS INFECCIONES? CORRECTO ¡CONSULTE SIEMPRE A SU MÉDICO!



COJA UN FOLLETO PARA MÁS INFORMACIÓN SOBRE Catarro - Faringitis - Gripe Sinusitis - Otitis - Bronquitis





		Number o	f doctors	Number o regis	of patients stered	Number of patients treated with antibiotics								
		2008	2009	2008	2009	2008	2009							
	Argentina	60	48	4374	3641	1780 (41%)	1170(32%)							
	Denmark	102	78	3904	3706	1351 (35%)	1185 (32%)							
	Lithauen	31	28	2706	1976	1152 (43%)	468 (24%)							
	Russia	39	37	3685	3284	1215 (33%)	481 (15%)							
	Spain	309	281	16751	12760	4675 (28%)	2530 (20%)							
-	Sweden	77	39	1853	895	764 (41%)	333 (37%)							
	Total	618	511	33273	26262	10937 (33%)	9669 (24%)							



INVESTIGATIONS



□16 **□**15 **□**14 **□**13 **□**12

Strep A positiv
Strep A negativ
CRP målt

15. Røntgen af thorax positiv16. Røntgen af thorax negativ17. Ingen af førnævnte

12. Strep A positive 13. Strep A negative 14. CRP (mg/l) 15. X-ray of thorax positive 16. X-ray of thorax negative

17. None of the above

What was the effect of introducing POC tests on the use of antibiotics?



Figure 1. Areas in Spain in the second register, 2009



HAPPY AUDIT intervention in Spain: Influence of antibiotic prescribing for all RTIs



- Intervention including the introduction of POC testing
 - Reduction in antibiotic prescribing: 36.4%
- Intervention without the introduction of POC testing
 - Reduction in antibiotic prescribing: 8.3%

HAPPY AUDIT intervention in Spain: Influence of antibiotic prescribing for acute bronchitis



- Intervention including the introduction of POC testing
 - Reduction in antibiotic prescribing: 51.5%
- Intervention without the introduction of POC testing
 - Reduction in antibiotic prescribing: 14.4%

Figure 4. Utilization of C-reactive protein stated by the 210 physicians assigned to the intervention group in 2009



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Figure 7. Contacts of sinusitis treated or not with antibiotics depending on the utilization of C-reactive protein testing and its result



Conclusions I

Use of CRP testing in Primary care

- CRP rapid-testing is of value in general practice
- Main indication areas in RTIs
 - Sinusitis validity moderate
 - Lower RTI validity high
- The result should always be interpreted in combination with a clinical evaluation
 - No specific defined cut-off point
 - Serial measurement is sometimes of great value



Conclusions II Use of CRP testing in Primary care



CRP testing in general practice helps the GP to avoid inappropriate prescribing of antibiotics

It leads to a considerable reduction in antibiotic use
"The more you use it, - the faster you lose it"

Burke JP, Lancet 1995;345:977



CRP Possible disadvantages

Medicalising effect of POC-testing?



