СПЕЦИАЛИЗИРАН НАУЧЕН СЪВЕТ ПО ИМУНОЛОГИЯ ПРИ В А К

Д-р Росица Стефанова Вачева

ВЪРХУ ИМУННИЯ ОТГОВОР ПРИ ЗАРАЗЯВАНЕ С PSEUDOMONAS AERUGINOSA В ЕКСПЕРИМЕНТ

А В Т О Р Е Ф Е Р А Т

на

Д И С Е Р Т А Ц И Я

за получаване на научната степен

"Кандидат на медицинските науки"

НАУЧЕН РЪКОВОДИТЕЛ:

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Плевен, 1990 година

ПРОУЧВАНИЯ ВЪРХУ ИМУНИТЕТА ПРИ ЕКСПЕРИМЕНТАЛНА ИНФЕКЦИЯ С ПСЕВДОМОНАС АЕРУГИНОЗА

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При изследване на имунитета срещу Pseudomonas aeruginosa освен ролята на антителата (Alexander et al.,1974; Pavlovskis et al. 1977) се проучва и значението на Т-клетъчните механизми (Markham et al.,1984). Инфекцията с P. aeruginosa потиска контактната чувствителност към оксазолон (Camp et al. ,1975).Стимулират се и супресорни клетки,сред които и супресорни Т-лимфоцити.Ефектът на последните се медиира от разтворим продукт,който в опитите на Powderly et al. (1986) инхибира Т-клетъчната пролиферация и потиска продукцията или освобождаването на бактерициден лимфокин.

В настоящия труд си поставихме за задача да изследваме имунния отговор на организма в експеримент при инфекция с P. aeruginosa

МАТЕРИАЛ И МЕТОДИ

Опитите бяха извършени върху инбредни мишки BALB/c -850 опитни и 237 контролни. За заразяването на мишките се използуваше 24 ч. култура от живи P. aeruginosa с гъстота $25x10^5$бакт./мл.Бактериалната суспензия се инокулираше по 0,5 мл i.p. . Прилагаха се следните методи на изследване.

Плаков хемолитичен тест за откриване на единични антителообразуващи клетки (ПОК) по Cunningham и Szenberg (1968) в далачни суспензии на животните,инжектирани допълнително с по 0,5 мл 10% овнешки еритроцити (Ер) 7 и 14 дни след инфекцията.

Е-розетъчен тест за установяване на Т-лимфоцити,формиращи розетки (РОК) с овнешки Ер по Mendes et al. (1973).Розетките се отчитаха на 15-та минута и след 1 час.

Лимфоцитен трансформационен тест (бластна трансформация) със суспензия от далачни лимфоидни клетки от заразени и контролни животни (нефилтрирани и филтрирани през колонката на Julius , 1973) при използуване на радиометричен метод.Измерваше се радиоактивност за 1 минута и се изчисляваше стимулационен индекс (I):

$$I = \frac{\text{cpm experimental}}{\text{cpm control}}$$

Индометацин зависима супресия.Към далачни лимфоцити,стимулирани с ФХА се прибавяше индометацин в концентрация 1 мкг/мл.Изчисляваше се Augmentation index (AI):

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Biotechnology & Biotechnological Equipment

ISSN: 1310-2818 (Print) 1314-3530 (Online) Journal homepage: www.tandfonline.com/journals/tbeq20

Molecular Characterization and Determination of Antibiotic Resistance of Acinetobacter Baumanii Isolates from a Bulgarian Hospital

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To cite this article: R. Vatcheva-Dobrevsky, E. Savov, A. Bernards, M. van den Barselaar & L. Dijkshoorn (2005) Molecular Characterization and Determination of Antibiotic Resistance of Acinetobacter Baumanii Isolates from a Bulgarian Hospital, Biotechnology & Biotechnological Equipment, 19:3, 166-169, DOI: 10.1080/13102818.2005.10817246

To link to this article: https://doi.org/10.1080/13102818.2005.10817246

RESEARCH NOTE

Genotypic diversity and antibiotic susceptibility of *Acinetobacter baumannii* isolates in a Bulgarian hospital

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ABSTRACT

A set of 18 *Acinetobacter baumannii* isolates, collected prospectively in a Bulgarian hospital during episodes of increased *A. baumannii* occurrence during 2000–2002, was investigated for genotypic diversity and antibiotic susceptibility. Four genotypes were identified by amplified fragment length polymorphism genomic fingerprinting, one of which (type 1) accounted for 13 isolates, indicating that a specific strain was predominant. The single isolate allocated to type 2 was identified to European clone I. All isolates were resistant to multiple antibiotics, but most retained susceptibility to tobramycin and colistin, and all except one were susceptible to imipenem.

Keywords *Acinetobacter baumannii*, AFLP typing, antibiotic susceptibility, Bulgaria, genotypes, nosocomal infection

Original Submission: 9 December 2005; **Revised Submission:** 1 March 2006; **Accepted:** 9 April 2006

Clin Microbiol Infect 2006; 12: 1135–1137
10.1111/j.1469-0691.2006.01530.x

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Most reports of multiresistant endemic or epidemic *Acinetobacter baumannii* are from western European countries, and information concerning this organism in central and eastern Europe is scarce. *A. baumannii* has been endemic in the hospital of the Military Medical Academy (MMA), Sophia, Bulgaria since the early 1990s. The present report investigated a set of *A. baumannii* isolates, collected prospectively in the MMA hospital during 2000–2002, for genotypic relatedness and susceptibility to antibiotics. The aims of the study were to determine whether a single strain predominated in the hospital during the collection period, and whether the isolates were related to clones I–III found in hospital outbreaks in several other European countries [1–3].

The MMA is a 500-bed university hospital for military personnel and civilians. It is a referral hospital that provides acute medical and surgical care, but not for paediatrics, obstetrics and burns patients. The hospital has two intensive care units, i.e., a 20-bed medical unit and a 16-bed surgical unit. Many patients admitted to the surgical intensive care unit are emergency cases with poly-trauma following car accidents or gunshot wounds. The hospital employs an infection control doctor and an infection control nurse, who both participate in the infection control committee of the hospital. The occurrence of multidrug-resistant *Acinetobacter* has increased steadily since the early 1990s, with recurrent clusters of cases, especially in the two intensive care units [4]. Control measures during such epidemic episodes usually include isolation of patients, as well as disinfection of the environment and surgical instruments on wards. Antibiotics for treatment of patients with infections caused by *Acinetobacter* spp. include imipenem, and amikacin plus ampicillin–sulbactam.

In total, 18 multidrug-resistant isolates of *Acinetobacter* spp. from 18 patients were investigated (Table 1). These isolates were selected from among 65 multidrug-resistant *Acinetobacter* isolates recovered during documented episodes of increased occurrence during 2000–2002. The isolates were selected to represent presumptive cases of cross-infection, based on their antibiotic susceptibility profile and their origin in time and space. Most isolates were from multi-trauma patients, i.e., a group susceptible to colonisation with *A. baumannii* [5]. The organisms were iden-

National Hand Hygiene Campaigns in Europe, 2000-2009

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Hand hygiene represents the single most effective way to prevent healthcare-associated infections. The World Health Organization, as part of its First Global Patient Safety Challenge, recommends implementation of multi-faceted strategies to increase compliance with hand hygiene. A questionnaire was sent by the European Centre for Disease Prevention and Control to 30 European countries, regarding the availability and organisation of their national hand hygiene campaigns. All countries responded. Thirteen countries had organised at least one national campaign during the period 2000-2009 and three countries were in the process of organising a national campaign. Although the remaining countries did not have a national campaign, several reported regional and local hand hygiene activities or educational resources on national websites.

Introduction

Healthcare-associated infections (HCAI) are estimated to affect 1.4 million people worldwide, causing longer hospital stay, increasing hospital costs and excess mortality [1-3]. HCAI are preventable and hand hygiene has been shown to be the single most effective way to prevent cross-transmission of microorganisms and

APPLIED AND ENVIRONMENTAL MICROBIOLOGY, Aug. 2011, p. 5562–5565 Vol. 77, No. 15
0099-2240/11/$12.00 doi:10.1128/AEM.02934-10

Detection of New *Francisella*-Like Tick Endosymbionts in *Hyalomma* spp. and *Rhipicephalus* spp. (Acari: Ixodidae) from Bulgaria[▽]

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Received 16 December 2010/Accepted 1 June 2011

We report on the identification of two new *Francisella*-like endosymbionts (FLEs) found in three different tick species from Bulgaria. The FLEs were characterized by 16S rRNA and *tul4* gene sequencing and seem to lack the molecular marker RD1. These two new taxa seem to be facultative secondary endosymbionts of ticks.

Francisella is an expanding genus of closely related Gram-negative coccobacilli. In the past 2 years, at least three new taxa that are pathogens either in fish or humans have been described (9). Yet the classification of many so-called *Francisella*-like endosymbiotic (FLE) bacteria found in both hard and soft ticks remains unresolved (13, 16, 18).

FLEs seem to replicate intracellularly, they are transmitted transovarially, and to date, there is no evidence of horizontal transmission through tick bites. FLEs have been found mainly in the female's reproductive tissues (16), but recently a *Dermacentor variabilis* endosymbiont (DVF) was detected in the hemolymph, potentially suggesting colonization of the salivary glands (7). The pathogenic potential of FLEs remains unknown, although sequences homologous to *iglC* and *mglA* genes of *Francisella tularensis* implicated in pathogenicity have been detected (4, 12).

Studies involving FLEs are hampered by their inability to grow on cell-free media. Hence, most of the molecular studies have been performed with total DNA extracts from ticks or tissues rather than on FLE cultures. This together with the fact that FLEs have never been detected outside ticks suggested that they represent secondary endosymbionts. FLEs seem to be widely distributed, and during the last decade, a number of diverse FLEs have been reported in various tick genera on at least four continents (12, 14, 16–18). To date, the only FLE ever reported from Europe has been isolated from *Dermacentor reticulatus* in Hungary (17), Portugal (5), and Serbia (GenBank accession numbers HM629448 and HM629449). The discrimination between FLEs and *F. tularensis* without gene sequencing is difficult, and the validation of new specific molecular markers is important (11).

Here we report on the detection and molecular characterization of two new, so far undescribed FLEs in three different tick species that seem to lack RD1, an important molecular marker for the discrimination of pathogenic *F. tularensis* subspecies.

A total of 472 ticks removed from human ($n = 32$) or animal ($n = 264$) hosts or collected from the environment ($n = 176$) during 2005 to 2008 were screened for the presence of *F. tularensis* and FLEs. The ticks originated from rural or urban areas of nine major districts in Bulgaria. Identification to species level was performed by using standard taxonomic keys and confirmed by mitochondrial 12S rDNA partial gene sequencing (2, 8). The ticks were either pooled according to region, source, species, developmental stage, and gender or analyzed individually. Each of the resulting 111 pools contained up to six imagoes (an average of two imagoes) or up to 10 nymphs (an average of six nymphs). The most prevalent tick species were *Rhipicephalus sanguineus* (31.4%; $n = 148$), *Dermacentor marginatus* (29.5%; $n = 139$), and *Ixodes ricinus* (25.4%; $n = 120$), followed by *Hyalomma marginatum marginatum* (5.9%; $n = 28$), *Dermacentor reticulatus* (3.6%; $n = 17$), *Rhipicephalus bursa* (3.4%; $n = 16$), *Rhipicephalus turanicus* (0.6%; $n = 3$), and *Hyalomma aegyptium* (0.2%; $n = 1$). Total nucleic acid extraction was done using the QIAamp viral RNA minikit (Qiagen, Germany), which was chosen on the basis of its good performance in a kit comparison (the RNA was used in another study).

Initially, all samples were screened with primers 153F/1281R (F stands for forward, and R stands for reverse) amplifying 1,151 bp of the *Francisella* 16S rRNA gene as previously described (1), which also amplifies the 16S rRNA gene of FLEs. The 16S rRNA gene-positive samples were further analyzed by PCR with tul4BF/tul4BR primers amplifying 838 bp of the *lpnA* (*tul4*) gene encoding the *Francisella* 17-kDa membrane lipoprotein as well as by RD1 assay capable of discriminating between different *F. tularensis* subspecies (3, 16). PCR extension temperatures were modified from the original reports (2, 3, 16) (65°C for the 12S rRNA gene assay, 68°C for the tul4B assay, and 65°C for the RD1 assay). DNA sequencing, multiple alignments, and generation of phylogenetic trees were conducted as previously described (12).

In total, 12 tick samples or pools, including *H. m. mar-*

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▽ Published ahead of print on 24 June 2011.

TOXIN ENCODING GENES CHARACTERIZATION OF BULGARIAN *CLOSTRIDIUM DIFFICILE* CLINICAL STRAINS

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Abstract

The prevalence and severity of *C. difficile* infections (CDI) has been increasing recently worldwide. *C. difficile* has been shown to be associated with asymptomatic colonization to severe diarrhea; pseudomembranous colitis, toxic megacolon, intestinal perforation and death. Asymptomatic carriers are an important hidden reservoir of *C. difficile*. The anaerobic bacterium is considered a causative agent of 25% of the total cases of antibiotic-associated

Journal of Medical Microbiology (2013), **62**, 1428–1434 DOI 10.1099/jmm.0.058149-0

Advances in molecular surveillance of *Clostridium difficile* in Bulgaria

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Received 21 January 2013
Accepted 16 April 2013

The increasing incidence of *Clostridium difficile* infection (CDI) in Bulgaria has indicated the need to implement better surveillance approaches. The aim of the present work was to improve the current surveillance of CDI in Bulgaria by introducing innovative methods for identification and typing. One hundred and twenty stool samples obtained from 108 patients were studied over 4 years from which 32 *C. difficile* isolates were obtained. An innovative duplex EvaGreen real-time PCR assay based on simultaneous detection of the *gluD* and *tcdB* genes was developed for rapid *C. difficile* identification. Four toxigenic profiles were distinguished by PCR: $A^+B^+CDT^-$ (53.1 %, 17/32), $A^-B^+CDT^-$ (28.1 %, 9/32), $A^+B^+CDT^+$ (9.4 %, 3/32) and $A^-B^-CDT^-$ (9.4 %, 3/32). PCR ribotyping and multilocus variable number of tandem repeat analysis (MLVA7) were used for molecular characterization of the isolates. In total, nine distinct ribotypes were confirmed and the most prevalent for Bulgarian hospitals was 017 followed by 014/020, together accounting for 44 % of all isolates. Eighteen per cent of the isolates (6/32) did not match any of the 25 reference ribotypes available in this study. Twenty-four MLVA7 genotypes were detected among the clinical *C. difficile* isolates, distributed as follows: five for 017 ribotype, two for 014/020, 001, 002, 012 and 046 each, and one each for ribotypes 023, 070 and 078. The correlation between the typing methods was significant and allowed the identification of several clonal complexes. These results suggest that most *C. difficile* cases in the eight Bulgarian hospitals studied were associated with isolates belonging to the outbreak ribotypes 017 and 014/20, which are widely distributed in Europe. The real-time PCR protocol for simultaneous detection of *gluD* and *tcdB* proved to be very effective and improved *C. difficile* identification and confirmation of clinical *C. difficile* isolates.

INTRODUCTION

Clostridium difficile is a well-known causative agent of infections in humans and animals worldwide. The spectrum of *Clostridium difficile* infection (CDI) varies from mild diarrhoea to severe colitis including pseudomembranous colitis, toxic megacolon, perforation, sepsis and death (Bartlett & Perl 2005).

C. difficile is an important problem in healthcare facilities, because it is easily transmitted via the faecal–oral route from the hands of healthcare workers to patients and to the environment (McFarland *et al.* 1989). The main predisposing factors for contracting *C. difficile* include advanced age, hospitalization, immune-compromising conditions and exposure to antimicrobial agents (McFarland 1998).

Abbreviations: CDI, *Clostridium difficile* infection; ECDC, European Centre for Disease Prevention and Control; Q-CGE, QIAxcel capillary gel electrophoresis; STRD, summed tandem-repeat difference; UPGMA, unweighted pair group method with arithmetic mean.

Since the Pan-European surveillance study conducted in 2008, the incidence of CDI in Bulgarian hospitals has increased from 3 to 7.94 per 10 000 patient admissions (Bauer *et al.* 2011), although it is believed that these numbers barely reflect the real picture. Currently, national reporting of CDI is not mandatory in Bulgaria, and most hospitals have only recently adopted diagnostic services for CDI.

The aim of the present work was to improve the current surveillance of CDI in Bulgaria by introducing innovative methods for identification and typing.

METHODS

Unformed stool samples (n=120), obtained from 108 patients admitted to eight hospitals in Sofia and one in Plovdiv, Bulgaria, were analysed over the period November 2008 to November 2012. The accepted criteria for CDI were fulfilled for all patients: age >2 years, mild to severe diarrhoea or antibiotic-associated diarrhoea and onset of diarrhoea after the third day of hospital admissions. The

MICROBIAL DRUG RESISTANCE
Volume 19, Number 5, 2013

DOI: 10.1089/mdr.2013.0004

Molecular Epidemiology and Multidrug Resistance Mechanisms of *Pseudomonas aeruginosa* Isolates from Bulgarian Hospitals

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A panel of 29 multidrug-resistant (MDR) *Pseudomonas aeruginosa* isolates recovered from seven hospitals as part of a country-wide surveillance of antimicrobial resistance in Bulgarian hospitals was studied. Molecular typing through multiple-locus variable number tandem-repeat analysis (MLVA6) yielded 23 different profiles. Phenotypic and genotypic tests for the detection of acquired carbapenemases yielded negative results in all cases. In contrast, 76% of the isolates produced other acquired β-lactamases, including extended-spectrum β-lactamases (ESBLs). Namely, 6 of the isolates (21%) produced a VEB-1 ESBL; 14 (48%) produced an OXA-10-type enzyme (7 OXA-10 and 7 OXA-10 ESBL variants, including 2 OXA-17 [A218G], 2 OXA-74 [C197T, A218G], and 3 OXA-142 [A218G, G470A]); 8 (28%) an OXA-2-type enzyme (all OXA-2); and 1 (3%) a PSE-1 carbenicillinase. Further analysis through multilocus sequence typing (MLST) revealed that the six VEB-1-producing strains, recovered from four hospitals, belonged to ST111 or ST244 international high-risk clones. Additionally, nearly all of the isolates (97%) lacked OprD production, explaining carbapenem resistance. Overexpression of AmpC was documented in 5 (17%) of the isolates, including most of the MDR isolates not producing any acquired β-lactamase. Particularly noteworthy was the very high prevalence of MexXY-OprM overexpression, documented in 72% of the isolates, whereas the prevalence of MexAB-OprM overexpression was lower (21%). In summary, while the production of metallo-β-lactamases is uncommon among *P. aeruginosa* isolates from Bulgarian hospitals, MDR profiles frequently result from the production of ESBLs combined with the lack of production of the carbapenem porin OprD and the overexpression of the MexXY-OprM efflux pump.

Introduction

The increasing prevalence of nosocomial infections produced by multidrug-resistant (MDR) *Pseudomonas aeruginosa* strains severely compromises the selection of appropriate treatments and is therefore associated with significant morbidity and mortality rates.[23] This growing threat results from the extraordinary capacity of this pathogen for developing resistance to nearly all available antibiotics by the selection of mutations in the chromosomal genes and from the increasing prevalence of transferable resistance determinants, particularly those encoding class B carbapenemases (metallo-β-lactamases [MBL]) or extended-spectrum β-lactamases (ESBLs), frequently cotransferred with genes encoding aminoglycoside-modifying enzymes.[19]

Among the mutation-mediated resistance mechanisms are particularly noteworthy those leading to an alteration of the carbapenem porin OprD, the hyperproduction of the chromosomal cephalosporinase AmpC or the upregulation of one of the several efflux pumps.[3,13,29] Further, the accumulation of these chromosomal mutations can lead to the emergence of MDR strains that may eventually be responsible for notable outbreaks in the hospital setting.[7] Likewise, multiple reports over the last decade have warned on the epidemic dissemination of the MDR strains producing transferable resistance mechanisms in multiple hospitals. Moreover, recent reports have provided evidence of the existence of MDR clones disseminated in several hospitals worldwide, denominated high-risk clones.[36] Among them, ST235, ST111, and ST175 are likely those more widespread.[2,4,8–10,20,31] In this work, we describe the first multicenter study aimed to deciphering the molecular epidemiology and resistance mechanisms of MDR *P. aeruginosa* from Bulgarian hospitals.

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BMC Public Health

RESEARCH ARTICLE Open Access

The role and utilisation of public health evaluations in Europe: a case study of national hand hygiene campaigns

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Abstract

Background: Evaluations are essential to judge the success of public health programmes. In Europe, the proportion of public health programmes that undergo evaluation remains unclear. The European Centre for Disease Prevention and Control sought to determine the frequency of evaluations amongst European national public health programmes by using national hand hygiene campaigns as an example of intervention.

Methods: A cohort of all national hand hygiene campaigns initiated between 2000 and 2012 was utilised for the analysis. The aim was to collect information about evaluations of hand hygiene campaigns and their frequency. The survey was sent to nominated contact points for healthcare-associated infection surveillance in European Union and European Economic Area Member States.

Results: Thirty-six hand hygiene campaigns in 20 countries were performed between 2000 and 2012. Of these, 50% had undergone an evaluation and 55% of those utilised the WHO hand hygiene intervention self-assessment tool. Evaluations utilised a variety of methodologies and indicators in assessing changes in hand hygiene behaviours pre and post intervention. Of the 50% of campaigns that were not evaluated, two thirds reported that both human and financial resource constraints posed significant barriers for the evaluation.

Conclusion: The study identified an upward trend in the number of hand hygiene campaigns implemented in Europe. It is likely that the availability of the internationally-accepted evaluation methodology developed by the WHO contributed to the evaluation of more hand hygiene campaigns in Europe. Despite this rise, hand hygiene campaigns appear to be under-evaluated. The development of simple, programme-specific, standardised guidelines, evaluation indicators and other evidence-based public health materials could help promote evaluations across all areas of public health.

Keywords: Hand hygiene, Healthcare associated infections, Evaluation, Evidence-based public health

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Journal of Hospital Infection 89 (2015) 351–356

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevierhealth.com/journals/jhin

Harmonizing and supporting infection control training in Europe

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ARTICLE INFO

Article history:
Received 10 November 2014
Accepted 16 December 2014
Available online 7 January 2015

Keywords:
Core competencies
Hospital hygiene
Infection control
Taxonomy
Training
Healthcare workers
Wiki

SUMMARY

Healthcare-associated infection (HCAI), patient safety, and the harmonization of related policies and programmes are the focus of increasing attention and activity in Europe. Infection control training for healthcare workers (HCWs) is a cornerstone of all patient safety and HCAI prevention and control programmes. In 2009 the European Centre for Disease Prevention and Control (ECDC) commissioned an assessment of needs for training in infection control in Europe (TRICE), which showed a substantial increase in commitment to HCAI prevention. On the other hand, it also identified obstacles to the harmonization and promotion of training in infection control and hospital hygiene (IC/HH), mostly due to differences between countries in: (i) the required qualifications of HCWs, particularly nurses; (ii) the available resources; and (iii) the sustainability of IC/HH programmes. In 2013, ECDC published core competencies for infection control and hospital hygiene professionals in the European Union and a new project was launched ['Implementation of a training strategy for infection control in the European Union' (TRICE-IS)] that aimed to: define an agreed methodology and standards for the evaluation of IC/HH courses and training programmes; develop a flexible IC/HH taxonomy; and implement an easily accessible web tool in 'Wiki' format for IC/HH professionals. This paper reviews several aspects of the TRICE and the TRICE-IS projects.

Introduction

Training of healthcare workers (HCWs) in infection control and hospital hygiene (IC/HH) lies at the centre of all

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http://dx.doi.org/10.1016/j.jhin.2014.12.005
0195-6701/

Local Probiotic Therapy for Vaginal Candida albicans *Infections*

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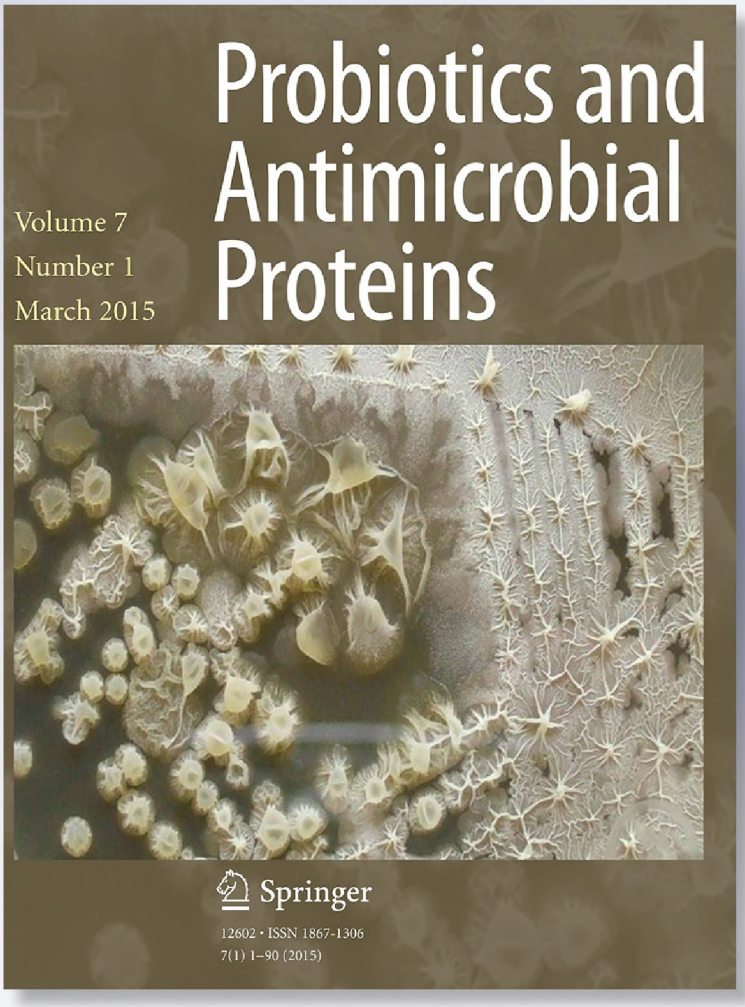
Probiotics and Antimicrobial Proteins

ISSN 1867-1306
Volume 7
Number 1

Probiotics & Antimicro. Prot. (2015)
7:38-44
DOI 10.1007/s12602-014-9176-0



Springer

Clinical Microbiology and Infection 22 (2016) 812.e9–812.e17

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Staffing for infectious diseases, clinical microbiology and infection control in hospitals in 2015: results of an ESCMID member survey☆

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ARTICLE INFO

Article history:
Received 25 January 2016
Received in revised form
16 June 2016
Accepted 21 June 2016
Available online 29 June 2016

Editor: Dr A. Huttner

Keywords:
Clinical microbiology
ESCMID
Infection control
Infectious disease
Staffing

ABSTRACT

We aimed to assess the current status of infectious diseases (ID), clinical microbiology (CM) and infection control (IC) staffing in hospitals and to analyse modifiers of staffing levels. We conducted an Internet-based survey of European Society of Clinical Microbiology and Infectious Diseases members and affiliates, collecting data on hospital characteristics, ID management infrastructure, ID/IC-related activities and the ratio of physicians per 100 hospital beds. Regression analyses were conducted to examine factors associated with the physician–bed ratio. Five hundred sixty-seven hospital responses were collected between April and June 2015 from 61 countries, 81.2% (384/473) from Europe. A specialized inpatient ward for ID patients was reported in 58.4% (317/543) of hospitals. Rates of antibiotic stewardship programmes (ASP) and surveillance activities in survey hospitals were high, ranging from 88% to 90% for local antibiotic guidelines and 70% to 82% for programmes monitoring hospital-acquired infections. The median ID/CM/IC physician per 100 hospital beds ratio was 1.12 (interquartile range 0.56–2.13). In hospitals performing basic ASP and IC (including local antibiotic guidelines and monitoring device-related or surgical site infections), the ratio was 1.21 (interquartile range 0.57–2.14). Factors independently associated with higher ratios included compliance with European Union of Medical Specialists standards, smaller hospital size, tertiary-care institution, presence of a travel clinic, beds dedicated to ID and a CM unit. More than half of respondents estimated that additional staffing is needed for appropriate IC or ID management. No standard of physician staffing for ID/CM/IC in hospitals is available. A ratio of 1.21/100 beds will serve as an informed point of reference enabling ASP and infection surveillance.
Y. Dickstein, CMI 2016;22:812.e9–812.e17

☆ Presented as a poster at the 2016 convention of the Israeli Society for Infectious Diseases.

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http://dx.doi.org/10.1016/j.cmi.2016.06.014
1198-743X/

Journal of Hospital Infection xxx (2017) 1–4

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevierhealth.com/journals/jhin

Short report

Infection control capacity building in European countries with limited resources: issues and priorities

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ARTICLE INFO

Article history:
Received 26 October 2016
Accepted 30 December 2016
Available online xxx

Keywords:
Infection control
Healthcare-associated infection
Patient safety

SUMMARY

We report the results of a panel investigation aimed at assessing the critical aspects regarding healthcare-associated infections in European countries with limited resources and pinpointing the highest priority issues that need to be addressed for effective infection control. Questionnaires were designed and information collected from national EUNETIPS representatives in Bulgaria, Hungary, Kosovo, Romania, and Serbia. Based on the data collected, we concluded that rigorous implementation of existing law, standardized training, and political commitment constitute a common relevant background and provide the lessons to be learnt for aligning healthcare systems in this area with internationally recommended standards of infection control.

Introduction

Hundreds of millions of patients are affected by healthcare-associated infections (HCAIs) worldwide each year, leading to significant mortality and financial losses for healthcare systems. Of every 100 hospitalized patients, between seven (in developed countries) and ten (in developing ones) suffer at least one HCAI, with a significantly higher endemic burden of HCAI for patients admitted to high-risk departments such as intensive care units (ICUs).[1] Whereas urinary tract infection (UTI) is the most frequent HCAI in high-income countries, surgical site infection (SSI) is the leading infection in areas with only limited resources, affecting up to one-third of the operated patients, i.e. the level being up to nine times higher than in developed countries.[1] In the 21st century, infection control (IC) and hospital hygiene activities face new challenges: a lack of funds for specific HCAIs, insufficient resources, and increasing pressure for publicly reporting surveillance data. Whereas managers and administrators too frequently fail to allocate adequate resources to IC programmes, there is nevertheless a huge disparity in the availability of resources

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http://dx.doi.org/10.1016/j.jhin.2016.12.024
0195-6701/

Journal of Hospital Infection 101 (2019) 248–256

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevier.com/locate/jhin

Infection control bundles in intensive care: an international cross-sectional survey in low- and middle-income countries

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ARTICLE INFO

Article history:
Received 6 June 2018
Accepted 13 July 2018
Available online 21 July 2018

Keywords:
Infection control
Bundles
Low and middle income
Healthcare-associated infection
Prevention
Ventilator-associated pneumonia

SUMMARY

Background: In low- and middle-income countries (LMICs), the burden of healthcare-associated infections (HCAIs) is not known due to a lack of national surveillance systems, standardized infection definitions, and paucity of infection prevention and control (IPC) organizations and legal infrastructure.

Aim: To determine the status of IPC bundle practice and the most frequent interventional variables in LMICs.

Methods: A questionnaire was emailed to Infectious Diseases International Research Initiative (ID-IRI) Group Members and dedicated IPC doctors working in LMICs to examine self-reported practices/policies regarding IPC bundles. Responding country incomes were classified by World Bank definitions into low, middle, and high. Comparison of LMIC results was then made to a control group of high-income countries (HICs).

Findings: This survey reports practices from one low-income country (LIC), 16 middle-income countries (MICs) (13 European), compared to eight high-income countries (HICs). Eighteen (95%) MICs had an IPC committee in their hospital, 12 (63.2%) had an annual agreed programme and produced an HCAI report. Annual agreed programmes (87.5% vs 63.2%, respectively) and an annual HCAI report (75.0% vs 63.2%, respectively) were more common in HICs than MICs. All HICs had at least one invasive device-related surveillance programme. Seven (37%) MICs had no invasive device-related surveillance programme, six (32%) had no ventilator-associated pneumonia prevention bundles, seven (37%) had no catheter-associated urinary tract infection prevention bundles, and five (27%) had no central line-associated bloodstream infection prevention bundles.

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[1] See Acknowledgements.

https://doi.org/10.1016/j.jhin.2018.07.022

European Journal of Clinical Microbiology & Infectious Diseases (2019) 38:2061–2068
https://doi.org/10.1007/s10096-019-03648-2

ORIGINAL ARTICLE

Organization and training at national level of antimicrobial stewardship and infection control activities in Europe: an ESCMID cross-sectional survey

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Received: 11 May 2019 / Accepted: 15 July 2019 / Published online: 8 August 2019

Abstract

Antimicrobial stewardship (AMS) and Infection prevention and control (IPC) are two key complementary strategies that combat development and spread of antimicrobial resistance. The ESGAP (ESCMID Study Group for AMS), EUCIC (European Committee on Infection Control) and TAE (Trainee Association of ESCMID) investigated how AMS and IPC activities and training are organized, if present, at national level in Europe. From February 2018 to May 2018, an internet-based cross-sectional survey was conducted through a 36-item questionnaire, involving up to three selected respondents per country, from 38 European countries in total (including Israel), belonging to the ESGAP/EUCIC/TAE networks. All 38 countries participated with at least one respondent, and a total of 81 respondents. Education and involvement in AMS programmes were mandatory during the postgraduate training of clinical microbiology and infectious diseases specialists in up to one-third of countries. IPC was acknowledged as a specialty in 32% of countries. Only 32% of countries had both guidance and national requirements regarding AMS programmes, in contrast to 61% for IPC. Formal national staffing standards for AMS and IPC hospital-based activities were present in 24% and 63% of countries, respectively. The backgrounds of professionals responsible for AMS and IPC programmes varied tremendously between countries. The organization and training of AMS and IPC in Europe are heterogeneous and national requirements for activities are frequently lacking.

Keywords Antimicrobial stewardship · Infection prevention and control · Clinical microbiology · Infectious diseases · Questionnaire

Alberto Enrico Maraolo and David S. Y. Ong contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10096-019-03648-2) contains supplementary material, which is available to authorized users.

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Journal of Hospital Infection 155 (2025) 40–50

Available online at www.sciencedirect.com

Journal of Hospital Infection

journal homepage: www.elsevier.com/locate/jhin

Infection prevention and control risk factors for SARS-CoV-2 infection in health workers: a global, multi-centre, case–control study

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ARTICLE INFO

Article history:
Received 13 August 2023
Accepted 2 April 2024
Available online 20 September 2024

Keywords:
COVID-19
SARS-CoV-2
Infection prevention and control
Health workers
Personal protective equipment
Occupational risk factors

SUMMARY

Background: Health workers were at higher risk for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection during the coronavirus disease 2019 (COVID-19) pandemic due to occupational risk factors. This study aimed to characterize these risk factors as part of the World Health Organization (WHO) Unity Studies initiative.

Methods: This global, multi-centre, nested, case–control study was conducted in 121 healthcare facilities in 21 countries. Cases were health workers who tested positive for SARS-CoV-2 infection with documented occupational exposure to COVID-19 patients in the 14 days pre-enrolment. Controls were enrolled from the same facilities with similar exposure but negative serology. Case and control status was confirmed with serological testing at baseline and after 3–4 weeks. Demographic and infection risk factor data were collected using structured questionnaires.

Findings: Between June 2020 and December 2021, data were obtained for 1213 cases and 1844 controls. Risk of SARS-CoV-2 infection was associated with non-adherence to personal protective equipment (PPE) guidelines [adjusted odds ratio (aOR) 1.67, 95% confidence

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https://doi.org/10.1016/j.jhin.2024.04.031

Diagnostic Microbiology & Infectious Disease 111 (2025) 116703

Contents lists available at ScienceDirect

Diagnostic Microbiology & Infectious Disease

journal homepage: www.elsevier.com/locate/diagmicrobio

Original Article

Whole genome sequencing characterization of *Clostridioides difficile* from Bulgaria during the COVID-19 pandemic☆

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ARTICLE INFO

Keywords:
Clostridioides difficile
Antimicrobial resistance genes
Whole-genome sequencing
cgMLST

ABSTRACT

Increased incidence of *Clostridioides difficile* infections were documented in Bulgarian hospitals during COVID-19. WGS was performed on 39 isolates from seven hospitals during 2015-2022. Antimicrobial resistance and toxin genes were inferred from genomes. MLST profiles, cgMLST, and wgMLST phylogeny analyses were performed. Isolates were grouped into eight MLST types as predominant were ST3 (46.15%) and ST1/RT027 (33.33%). ST3 was detected in a single hospital (16/18) and characterized by two toxin variants: *tcdA+/tcdB+* (14) and *tcdA-/tcdB+* (4). Twelve ST3 strains belonged to the country-specific cgMLST HC2_6485 cluster and ten were identified as a putative outbreak in the infectious disease ward. All the ST1/RT027 isolates were distributed in six hospitals and clustered in an HC2_4711 with strains from neighbouring countries. All *C. difficile* were susceptible to vancomycin despite the Thr349Ile mutation in *vanS* in three isolates. We report the first insights into the *C. difficile* genotype hospital prevalence during the pandemic.

1. Introduction

Clostridioides difficile (CD) is an anaerobic Gram-positive bacteria causing Clostridioides difficile infections (CDIs) ranging from asymptomatic, mild diarrhoea, to haemorrhagic diarrhoea and pseudomembranous colitis. It is the leading cause of antibiotic-associated diarrhoea worldwide [1]. The risk of acquiring CDI is associated with prolonged stay in healthcare settings, exposure to broad-spectrum antibiotics disrupting the microbiome, advanced age, underlying diseases, the use of proton pump inhibitors, and various immunocompromising conditions [2,3,4,5].

Clinical strains produce either one or both pathogenic factors causing intestinal inflammation: cytotoxin toxin B (TcdB, 270kDa) and/or enterotoxin toxin A (TcdA, 308 kDa) encoded by the tcdB and tcdA respectively on the chromosomal Pathogenicity Locus (PaLoc, 19.6kbp) [6]. Apart from TcdA and TcdB, about 6%–30% of *C. difficile* produce an additional toxin CDT (C. difficile transferase, or binary toxin) encoded by the *cdtA* (enzymatic component) and *cdtB* (binding component) genes located chromosomally in 6.8kbp CdtLoc. [7]. CDT alone is insufficient to cause disease, but in combination with high levels of TcdA/TcdB toxins, it can contribute to severe outcomes [3,8]. The epidemic *C. difficile* NAP1/BI/RT027 was spread in 2005-2006 in Europe and North America and is characterized by increased production of TcdA and TcdB, synthesis of the binary toxin, high-level fluoroquinolone resistance and sporulation activity [3,9].

For over 40 years, metronidazole and vancomycin have been the first-line therapies, while fidaxomicin has been largely used to treat recurrent CDIs [10]. Presently, the CDI treatment guidelines have changed, with fidaxomicin as the drug of choice, vancomycin as an alternative, and metronidazole only if the other two options are

☆ This work was partially presented as a poster: P0838 Whole genome sequencing characterization of *Clostridioides difficile* from Bulgaria during the COVID-19 pandemic with authors E. Dobreva, I. Stoikov, D. Donchev, R. Hristova, R. Vatcheva-Dobrevska, M. Murdjeva, I. Ivanov at 33rd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), 15-18 April 2023 in Copenhagen, Denmark.

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https://doi.org/10.1016/j.diagmicrobio.2025.116703
Received 1 August 2024; Received in revised form 14 January 2025; Accepted 17 January 2025
Available online 18 January 2025

International Journal of Probiotics and Prebiotics Vol. 9, No. 4, pp. 129-134, 2014
ISSN 1555-1431 print, Copyright © 2014 by New Century Health Publishers, LLC
www.newcenturyhealthpublishers.com

BACTERIAL VAGINOSIS - LOCAL *LACTOBACILLUS CASEI VAR RHAMNOSUS DÖDERLEIN* MONOTHERAPY

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[Received June 18, 2014; Accepted August 26, 2014]

[Communicated by Prof. Francesco Marotta]

ABSTRACT: *The objective of the current research is to establish the efficacy of the local probiotic monotherapy in the treatment of bacterial vaginosis. 139 (100%) women with bacterial vaginosis, randomized into two groups are included in the research. In the first group 85 women were treated with local (10 applications) probiotic medicine, containing lactobacillus type Lactobacillus casei var rhamnosus Döderlein – Lcr35®. In the second group 54 patients were treated with five days, oral administration of Clindamycin (600mg) BID and local therapy of two vaginal ovules containing 1000mg Metronidazole each, which were administered locally every other day. Additionally in this group was administered again the same local probiotic. The efficacy of the therapeutic scheme was evaluated via comparison of patients' clinical complains in the different groups, of data from clinical examinations and microbiological tests for each patient. One month after the probiotic monotherapy, the clinical efficacy in this group is 42.7% and microbiological efficacy – 41.3%. They are lower than in the second group with combine treatment: clinical efficacy – 87.5%, microbiological efficacy – 80.3 %. Our results show that the local probiotic monotherapy has fewer efficacies in comparison to the nitroimidazole/lincozamide/ probiotic scheme for treatment of bacterial vaginosis.*

KEY WORDS: Bacterial vaginosis, *Lactobacilli*, Monotherapy, Probiotic, Vaginal flora

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INTRODUCTION

The use of probiotics to restore and maintain normal vaginal flora represents a promising alternative or addition to conventional therapy for the treatment of bacterial vaginosis (Fredricsson et al., 1989; Chimura et al., 1995; Hemalatha et al., 2012). Probiotics can be used independently or in addition to the primary therapy of bacterial vaginosis (Fredricsson et al., 1989; Chimura et al., 1995). Are conducted clinical trials for their action in both cases of application (Fredricsson et al., 1989; Chimura et al., 1995; Hemalatha et al., 2012). These studies apply specific strains of *Lactobacilli* orally or locally and tracked their ability to colonize the vagina of patients with symptomatic and asymptomatic bacterial vaginosis, to reduce colonization of pathogens and to remove the symptoms of it, when they are presented. Therefore, the use of probiotics in the treatment of bacterial vaginosis, to restore and maintain normal vaginal flora represents a promising alternative to conventional therapy (Fredricsson et al., 1989; Chimura et al., 1995; Hemalatha et al., 2012).

The aim of our study was to establish the clinical and microbiological efficacy of local probiotic *Lactobacillus casei var rhamnosus Döderlein* monotherapy of bacterial vaginosis and effect on the vaginal flora.

MATERIALS AND METHODS

The survey is open, single-site and was conducted in our, gynecological outpatient clinic – Military Medical Academy – Sofia, Bulgaria, between 2011-2013 year. To patients was provided information for the purposes of the investigation and the conditions of inclusion. We have the informed consent of each patient. The study included a total of 206 women aged between 17 and 50 years with clinical and/or microbiological established bacterial vaginosis. Of the inspection review 35-40 days after incorporation came forward 139 women. Only their data and results are handled in the survey. Excluded are patients with established *Neisseria Gonorrhoae, HSV, HPV, Chlamydia Trachomatis, HIV* and other vaginal infections. Not included pregnant women and those taking corticosteroids, antibiotics,

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АКУШЕРСТВО И ГИНЕКОЛОГИЯ

OBSTETRICS AND GYNECOLOGY

The official journal of the Bulgarian Scientific Society of Obstetrics and Gynecology

Volume 50
ISSN 0324-0959

3'2011

КРАТКОТРАЙНО КОМБИНИРАНО НИТРОИМИДАЗОЛОВО ЛЕЧЕНИЕ НА ВАГИНАЛНА ДИСБАКТЕРИОЗА С ДОМИНИРАЩИ АНАЕРОБНИ МИКРООРГАНИЗМИ

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Резюме. Целта *на настоящото изследване е да проучи ефективността на комбинирана 5-нитроимидазолова терапия при лечение на вагинална дисбактериоза с доминиращи анаеробни видове. Дисбактериозата е доказана с гинекологичен преглед, микроскопско и микробиологично изследване на влагалищно съдържимо. В проучването са включени 179 пациентки. Терапията им се състои в двудневна перорална доза тинидазол (2 g Tinidazol - film-tabl.x 500 mg), разделена на два приема по 1 g през 12 часа и локална терапия от две вагинални овули, съдържащи по 1000 mg метронидазол (Arilin Rapid ovules x 1000 mg) , които се поставят вагинално през ден. Първата вагинална овула се поставя в деня на първото пероралнато приемане на тинидазол. Клиничен преглед, микроскопско и микробиологично изследване са направени на ден 0 и на 8 ден след проведената терапия. При 132 (73.7%) от включените в проучването жени е доказан микробиологично Gardnerella vaginalis, като единствен доминиращ вид, докато при 47 (26.3%) е доказана съвкупност от няколко анаеробни вида. Клиничните прегледи и микробиологични изследвания на 8 ден след проведената терапия, показват клинична и микробиологична ефикасност съответно 83.2% и 73.7%. Тези резултати ни дават основание да заключим, че комбинираната краткотрайна 5-нитроимидазолова терапия, която приложихме в нашето проучване е ефективна при лечение на вагинална дисбактериоза с доминиращи анаеробни щамове с високи нива на клинично и микробиологично излекуване.*

SHORT – TERM COMBINED 5-NITROIMIDAZOLE TREATMENT IN VAGINAL DYSBACTERIOSIS WITH DOMINANT ANAEROBIC SPECIES

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Abstract*. The aim of this study is to investigate the effectiveness of short-term, combined 5-nitroimidazole treatment in vaginal dysbacteriosis with dominant anaerobic species. The presence of infection was proven by microscopic examination of vaginal fluid (Nugent, modified by Ison-Hay-Keane scale), microbiological culture, and by clinical symptoms (Amsel). 179 patients were included in our study. Clinical and microbiological examinations were performed prior to the treatment and at the end of the study (day 8 after the first dose of short- term combined 5-nitroimidazole treatment). The treatment included applications of 1g BID tinidazole for two days and vaginal suppositories of 1000mg metronidazol at day 1 and 3.*

Based on the microbiological tests prior to the treatment Gardnerella vaginalis alone was present in 132 patients (73.7%). The rest of the patients, 47 or 26.3% of the treatment group, the infection was present by mixture of several anaerobic species.

At the end of the treatment 83.2% of the treated population showed no clinical symptoms of dysbacteriosis, and 73.7% of the treated patients showed no dysbacteriosis in microbiological test results.

Based on the results mentioned above it was determined that the short-term combined 5-nitroimidazole therapy was effective in treatment of vaginal dysbacteriosis with dominant anaerobic species.

С термина "Дисбактериоза" се означава количествено и качествено нарушение на нормалната микрофлора в дадена екосистема (28). Тя може да засегне всеки жив организъм, безсимптомно или да се изяви с определени клинични симптоми (28). Влагалищната флора е балансирана екосистема, състояща се от ацидофилни лактобацили (над 95%), наречени

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The official journal of the Bulgarian Scientific Society of Obstetrics and Gynecology

Volume 51
ISSN 0324-0959

6'2012

- схеми на антибиотична профилактика intrapartum за жени с пеницилинова алергия;

- алгоритъм за третиране на новородените с оглед на риска от GBS заболяване с ранно начало.

Настоящето проучване има за цел да проследи разпространението на GBS заболяването с ранно начало в нашата страна на основата на данни от водещи АГ клиники и отделения. Целта е да се диференцират клинично случаите и да се изследва влиянието на известните рискови фактори от страна на майката. Специален акцент се поставя върху микробиологичната диагностика на случаите предвид разширените препоръки относно лабораторните методи за идентификация на GBS в ревизираните указания на CDC. Като окончателен извод се подчертава необходимостта от въвеждането на официалната регистрация на GBS заболяването с ранно и късно начало в страната.

Ключови думи: *група „в" стрептококовата неонатална инфекция, GBS заболяване с ранно и късно начало, GBS скрининг, интрапартална антибиотична профилактика*

A STUDY ON EARLY-ONSET GROUP „B" STREPTOCOCCAL NEONATAL INFECTION

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Abstract*. The results achieved with 80% reduction in the incidence of early-onset neonatal group B streptococcal (GBS) sepsis following the implementation of the preliminary (1996, 2002) and subsequently the revised (2010) guidelines for intrapartum antibiotic prophylaxis imposed the discussion on a large scale of* ***the updated****:*

- algorithms for GBS screening (35-37 weeks of gestation) with the recommended dosage of penicillin-G for intrapartum antibiotic prophylaxis for women having normal labor and delivery;

- algorithms for GBS screening and intrapartum antibiotic prophylaxis for women with preterm labor (PPROM) or premature rupture of membranes (PROM);

- intrapartum antibiotic prophylaxis regimens for women with penicillin allergy;

- algorithm for management of newborns with respect to risk of early-onset GBS disease.

The present study is aimed at studying the distribution of the early-onset GBS disease in our country based on the data of leading obstetrics & gynecology clinics and wards. The aim is to diferrentiate clinically the cases and investigate the influence of the known risk factors on the part of the mother. A special accent is put over the microbiological diagnostics of cases in view of CDC expanded recommendations on the laboratory methods for identification of GBS. As a final conclusion the necessity for introduction of an official registration of the early- and late-onset GBS disease in the country is emphasized.

Keywords*: group „B" streptococcal neonatal infection, early-and late-onset GBS disease, GBS screening, intrapartum antibiotic prophylaxis*

Въведение

Група В стрептококите [group B streptococci (GBS или S. agalactie)] нормално се изолират от чревния тракт и вагината при здрави лица, има случаи на изолиране от назофаринкс и устната кухина. Намират се в урогениталния сегмент на 5-50% от бременните(1). Група В стрептококите са значима причина за **неонатални инфекции**, придобити по време на преминаването през родовия канал – т.нар. вертикално предаване. Проучвания в САЩ, датиращи от началото на 70-те години доказват, че те са най-честата бактериална причина за животозастрашаващо заболяване на новородените при леталитет от 20 до 80% (1). През първата седмица от живота клиничните прояви, характеризиращи GBS заболяването с ранно начало [Early-Onset Group B Streptococcal Disease (EOGBSD)], са **бактериемия и пневмония**, между първата и осмата седмица, според други данни - 7-ми до 90-ти ден (4) - GBS заболяване с късно начало [Late-Onset Group B Streptococcal Disease (LOGBSD)] – **менингитът и бактериемията** са най-честите прояви (1-4).

От началото на 90-те години в САЩ се препоръчват и регламентират последователно 3 сета от указания, фокусирани върху предпазването от перинаталната GBS инфекция с ранно начало, базирани на антибиотична профилактика intrapartum [intrapartum antibiotic prophylaxis (IAP)] след всеобщ скрийнниг на бременните в 35-37-ма г.с. (1996, 2002, 2010). В резултат се отчита намаляване до 80% в честотата на неонаталния

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XVII НАЦИОНАЛНА ГИНЕКОЛОГИЧНА КОНФЕРЕНЦИЯ

Боровец, 14–16.03.2013

Supplement 1
Volume 52
ISSN 0324-0959

2013

съответно 83%, 82% и 82%

• Едно-, три-, пет- и деветгодишната обща преживяемост по Каплан–Майер за цялата популация е съответно 97%, 86%, 83%, 81%.

• От 132 пациентки 15 са екзитирали (12,5%) от изследваното заболяване за среден перио проследяване от 44 месеца (1-114 мес.)

• По-голямата част от всички смъртни случа или 82,4%) са настъпили в рамките на първи мес. след терапията.

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ПРОБИОТИЧНА МОНОТЕРАПИЯ НА БАКТЕРИАЛНА ВАГИНОЗА

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***Резюме. Целта** на нашето изследване е да се установи клиничната и микробиологична ефикас на терапия с локални пробиотици в лечението на анаеробни влагалищни инфекции и ефектът й е влагалищната флора.*

***Материал и Методи:** В изследването са включени 381 (100%) жени с бактериална ваги рандомизирани в три групи. В първа група 143 жени, които проведоха лечение с локално прилож (10 апликации) на пробиотичен вагинален препарат, съдържащ живи лактобацилни видове Lactoba acidophilus, Lactobacillus rhamnosus. Във втора група 126 пациентки проведоха лечение с пет дн перорална доза клиндамицин, разделена на два приема по 600 mg през 12 часа и локална терапи две вагинални овули, съдържащи по 1000 mg метронидазол, които се поставяха вагинално през В трета група 112 жени са лекувани със същата терапия като тези във втора, но от петия след нея прилагаха локален пробиотичен препарат с Lactobacillus acidophilus и Lactobacillus rhamn Ефективността на проведената терапевтична схема се оценяваше чрез сравнение на клинич оплаквания на пациентките по групи, данните от клиничния преглед (Amsel) и микробиологич изследвания (Nugent) за всяка една от тях.*

***Резултати**: Клинична ефикасност (Amsel) на проведената пробиотична терапия 42.* микробиологична ефикасност (Грам препарат-Nugent) - 41.3%. Те са по-ниски от резултатите, к получихме в групите, където беше проведена комбинирана нитроимидазолова/линкозамидна тер с или без локален пробиотик. Втора група: клинична ефикасност - 51.6%, микробиологична (Nu - 46.4%. Най-висока клинична - 87.5% и микробиологична - 80.3% ефикасност показа комбинира нитроимидазоли/линкозамиди/пробиотици терапия в трета група.*

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Боровец, 14–16.03.2013

Supplement 1
Volume 52
ISSN 0324-0959

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ПРОБИОТИЧНИЯТ ВИД LACTOBACILUS CASEI VAR RHAMNOSUS (GYNOPHILUS) – БАКТЕРИАЛНА ВАГИНОЗА И ВЪЗСТАНОВЯВАНЕ НА НОРМАЛНАТА ВАГИНАЛНА ФЛОРА

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***Резюме**. Вагиналните пробиотици могат да повишат клиничната и микробиологична ефикасност на използваните в лечението на бактериална вагиноза терапевтични схеми.*

***Целта** на нашето изследване е да установим ефектът от приложението на Lactobacillus casei var rhamnosus (Gynophilus - пробиотичен вид Lcr 35) за възстановяване на влагалищната флора и предпазване от рецидив при жени с анаеробна вагинална инфекция, провели конвенционална (нитроимидазолова) локална и обща терапия.*

***Материал и Методи:** В изследването включихме 60 жени с установена Amsel/Nugent бактериална вагиноза, които рандомизирахме в две групи. В първа група пациентките (n-30 начало/n-25 контрола) проведоха терапия с пет дневно перорално приложение на метронидазол 500 мг двукратно дневно, като на първи и трети ден локално се прилагаха овули от 1000 мг метронидазол (**M+M**). Във втора група (n-30 начало /n-26 контрола) терапевтичната схема е като първа, но с добавено седем дневно лечение с Lactobacillus casei var rhamnosus – Lcr 35. (Gynophilus) вагинални овули двукратно дневно (**M+M+G**).*

***Резултати**: От 30% до 40% е разликата/повишаването на клиничната ефикасност по различните клинични показатели, когато към стандартната нитроимидазолова терапия се прибави Lactobacillus casei var rhamnosus – Lcr 35. За основният клиничен показател – критерии на Amsel в първа група (M+M) подобрението след терапията е с 60% (n-15), докато във втора група (M+M+G) е с 88.5% (n-23). При микробиологичните показатели подобрението в първа група (M+M) на база оценката на вагиналната флора по Nugent е 60% (n-15), като във втора група след прибавяне на Lcr.35, тя нараства отново до 88.5% (n-23).*

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OBSTETRICS AND GYNECOLOGY

The official journal of the Bulgarian Scientific Society of Obstetrics and Gynecology

Volume 52
ISSN 0324-0959

3'2013

КОМБИНИРАНА 5-НИТРОИМИДАЗОЛОВА И ПРОБИОТИЧНА ТЕРАПИЯ НА ВАГИНАЛНА ДИСБАКТЕРИОЗА С ДОМИНИРАЩИ АНАЕРОБНИ ВИДОВЕ – КЛИНИЧНА И МИКРОБИОЛОГИЧНА ЕФИКАСНОСТ

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Резюме. Целта *на настоящото изследване е да се установи клиничната и микробиологична ефективност на 5-нитроимидазоловата терапия за лечение на анаеробните влагалищни инфекции, самостоятелно и в комбинация с пробиотици и ефектът й върху влагалищната флора.*

Материал и Методи. *В изследването са включени 539 жени с бактериална вагиноза, изпълнили необходимите условия. Те са рандомизирани в две групи, които проведоха следните терапевтични схеми:* ***първа*** *група (n=242 жени) лечение с двудневна перорална доза тинидазол (2g. Tinidazol- film-tabl. x 500 mg), разделена на два приема по 1 g през 12 часа и локална терапия от две вагинални овули, съдържащи по 1000 mg метронидазол (Arilin Rapid ovules x 1000 mg), които се поставяха вагинално през ден (**Т+М**). Първата вагинална овула се поставяше в денят на първото перорално приемане на тинидазол. Във втора група (n=297) жени провеждаха същото лечение като тези в първа, но от петия ден след краткотрайното 5-нитроимидазолово лечение, прилагаха локално пробиотичен вагинален препарат, съдържащ живи лактобацилни видове Lactobacillus acidophilus, Lactobacillus rhamnosus (Lactofem-vag.gel, vag. capsules; Lactagyn-vag.capsules -10 апликации) (**Т+М+П**). Ефикасността на терапията се оценяваше според клиничните оплаквания на жените, данните от клиничния преглед и проведените микробиологичните изследвания.*

Резултати. *Нашите резултати 35-40 дни след терапията очаквано показват повишаване на клиничната ефикасност (Amsel-критерии) от 42.8% за първа група (**Т+М**; n=211/242) на 84.06% при втора (**Т+М+П**; n=274/297) и на микробиологичната (Nugent) от 44.7% (**Т+М**, n=211) до 83.3% (**Т+М+П**, n=274), като процентът на жените с нормална вагинална флора се увеличава в групата (**Т+М**) с 57%, докато в групата с добавен пробиотик (**Т+М+П**) с 94%.*

EFFICACY OF COMBINED 5-NITROIMIDAZOLE AND PROBIOTIC THERAPY OF BACTERIAL VAGINOSIS: RANDOMIZED OPEN TRIAL

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Abstract. *The* ***aim*** *of the current research is to identify the clinical and microbiological effect of 5-nitroimidazol therapy for the treatment of bacterial vaginosis and in combination with probiotics and the influence of such therapy upon vaginal flora.*

Materials and Methods. *Women (n=539) with bacterial vaginosis who meet the criteria were included in the study. They were randomized into two groups with the following therapeutic regimes: in the first group (n=242 women) the treatment included applications of 2g BID tinidazole for two days and vaginal suppositories of 1000mg metronidazol at day 1 and 3 (**T+M**). In the second group (n=297) the women were cured with the same treatment as those in the first group. In addition to it from the fifth day of the treatment was added a topical administration of vaginal probiotic which contains species of alive lactobacilli: Lactobacillus acidophilus, Lactobacillus rhamnosus (**T+M+P**). The efficacy from the therapy was evaluated using the clinical compliances of the women, the data from the clinical examination and the microbiological tests results.*

Results. *The results showed expected increase of clinical therapy efficacy (Amsel – criteria) from 42.8% (**T+M**; n=211/242) to 84.06% (**T+M+P**; n=274/297) in groups and of microbiological efficacy (Nugent) from 44.7% (**T+M**; n=211/242) to 83.3% (**T+M+P**; n=274/297), in follow up 35-40 days from the beginning of treatment. The percentage of women with normal vaginal flora on 35-40 day after the therapy increase with 57% in the (**T+M**) first group while in the second group (**T+M+P**) with 94%.*

FIRST CASES OF SEVERE HOSPITAL-ACQUIRED CLOSTRIDIUM DIFFICILE INFECTIONS IN SOFIA, BULGARIA

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SUMMARY:
Background: Clostridium difficile has become a critically important pathogen worldwide, particularly in hospitalized patients. In 2008, the European Center for Disease Prevention and Control (ECDC) initiated a pan European surveillance study to collect epidemiological and microbiological data of C. difficile associated diseases (CDAD). Since Bulgaria has joint this study a number of CDAD cases were discovered. The objective of the present work is to report the first cases of CDAD occurring in Sofia, Bulgaria.
Material and Methods: For the period November 2008 - February 2009, thirty six fecal samples from patients with severe enterocolitis and previous antibiotic treatment have been investigated. The stool samples derived from 3 hospitals in Sofia. Strains were typed and further characterized for the presence of toxins A (TcdA), B (TcdB) and binary toxins (CdtA and CdtB).
Results: No outbreaks were reported and the incidence of C. difficile infection (CDI) in the hospitals was 3.12 per 10,000 patient admissions (0.7 per 10,000 patient-days). Four patients with severe CDI were identified of which two patients died due to complications of the infection. Two of the isolates belonged to PCR ribotypes 017 (TcdA-; TcdB+; CdtA/B-), one was 046 (TcdA+; TcdB+) and one was 078 (TcdA+: TcdB+; CdtA/B+). All of these ribotypes have been reported to cause oubreaks worldwide.
Conclusion: These are the first well documented cases of CDI in Sofia, Bulgaria. Despite the fact that none of the Bulgarian isolates belonged to the hypervirulent C. difficile NAP1/BI/027, C. difficile ribotypes 078, 046 and 017 were found to be associated with a severe CDI.

Key words: Clostridium difficile, toxins, ribotypes, Bulgaria.

INTRODUCTION

Clostridium. difficile was first discovered by Hall and O`Toole in 1935 as a part of the normal intestinal flora of newborns. It was found in 1974 that C. difficile causes antibiotic-associated colitis by producing toxins with high lethality in mice. Since 2003 outbreaks associated with the emerging hypervirulent strain – C. difficile PCR ribotype 027 have been reported worldwide. The increased virulence of this strain is assumed to be associated with increased production of toxins A and B (1) . C. difficile PCR ribotype 027 was designated as a PCR ribotype 027 C. difficile NAP1/BI/027; North American pulsed-field gel electrophoresis (PFGE) type 1 (NAP1), restriction endonuclease analysis (REA) type BI and toxinotype III (1-6).

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C. difficile NAP1/BI/027 has a binary toxin genes and contains a deletion at position 117 in tcdC gene, causing a frame shift and a dysfunction of the toxin-negative regulation by TcdC (7-9).
Various methods have been applied to characterize and type C. difficile. The most widely accepted typing method in North America is the Pulse-field gel electrophoresis (PFGE) and for this region the new emerging strain is designated as NAP1. In Europe, PCR ribotyping is the method of first choice and the same C. difficile strain is known as ribotype 027 (10).
Another important characteristic of the hypervirulent C. difficile ribotype 027 strain is its resistance to fluoroquinolones leading to increasing rate of fluoroquinolones-associated diarrhoea (1,2).
A number of large outbreaks have been reported recently in hospitals and nursing homes in Canada, Finland, France, Germany, United Kingdom etc. (11-14). In Europe, the strain was first described as a causative agent of outbreaks in 2004 in England and shortly thereafter – in 2005 in The Netherlands (8). In 2008, the European Center for Disease Prevention and Control (ECDC) initiated a pan European surveillance study to collect epidemiological and microbiological data of C. difficile associated diseases (CDAD). Bulgaria also participated and continued the surveillance for two extra months (15).
The aim of the present work is to report on the initial results of the Bulgarian surveillance study.

MATERIAL AND METHODS

Patients
For the period of four months, November 2008 - February 2009, thirty six fecal samples have been investigated at the National Reference Laboratory for Enteric Pathogens, at the National Center of Infectious and Parasitic Diseases (NCIPD), Sofia, Bulgaria. Three hospitals participated in the surveillance study. The incidence of CDI in the selected hospitals was 3.12 per 10,000 patient admissions (0.7 per 10,000 patient-days). Patients with enterocolitis were selected according to some of the following criteria:
Age over 2 years.
Antibiotic associated diarrhea.
Onset of diarrhea after the third day of hospital admission.
Patients admitted to hospital with diarrhea.
Patients with colonic endoscopy findings characteristic of C. difficile infection.
Negative laboratory results for Salmonella, Shigella, Campylobacter, Enteropathogenic Escherichia coli.
Patients with complications like: toxic megacolon, pseudomembanous colitis, ileus,
peritonitis.
Laboratory diagnosis
All 36 stool samples were tested for the presence of C. difficile toxins. Subsequently, positive tested stool samples were cultured for C. difficile. Determination of toxins in stool samples was performed using Immuno Card Toxins A&B- EIA (Meridian, Bioscience, USA) rapid test kit.
Culture method
Fecal samples were divided into two portions. The first portion was processed with the alcohol shock procedure. For that purpose 0.5 ml absolute CH2OH were mixed with 0.5 ml liquid feces, following incubation for 1 h at room temperature and culture on Brucella agar plates with 10% sheep blood. The second portion was directly cultured on Brucella agar plates with 10% sheep blood containing cefoxitin, cycloserine and amphotericin B. All plates were incubated 2-5 days at 37°C in anaerobic conditions.
Identification
Suspected colonies were identified as C. difficile by performing Gram stains and latex co-agglutination tests for detection

PCR- RIBOTYPING AND PCR METHODS FOR DETECTION OF TOXIN CODING GENES IN CLOSTRIDIUM DIFFICILE STRAINS

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SUMMARY

C. difficile infections (CDI) are associated with patients who have contact with health care settings and with antibiotic exposures. This anaerobic bacterium causes asymptomatic colonization to severe diarrhea; pseudomembranous colitis, toxic megacolon, intestinal perforation and death.

C. difficile is recognized as a gut colonizer and a cause of diarrhea in several animal species.

The enteropathogen produces enterotoxin A and cytotoxin B. The majority of strains with changes in coding genes tcdA and tcdB produce a binary toxin CDT.

PCR-ribotyping method and PCR methods for detection of toxin coding genes were presented for characterization of C. difficile strains. Ninety stool samples from patients (65/90) and animals (25/90) were investigated for C. difficile. 20% (18/90) of all samples were positive for C. difficile. 23% (15/65) from clinical samples and 12% (3/25) from horses were positive for C. difficile by culture test. 21, 5% (14/65) of clinical isolates produce toxins A and B by EIA. 86,7% (13/15) from clinical samples were PCR positive for tcdA gene. Deletion in tcdA gene (714bp) was detected in 40% (6/15) of the clinical strains. 93,3% (14/15) C. difficile clinical strains were positive for tcdB gene. Three toxigenic variants C. difficile have been distinguished among clinical strains by PCR: 46,67% (7/15) toxin A+B+; 46,67% (6/15) A–B+ and 6,67% (2/15) A-B-. The binary-toxin genes cdtA and cdtB was PCR detected in one of the A+B+ strains. The genes tcdA, tcdB and cdtA/cdtB were not detected in C. difficile isolates from horses by PCR.

The most prevalent ribotypes among C. difficile clinical strains were: 017- 40% (6/15); 002- 13%; 014/020-13% and 012, 046, 078 were represented by 7% each. Patterns were compared to reference ECDC C. difficile collection. Thirteen percent of C. difficile clinical strains were corresponded to unknown PCR-ribotypes. PCR-ribotyping patterns of the C. difficile isolates from horses were different from patterns of the clinical strains.

The significant number of cases C. difficile diagnosed with outbreak ribotypes may represent a significant problem in the future.

Key Words: toxin genes, PCR, PCR-ribotyping, ribotypes

INTRODUCTION

Clostridium difficile is an anaerobic, Gram-positive, motile and spore forming bacterium. The microorganism was isolated from stools of healthy newborn infants by Hall and O'Tool in 1935 (11). It was not known as a pathogen so the "toxin" of the organism was not studied until 1970 (21). Later the investigators have associated C. difficile with pseudomembranous colitis (PMC). Authors have discovered that the clinical samples from patient with PMC contain high levels of cytotoxic activity.

C. difficile causes disease in humans and animals (10). C. difficile infections (CDI) has been associated with patients who have contact with health care settings and who have taken antibiotics (3, 32). This anaerobic bacterium transmitted via fecal-oral route and can contaminate hands of health care workers and patients, and patient care environment (29, 32). The organism can be isolated from the clothing and room fixtures of the patient. C. difficile once fall into environment can persist for months, because of spore producing.

In the recent years, CDI are recognized as a cause of diarrhea in outpatients and person with no health care contacts. Community-associated infections have been described among young people and people without antibiotic exposures (7).

C. difficile is associated with asymptomatic colonization to severe diarrhea; pseudomembranous colitis, toxic megacolon, intestinal perforation and death (3, 29). It causes approximately 25% of the cases of antibiotic-associated diarrhea (CDAD) (4, 21). Asymptomatic carriers are an important hidden reservoir of C. difficile and they can spread the infection to other patients. Clinical symptoms develop in one third of colonized patients (27).

The incidence of PMC varied widely between different hospitals and even between different wards in the same hospital. Some investigators reported rates as high as 10% in patients treated with clindamycin (21).

C. difficile is recognized as a gut colonizer and cause of diarrhea in several animal species (horses, dogs, ostriches, rabbits, cats and pigs). The prevalence of this enteropathogen in the faeces of dogs is 6% and in cats to 40%. Reported faecal carriage rates in horses is 2%-29% (1). C. difficile is pathogen in domestic and food animals but there were little investigation regarding transmission of this organism (22).

C. difficile produces two toxins: enterotoxin A (Tcd A, 308 kDa) and cytotoxin B (Tcd B, 270 kDa). Toxin B acts synergistically with toxin A after the epithelium has been injured by TcdA (23). The coding chromosome genes tcdA and tcdB are located within a ≈19,6-kb region of PaLoc (pathogenicity locus) (32, 34). TcdA and TcdB are known as virulence factors and markers for diagnosis of C. difficile disease. Not all toxigenic strains produce both toxins A and B. There are different variant C. difficile strains among people and animals, some of them produce both toxins (A+B+); others produce only TcdB (A-B+) and third produce only parts of the toxin genes (A-B-) (16, 17). The majority of strains with changes in genes tcdA and tcdB produce a binary toxin (8). The role of the binary toxin CDT A/B in enteropathogenecity of C. difficile is unclear. Toxins can be found in 15%-25% of the stool of patients with CDAD and more than 95% of patients with pseudomembranous colitis (29).

The diagnostic tests for C. difficile are divided into: (i) test based on detection of C. difficile products; (ii) culture methods; (iii) molecular methods for gene detection (6) . The cell culture cytotoxicity assay (CCA) is regarded as the reference standard. Many laboratories use enzyme immunoassays (EIA) and PCR for detection of C. difficile toxin genes (4, 6).

PCR- ribotyping method have been used to determine the role of the environment; patient-to-patient transmission and for investigation of outbreaks in hospitals and nursing homes (19, 33). This method has a number of advantages over other typing methods: specifically; high discriminatory power; and it is quicker and simplier for performance. PFGE is considered as a "gold standart" for genotyping, but due to DNA degradation in some C. difficile strains (produce endogenous nucleases), other typing technique is preferred (5, 12).

OBJECTIVES

Presentation of PCR-ribotyping method and PCR methods for detection of toxin coding genes for characterization of C. difficile strains isolated from human and animal samples.

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Доклади на Българската академия на науките
Comptes rendus de l'Académie bulgare des Sciences
Tome 64, No 7, 2011

MEDECINE
Microbiologie et virologie

PREVALENCE OF *CLOSTRIDIUM DIFFICILE* PCR RIBOTYPES IN BULGARIA, 2008–2010

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(*Submitted by Academician B. Petrunov on March 23, 2011*)

Abstract

Clostridium difficile is one of the most important causative agents of severe diarrhoea in hospitalised patients treated with antibiotics. Since 2008, Bulgaria participated in the Pan-European Surveillance Study investigating the prevalence of *C. difficile* infections (CDI) in different European countries. In the period November 2008 – March 2010, the incidence of CDI in nine participating hospitals was 7.94 per 10 000 patient admissions (0.34 per 10 000 patient-days). In total, sixty five fecal samples from patients with mild to severe enterocolitis and previous antibiotic treatment were investigated for CDI. Strains were typed and further characterized for the presence of toxins A (TcdA), B (TcdB) and binary toxins (CdtA and CdtB). Of 65 stool samples included, 15 were toxin and culture positive for *C. difficile*. Six of the isolates (40%) belonged to PCR ribotype 017 ($TcdA^-$; $TcdB^+$; $CdtA/B^-$), followed by 002 ($n = 2$ isolates) and 014 ($n = 2$ isolates). The remaining *C. difficile* isolates were typed as 012 ($n = 1$), 046 ($n = 1$), 078 ribotypes ($n = 1$) and 2 isolates were untypable. In conclusion, after the Pan-European surveillance study, a laboratory-based surveillance of CDI has been introduced in Bulgaria. The most prevalent *C. difficile* ribotype in Bulgaria was 017 (40%). All determined PCR ribotypes were

Original article

Received :
18 February 2013
Accepted :
17 June 2014
Disponible en ligne
24 July 2014

A study on early-onset neonatal group B streptococcal infection, Bulgaria, 2007–2011☆

Infection néonatale à streptocoques du groupe B, expérience bulgare

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Summary

This study examines neonatal group B streptococcal (GBS) colonization and its relation to early-onset GBS disease (EOGBSD), based upon the experience of leading obstetrics and gynecology centers in Bulgaria. The objectives of the study were to update neonatal colonization rates and to assess relationships between clinically differentiated cases (culture-proven GBS newborns) and risk factors inherent to the infant and mother, using a computerized file. The neonatal GBS colonization rate ranged from 5.48 to 12.19 per 1000 live births. Maternal-fetal infection (MFI, a provisional clinical diagnosis in culture-proven colonized infants with initial signs of infection that is usually overcome with antibiotic treatment) and/or intrapartum asphyxia (IA) have been demonstrated as the most frequent clinical manifestations, with significant correlations for the primary diagnosis, but not affirmative for the final diagnosis at discharge, resulting from adequate treatment of neonates. MFI and IA were significantly related to prematurity, and reciprocally, prematurity was associated with the risk of MFI, indirectly suggesting

Résumé

L'étude examine la colonisation néonatale à SGB (comprise entre 5,48 et 12,19 pour 1000 naissances vivantes) et sa relation à la MSGBDP d'après l'expérience des principaux centres d'obstétrique et de gynécologie de Bulgarie. Elle évalue les corrélations entre les cas d'isolement de SGB cliniquement différenciés et les facteurs de risque inhérents à l'enfant et à la mère. L'IMF et/ou l'AI ont été démontrées comme les diagnostics les plus fréquents : l'IMF est posé en tant que diagnostic provisoire pour les nourrissons colonisés, présentant des signes initiaux d'infection qui sont généralement surmontés au cours du traitement antibiotique. Ces deux pathologies ont été liées à la prématurité dans une relation réciproque, indiquant indirectement en tant que facteur de risque considérable pour la MSGBDP l'accouchement avant terme ou la rupture prématurée des membranes prétermes (RPMP – une des raisons principales pour l'accouchement avant terme). L'analyse de régression a démontré que dans le cas d'un nouveau-né diagnostiqué avec l'IMF, l'on peut constater un poids à la naissance de 593,58 g inférieur au poids à la

☆ A preliminary report of the results of the present study was published in the Official Journal of the Bulgarian Scientific Society of Obstetrcs and Gynecology "AKUSHERSTVO I GINEKOLOGIYA", 2012: Vacheva R, Todorova M, Decheva A, Nikolov A, Slancheva B, Stoichkova D, Christova E, Shopova E, Hitrova S, Masseva A, Yarakova N, Kraleva I, Takova TS, Dimitrova N, Dobreva A. A study on early-onset neonatal group B streptococcal infection. Akusherstvo I Ginekologiya 2012;51(6):10–21.

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http://dx.doi.org/10.1016/j.arcped.2014.06.023 Archives de Pédiatrie 2014;21:953-960
0929-693X/

International Journal of Antimicrobial Agents ■■ (2017) ■■–■■

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Selective reporting of antibiotic susceptibility test results in European countries: an ESCMID cross-sectional survey

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ARTICLE INFO

Article history:
Received 6 September 2016
Accepted 12 November 2016

Keywords:
Antibiotic stewardship
Questionnaire
Antibiotic susceptibility testing
Selective reporting
Antibiotic prescription
Antibiotic resistance

ABSTRACT

Selective reporting of antibiotic susceptibility test (AST) results is one possible laboratory-based antibiotic stewardship intervention. The primary aim of this study was to identify where and how selective reporting of AST results is implemented in Europe both in inpatient and in outpatient settings. An ESCMID cross-sectional, self-administered, internet-based survey was conducted among all EUCIC (European Committee on Infection Control) or EUCAST (European Committee on Antimicrobial Susceptibility Testing) national representatives in Europe and Israel. Of 38 countries, 36 chose to participate in the survey. Selective reporting of AST results was implemented in 11/36 countries (31%), was partially implemented in 4/36 (11%) and was limited to local initiatives or was not adopted in 21/36 (58%). It was endorsed as standard of care by health authorities in only three countries. The organisation of selective reporting was everywhere discretionally managed by each laboratory, with a pronounced intra- and inter-country variability. The most frequent application was in uncomplicated community-acquired infections, particularly urinary tract and skin and soft-tissue infections. The list of reported antibiotics ranged from a few first-line options, to longer reports where only last-resort antibiotics were hidden. Several barriers to implementation were reported, mainly lack of guidelines, poor system support, insufficient resources, and lack of professionals' capability. In conclusion, selective reporting of AST results is poorly implemented in Europe and is applied with a huge heterogeneity of practices. Development of an international framework, based on existing initiatives and identified barriers, could favour its dissemination as one important element of antibiotic stewardship programmes.

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http://dx.doi.org/10.1016/j.ijantimicag.2016.11.014
0924-8579/

Please cite this article in press as: Céline Pulcini, et al. on behalf of the EUCIC-ESGAP-EUCAST Selective Reporting Working Group, Selective reporting of antibiotic susceptibility test results in European countries: an ESCMID cross-sectional survey, International Journal of Antimicrobial Agents (2017), doi: 10.1016/j.ijantimicag.2016.11.014

J Antimicrob Chemother 2018; **73**: 2275
doi:10.1093/jac/dky219 Advance Access publication 12 June 2018

Journal of Antimicrobial Chemotherapy

Erratum

Results from the Survey of Antibiotic Resistance (SOAR) 2014–16 in Bulgaria, Romania, Serbia and Croatia

D. Torumkuney, M. Nica, I. Nistor, R. Vatcheva-Dobrevska, V. Petrovic, A. Stoica, B. Hanicar, Dj. Antic and I. Morrissey

J Antimicrob Chemother 2018; **73** Suppl 5: v2–13

In Table 1, the PK/PD breakpoint for moxifloxacin was incorrectly stated as ≤2 mg/L and should have been ≤1 mg/L. The data analysis was conducted using the correct breakpoint value and therefore the results in this article are unaffected. The error in Table 1 has now been corrected.

The authors apologize for this error.

Доклади на Българската академия на науките
Comptes rendus de l'Académie bulgare des Sciences

Tome 73, No 12, 2020

MEDICINE

Clinical medicine

DIAGNOSTIC ACCURACY AND PREDICTIVE VALUE OF SERUM FIBROBLAST GROWTH FACTOR 19 (FGF19) AND TOTAL FREE FECAL BILE ACIDS AS BIOMARKERS OF BILE ACID MALABSORPTION IN PATIENTS WITH CHRONIC DIARRHEA: A PILOT STUDY

Ivan Lyutakov, Radislav Nakov, Borislav Vladimirov, Ventsislav Nakov, Anastas Dimov, Boyana Asenova*, Milena Chetirska*, Rositsa Vatcheva-Dobrevska*, Diyana Kyoseva***, Nedelina Terzieva***, Plamen Penchev**

(*Submitted by Academician D. Damianov on October 2, 2018*)

Abstract

Excessive amounts of bile acids (BA) entering the colon due to bile acid malabsorption (BAM) cause chronic bile acid diarrhea (BAD). Fibroblast growth factor 19 (FGF19) is the ileal hormone providing feedback inhibition of BAs synthesis in the liver. Little is known about the mechanisms of BA dysregulation in patients with inflammatory bowel disease (IBD), irritable bowel syndrome (IBS-D) and microscopic colitis (MC).

The aim of this study is to evaluate the diagnostic accuracy of serum levels of FGF19, total free faecal bile acids (TFFBA) and faecal calprotectin (FC) in patients with chronic diarrhoea.

In a prospective study we enrolled 40 adult patients with chronic diarrhea who underwent standard laboratory tests, colonoscopy, serum FGF19, FC, TFFBA. Patients were divided into five groups: 14 patients with active IBD, five patients with IBD in remission, five patients with IBD after surgery, 11 patients with IBS-D and five patients with MC. Fasting serum FGF19, TFFBA were measured by ELISA test and FC by quantitative immunochromatographic method.

DOI:10.7546/CRABS.2020.12.16

Serum Levels of Fibroblast Growth Factor 19 Correlate with the Severity of Diarrhea and Independently from Intestinal Inflammation in Patients with Inflammatory Bowel Disease or Microscopic Colitis

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Cite this article as: Lyutakov I, Nakov R, Valkov H, Vatcheva-Dobrevska R, Vladimirov B, Penchev P. Serum levels of fibroblast growth factor 19 correlate with the severity of diarrhea and independently from intestinal inflammation in patients with inflammatory bowel disease or microscopic colitis. *Turk J Gastroenterol.* 2021; 32(4): 374-381.

ABSTRACT

Background: *In chronic diarrhea patients, massive over-reporting symptom-based criteria for functional bowel disorders are pitfalls. There is currently no objective biomarker that may provide a correct correlation with the severity of chronic diarrhea. To clarify the role of fibroblast growth factor-19 (FGF-19) as a biomarker of objective measurements of the severity of diarrhea in comparison with a patient-reported outcome, based on the Bristol Stool Form (BSF) Scale.*

Methods: *Consecutive 100 patients with chronic diarrhea underwent standard investigations with laboratory tests, fecal calprotectin (FC), endoscopy with biopsies, and serum FGF-19. All patients and 14 healthy controls completed a diary recording, BSF, and stool frequency.*

Results: *We found that irritable bowel syndrome with diarrhea (IBS-D) n = 21/23 (91%) reported a high number on BSF ≥6, compared to patients with inflammatory bowel diseases (IBD) 56/77 (72%) with BSF ≥ 6 (P = .011). FGF-19 median serum levels were significantly lower in Microscopic colitis (0.010 pg/mL) and IBD patients (0.009 pg/mL) compare to IBS-D (266.9 pg/mL) and high levels in healthy subjects (463 pg/mL) (P < .001). Strong inverse correlation of FGF-19 with the stool frequency/day and stool index was found (r = –0.800, P < .001; r = –0.739, P < .001), independently from disease activity (r = –0.718, P = .001; r = –0.792, P = .001).*

Conclusion: *Serum FGF-19 can become a new biomarker for evaluating the severity of diarrhea with objectively and independently from intestinal inflammation. FC and FGF-19 are predictive biomarkers for the organic cause of diarrhea.*

Keywords: *Fibroblast growth factor-19, FGF-19, BAM, IBD, MC, IBS-D*

INTRODUCTION

The reported prevalence of chronic diarrhea is 4-5% in the Western population, which is a common disorder in many conditions. The incidents vary a lot and depend on the definition of diarrhea and reported by the patients. A large number of other diseases may cause diarrhea that is not related to the gastrointestinal tract.[1,2] The standard definition of chronic diarrhea is ≥ 3 loose stools per day with a fecal weight ≥ 200 g/day, lasting for at least 4 weeks.[2] The term 'Diarrhea' may be defined as stool frequency, consistency, volume, or weight of the feces, but this differs from patients reporting the number of stools and often focuses around stool consistency.[2,3] The most common causes of diarrhea are functional bowel disorders, such as irritable bowel syndrome (IBS) and functional diarrhea.[4] However, from organic diseases with chronic diarrhea, the most common causes are inflammatory bowel disease (IBD), microscopic colitis (MC), and bile acid diarrhea.[1,4] In chronic diarrhea patients, there is a situation of substantial over-reporting symptoms and more often only symptom-based criteria, but these reports of high number loss of stools per day can lead to exhausting diagnostic procedures and broad differential diagnosis.[5,6]

The reporting precision of the correct number of stools per day has been questioned by fecal water content (FWC) measured on pooled feces by freeze-drying in patients with chronic diarrhea with defined as ≥78% water.[1,7] The degree of dissatisfaction with stool consistency correlated poorly with the FWC and Bristol stool form (BSF) scale changes.[7,8] The measure of fecal weight is 'cumbersome,' and this test is not popular

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Received: ***April 12, 2020*** *Accepted:* ***September 14, 2020***

DOI: ***10.5152/tjg.2021.20247***

European Review for Medical and Pharmacological Sciences 2021; 25: 390-396

Establishment of the first stool bank in an Eastern European country and the first series of successful fecal microbiota transplantations in Bulgaria

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Abstract. – OBJECTIVE: For safe implementation and broader application of fecal microbiota transplantation (FMT), quality controlled stool banking is a must. Establishing a stool bank is a complex, time-consuming, and expensive process, making it a real challenge in an Eastern European country. We aimed to establish the first stool bank in Eastern Europe – in Bulgaria.

SUBJECTS AND METHODS: A multidisciplinary team of gastroenterologists, microbiologists, infectionists, and geneticists was set up. We used a questionnaire based on the First European FMT Consensus in order to recruit possible stool donors. Laboratory blood and stool tests were performed on all potential donors.

RESULTS: Between October 2018 and April 2019, 112 donor volunteers completed a questionnaire; 70 (62.5%) were excluded, mainly because of age above 50, an unhealthy BMI, and risk behavior. Fourty-two (37.5%) donor candidates were invited for laboratory testing of blood and feces, of which 12 (28.6%) passed this screening. Of 12 donors, 4 (33%) failed at the following screening test, which is performed every 3-6 months. Finally, 8 (7.14%) active donors were enrolled. Ten successful FMTs were performed on patients with recurrent Clostridium difficile infection.

CONCLUSIONS: Even though we found many healthy volunteers, only a low percentage (7.14%) of them were suitable to become feces donors. Establishing a stool bank in an Eastern European country is essential for making FMT safe and more popular as a treatment method, finding further implementation and regulation of FMT and supporting physicians offering this treatment to their patients.

Key Words:
Stool bank, Microbiota, Fecal microbiota transplantation, Donors.

Introduction

Clostridioides difficile infection (CDI) is the main cause of antibiotic-associated gastrointestinal disease inducing significant morbidity and mortality[1]. The clinical answer to antibiotic treatment of CDI is 80% in the first episode[2] and rapidly drops to only 30-40% in recurrent disease[3].

Fecal microbiota transplantation (FMT) is an extremely efficient treatment against recurrent *Clostridium difficile* infection (rCDI)[1-5]. Guidelines now recommend FMT as a treatment choice for both mild and severe recurrent CDI and refractory CDI[4]. However, there is still inadequate evidence to recommend FMT as a treatment for the first episode of CDI[4]. FMT is increasingly being used for other disorders, including irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), metabolic syndrome, and critically ill patients[6,7], but none of them emerged an evidence-based recommendation to use FMT except that in the context of research[4,5]. Several case reports have demonstrated positive outcomes of using FMT for treating septic shock and intractable diarrhea in the intensive care unit (ICU)[8,9].

To ensure a safe, disseminated, and cost-effective implementation of FMT, stool banks that produce ready-to-use donor feces suspensions

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Clinical Microbiology and Infection 30 (2024) 469–480

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Guidelines

Pseudomonas aeruginosa antimicrobial susceptibility profiles, resistance mechanisms and international clonal lineages: update from ESGARS-ESCMID/ISARPAE Group

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https://doi.org/10.1016/j.cmi.2023.12.026

Нозокомиални инфекции | Nosocomial Infections

Бюлетин на БулНозо — BulNoso Bulletin

Том 6, Брой 1–2, 2009 Volume 6, No 1–2

ISSN 1312-4765

Адрес на редакцията:
Национален център по заразни и паразитни болести (НЦЗПБ)
бул. „Я. Сакъзов" 26, 1504 София, България
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For full author instructions and information for readers, please, visit the BulNoso website
www.bulnoso.org

Бюлетин на Българската асоциация по превенция и контрол на нозокомиалните инфекции – БулНозо
Offitial Journal of Bulgarian Association for Prevention and Infection Control – BulNoso

Предпечатна подготовка: издателство „БулВест 2000"
Печат: БУЛВЕСТ – СОФИЯ АД, печатница „Вулкан"

Епидемиологично проучване на взрив, причинен от множествено-резистентни щамове *Serratia marcescens* в неонатологично отделение

Р. Вачева-Добревска[1]* , Т. Каменова[2], В. Войнова[1], Н. Гачева[1], Е. Ташева[2], И. Иванов[1], Е. Добрева[1], И. Томова[3], В. Генова[4], И. Маева[5]

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Key words: nosocomoal, outbreak, *Serratia marcescens*, genotyping

Ключови думи: Вътреболничен, Взрив, *Serratia marcescens*, генотипиране

EPIDEMIOLOGICAL STUDY OF A MULTIDRUG-RESISTANT S. MARCESCENS OUTBREAK IN A NEONATAL UNIT

R. Vatcheva-Dobrevska[1], T. Kamenova[2], V. Voynova[1], N. Gatcheva[1], E. Tasheva[2], I. Ivanov[1], E. Dobreva[1], I. Tomova[3], V. Genova[4], I. Maeva[5]*

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Summary. The nosocomial spread of ESBL producing *S. marcescens* remains a significant world-wide problem.This study investigates the epidemiology of a nosocomial outbreak of ESBL producing *S. marcescens* in a neonatal unit.
Methods: A total of six infants were clinically studied. Three of them have experienced various clinical symptoms, one died with meningitis and two were clinically healthy. Six isolates *S. marcescens* were cultured from CSF (1), throat aspirate (3), nasal swabs (2). Identification, antimicrobial susceptibility and tests for ESBL production were performed by VITEK 2 (BioMerieux, France) and conventional methods. PCR detection and sequencing analysis of CTX-M, SHV and TEM ESBL encoding genes was performed. Molecular typing was carried out by using ERIC-PCR and REP-PCR. The fragment analysis was carried out in a novel capillary electrophoresis instrument that generates results within eight minutes.
Results: The antibiotic susceptibility testing revealed two types: five isolates were multidrug resistant, susceptible only to fluoroquinolones and carbapenems and one isolate was generally susceptible. Only CTX-M-3 ESBL gene was found among the five MDR strains. The molecular typing grouped the isolates in two clusters: one containing the five identical MDR isolates and a second one including the unrelated susceptible strain. The two methods applied generated concordant results.
Conclusions: This study is the first analyzed by methods of molecular epidemiology and detection of resistance genes nosocomial *S. marcescens* outbreak in neonatology unit in Bulgaria. The applied PCR typing systems ERIC-PCR and REP-PCR proved efficient for discrimination of closely related as well as unrelated nosocomial isolates.

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Нозокомиални инфекции | Nosocomial Infections

Бюлетин на БулНозо — BulNoso Bulletin

Том 6, Брой 1–2, 2009 Volume 6, No 1–2

ISSN 1312-4765

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Предпечатна подготовка: издателство „БулВест 2000"
Печат: БУЛВЕСТ – СОФИЯ АД, печатница „Вулкан"

Подходи за превенция и контрол на инфекцията при пациенти с *Clostridium difficile* – асоциирана болест

Р. Вачева

Национален референтен център по ВБИ, НЦЗПБ – София

Clostridium difficile е анаеробен бактерий, широко разпространен в почвата и чревния тракт на животните. Микроорганизмът е Грам-положителен и образува спори.

Клиничният спектър на инфекциите, причинени от *C.difficile* обхваща случаите от умерено изразена диария, най-често нозокомиална, антибиотик-свързана, до тежък животозастрашаващ псевдомембранозен колит [4]. Заболяването не винаги е свързано с предхождаща антибиотична терапия. За неговото означаване се използва терминът *Clostridium difficile* – асоциирана болест (*Clostridium difficile* – associated disease, CDAD). Съществуват данни за зачестяване на случаи от CDAD, придобити в обществото, при лица без данни за предразположение, наблюдава се и увеличаване на случаите сред различни животински видове [1, 2].

Предаването на *C.difficile* от пациент на пациент може да става посредством контакт с ръцете на медицинския персонал или контаминирана болнична среда. Влиянието на инфекциите, причинени от *C. difficile* върху съвременното здравеопазване е сериозно, както по отношение на заболяемост и смъртност, така и относно високите разходи за лечение [8]. Икономическият ефект е оценен на 5 000–15 000 EUR на случай в Англия и съответно – 1,1 млрд USD годишно в САЩ.

От 2003 г. се съобщава за зачестяване на случаите от CDAD в Канада и САЩ с по-тежко протичане, по-висока смъртност и повече усложнения [3,6]. При тях е установен като причинител високовирулентен щам *C. difficile*, продуциращ по-високи количества токсин, резистентен на хинолонови препарати и отнасящ се към определен PCR риботип 027, токсинотип III и PFGE NAP1 тип [9]. Случаи на CDAD, причинени от този нов, високовирулентен щам *C. difficile* PCR риботип 027 са докладвани в Белгия, Германия, Финландия, Франция, Ирландия, Люксембург, Холандия, Швейцария и Обединеното Кралство (Англия, Уелс и Северна Ирландия), доказани са, също така и в Австрия, Дания, Унгария, Норвегия, Полша, Испания и Шотландия [10].

Взривовете от тази инфекция са много трудни за овладяване. Опитът от Канада показва, че възможностите за успех се увеличават, ако се комбинират мерките за контрол на инфекциите с оптимизиране предписването на антибиотици [5,7].

КАКВО ПРЕДСТАВЛЯВА *C. DIFFICILE* – АСОЦИИРАНАТА БОЛЕСТ (CDAD) ?

Това са заболявания, в резултат на инфекция с *C. difficile*:

- псевдомембранозен колит (PMC)
- токсичен мегаколон
- перфорация на колона
- сепсис
- случаи на смърт

ОПРЕДЕЛЕНИЕ ЗА СЛУЧАЙ НА CDAD. Потвърден случай на CDAD е пациент на възраст 2 и повече години, за който могат да бъдат при-

ISSN 1312-2746

ВОЕННА МЕДИЦИНА

ОФИЦИАЛНО ИЗДАНИЕ НА ВОЕННОМЕДИЦИНСКА АКАДЕМИЯ
БЪЛГАРСКО НАУЧНО ДРУЖЕСТВО ПО ВОЕННА МЕДИЦИНА

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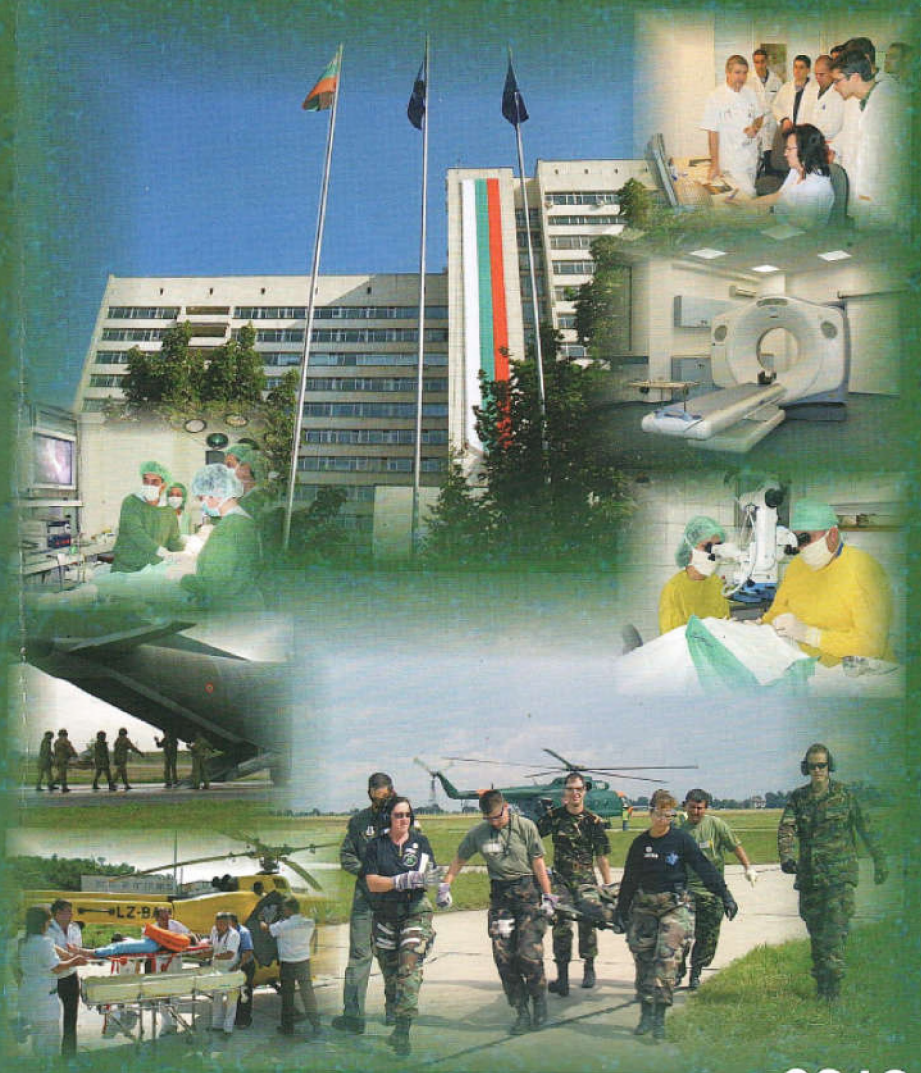

БРОЙ 3

2010

ПОДХОДИ ЗА ХАРАКТЕРИЗИРАНЕ НА ИЗОЛАТИ CLOSTRIDIUM DIFFICILE ПОСРЕДСТВОМ PCR-РИБОТИПИРАНЕ

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APPROACHES FOR CHARACTERIZATION OF CLOSTRIDIUM DIFFICILE ISOLATES BY PCR-RIBOTYPING METHOD

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РЕЗЮМЕ

Clostridium difficile се среща като причинител на инфекции, свързани с медицинското обслужване в целия свят. Вариациите са от безсимптомна колонизация на чревния тракт до *C. difficile* асоциирана болест (CDAD – *C. difficile* Associated Disease). Честотата на *C. difficile* инфекциите, водещи до сериозни поражения и леталитет, се увеличава през последните години и в България. В настоящето проучване се представят подходите за характеризиране на клинични изолати *C. difficile* посредством PCR-риботипиране с последваща капилярна гел-електрофореза. В периода ноември 2008 г. - март 2010 г. са изследвани 65 фецеса, получени от девет болници в региона на гр.София и гр.Пловдив. Чрез прилагане на културелни методи в 23% от материалите се доказва *C. difficile*. 21.5% от щамовете *C. difficile* продуцират токсини, които се доказват във фецес чрез имуноензимен тест. Идентификацията на щамовете е потвърдена чрез оцветяване по Грам и латекс-ко-аглутинационен тест. Сред изследваните клинични изолати *C. difficile* с PCR-риботипиране се установи, че най-често срещаните риботипове са: 017 (40%); 002 (13%); 014/020 (13%); 012 (7%); 046 (7%); 078 (7%) като преобладаващ е 017. В значителен брой от представените случаи се диагностицират риботипове *C. difficile*, предимно асоциирани с вътреболнични взривове, които в бъдеще могат да доведат до сериозни проблеми в страната.

Ключови думи: C. DIFFICILE; PCR-РИБОТИПИРАНЕ, РИБОТИПОВЕ

SUMMARY

Clostridium difficile is recognized as an important pathogen , connected to healthcare-associated infections worldwide. Asymptomatic colonization can occur and *C. difficile* Associated Disease (CDAD). The incidence of *C. difficile* infections increase in the recent years in Bulgaria and can lead to serious outcomes and dead. In this study are presented approaches for characterization of *C. difficile* isolates by PCR-ribotyping method based on capillary gel-electrophoresis. Sixty five stool samples received from nine hospitals in Sofia and Plovdiv regions have been investigated from November 2008 to March 2010. 23% from samples were positive for *C. difficile* with culture test. In 21.5% from investigated stools by enzyme-immunoassay (EIA) was detected production of Toxin A and Toxin B. Identification of the strains *C. difficile* was confirmed with Gram-staining and latex-co-aggutination test. We distinguished several ribotypes among clinical isolates

Нозокомиални инфекции | Nosocomial Infections

Бюлетин на БулНозо — BulNoso Bulletin

Том 8, Брой 1–2, 2011 Volume 8, No 1–2

ISSN 1312-4765

Адрес на редакцията:
Национален център по заразни и паразитни болести (НЦЗПБ)
бул. „Я. Сакъзов" 26, 1504 София, България
Тел./факс: + 359 2 946 15 89

Editorial office:
National Centre of Infectious and Parasitic Diseases (NCIPD)
26, Y. Sakazov Blvd, 1504 Sofia, Bulgaria
Tel./Fax + 359 2 946 15 89

For instructions to authors and information for readers, please, visit the BulNoso website
www.bulnoso.org

Бюлетин на Българската асоциация по превенция и контрол на нозокомиалните инфекции – БулНозо
Official Journal of Bulgarian Association for Prevention and Infection Control – BulNoso

Предпечатна подготовка: Издателство „БулВест 2000" **Publisher**: "Bulvest 2000" E-mail:bulvest@bulvest2000.com
Печат: БУЛВЕСТ – СОФИЯ АД, печатница Вулкан" **Printer**: Bulvest-Sofia AD

Представители на сем. *Enterobacteriaceae*, продуценти на карбапенемази: съвременна заплаха за ефективна антимикробна терапия

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Key words:
Enterobacteriaceae, carbapenemase, infection, antimicrobial treatment

Ключови думи:
Enterobacteriaceae, карбапенемази, инфекция, антимикробна терапия

CARBAPENEMASE-PRODUCING ENTEROBACTERIACEAE: A CURRANT THREAT FOR THE EFFICIENT ANTIBACTERIAL TREATMENT

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Summary. Infections with carbapenem-resistant *Enterobacteriaceae* (CRE) or carbapenemase-producing *Enterobacteriaceae* are emerging worldwide as an important cause of fatal patient outcome. Bacterial isolates producing these enzymes are capable of hydrolysing a broad spectrum of β-lactams including the penicillins, cephalosporins, carbapenems and monobactam. Carbapenem-resistant Klebsiella pneumoniae is the species of CRE resistant to almost all available antimicrobial agents, causing infections associated with high rates of morbidity and mortality, particularly among critically ill persons, these with prolonged hospital stay and with invasive devices (e.g., ventilators, central venous catheters). The recommendations are for strong infection control strategy, including managing all patients with CRE using contact precautions and implementation of methods for detection of carbapenemase production.

Карбапенемите (имипенем, меропенем) са антибиотици, които са пръв избор за терапия на тежки инфекции, причинени от представители на сем. *Enterobacteriaceae*, продуциращи широкоспектърни β-лактамази (ESBLs). Появата и разпространението на карбапенем-резистентни *Enterobacteriaceae* в глобален мащаб е изключително тревожен факт, тъй като застрашава възможностите за антимикробна терапия с наличните антибиотици.

Резистентността към карбапенеми се развива по следните механизми: модификации във външно-мембранната пропускливост; участие на системите за ефлукс; хиперпродукция на AmpC β-лактамази (цефалоспориназа) или ESBLs; продукция на специфични карбапенем-хидролизиращи β-лактамази (карбапенемази) [45].

Карбапенемазите (КП) са докладвани с повишена честота при сем. *Enterobacteriaceae* в последните десет години. Откриването на

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Нозокомиални инфекции | Nosocomial Infections

Бюлетин на БулНозо — BulNoso Bulletin

Том 7, Брой 1–2, 2010 Volume 7, No 1–2

ISSN 1312-4765

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Бюлетин на Българската асоциация по превенция и контрол на нозокомиалните инфекции – БулНозо
Offitial Journal of Bulgarian Association for Prevention and Infection Control – BulNoso

Предпечатна подготовка: издателство „БулВест 2000"
Печат: БУЛВЕСТ – СОФИЯ АД, печатница „Вулкан"

Молекулярно-епидемиологично проучване на вътреболничен взрив от *Pseudomonas aeruginosa* в детско онкохематологично отделение

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Key words:
nosocomial outbreak, *Pseudomonas aeruginosa*, molecular typing

Ключови думи:
нозокомиален взрив, *Pseudomonas aeruginosa*, молекулярно типиране

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MOLECULAR-EPIDEMIOLOGY INVESTIGATION OF *PSEUDOMONAS AERUGINOSA* NOSOCOMIAL OUTBREAK IN AN ONCOHEMATOLOGICAL PEDIATRIC UNIT.

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Summary. Objectives: Epidemiologic investigation of nosocomial outbreak in an oncohematological pediatric unit using molecular genotyping methods

Methods: During June to July 2009, six children hospitalized with acute lymphoblastic leukemia were found experiencing similar symptoms for transient bacteremia including fever and elevated body temperature. Blood cultures (5 cases) and culture from intravenous catheter abscess (1 case) revealed *P. aruginosa* to be involved in all cases. Five isolates from blood cultures, one from i.v. catheter sample and four from hospital environment/solutions were further studied with respect to phenotypic and genotypic characterization. Antibiotic resistance patterns were studied by conventional methods and VITEK2 BioMerieux, France. Presence of genes encoding beta-lactamases (VEB, OXA, PSE, PER.) and carbapenemases (IMP, VIM, SPM, GES, SIM, GIM) was tested by PCR. Molecular typing was performed by MLVA6.

Results: All isolates from patients were found to be multiple resistant to antibiotics including imipenem, meropenem, ceftazidime and piperacillin/tazobactam. The isolates from the hospital environment and solutions were mostly susceptible with one exception. The molecular typing clearly revealed that all patient isolates represented a single genotype that was also detected in one isolate from a hospital sink. This isolate however had slightly different resistotype from the patient isolates (sensitive to meropenem and piperacillin). The same *bla* genes (OXA-10 group and VEB-1) were detected in the patient isolates and the isolate from sink. No carbapenemase genes were detected suggesting non-enzyme mediated resistance mechanism.

Conclusions: The epidemiological and molecular typing data suggest that the outbreak might have occurred following contamination of the intravenous catheters with a strain derived from the hospital environment.

Нозокомиални инфекции | Nosocomial Infections

Бюлетин на БулНозо — BulNoso Bulletin

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ISSN 1312-4765

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Offitial Journal of Bulgarian Association for Prevention and Infection Control – BulNoso

Предпечатна подготовка: издателство „БулВест 2000"
Печат: БУЛВЕСТ – СОФИЯ АД, печатница „Вулкан"

Сравнителни данни за болестност и заболяемост от индикаторни инфекции в хирургични и интензивни отделения на МБАЛ в Софийска област, 2007 – 2008 г.

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Key words:
infections, prevalence survey, surveillance, prevention and infection control

Ключови думи:
нозокомиални инфекции, преваленто проучване, надзор, превенция и контрол на инфекциите

COMPARATIVE DATA ON PREVALENCE AND INCIDENCE OF THE INDICATOR INFECTIONS IN SURGICAL AND INTENSIVE CARE UNITS OF MULTIPROFILE HOSPITALS IN SOFIA REGION, 2007-2008

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Summary: Prevalence studies of the indicator infections (urinary tract, surgical-site infections, bacteraemia and nosocomial pneumonia) were performed in surgical and intensive care units in seven medium- and small-sized hospitals of Sofia region in 2007 – 2008. Incidence data on the frequency of the same nosocomial infections and the same units from the routine surveillance system were analyzed comparatively. The overall prevalence observed in 116 patients in 2007 was 20.7% (95% confidence interval [CI95], 13.2-28.1), and in 98 patients in 2008 was 15.3% (CI95, 8.1-22.5). Overall incidence was much lower – 2.2% in 2007, and < 1.5% in 2008. Information about the risk factors, ASA score and wound class, antimicrobial usage, etc, was gathered during the prevalence studies. Results were used to increase the awareness of the medical personnel of nosocomial infections/NIs, and in order to take measures to prevent these infections.

Увод

Нозокомиалните инфекции (НИ) в световен мащаб са здравен проблем със значителни социални и икономически последствия. Двете средства за събиране на данни за надзор на НИ са използването на проучванията за болестност (срезови/преваленти проучвания) и заболяемост [1,2]. Авторите си поставиха за цел да използват и двете средства, като сравнят данните и направиха оценка на ситуацията в рискови отделения на лечебни заведения на Софийски регион за 2007 и 2008 г. Добре известно е, че основната

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МЕДИЦИНСКИ УНИВЕРСИТЕТ – СОФИЯ
ЦЕНТРАЛНА МЕДИЦИНСКА БИБЛИОТЕКА

ДЕТСКИ И ИНФЕКЦИОЗНИ БОЛЕСТИ

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Списанието се обработва в БД
БЪЛГАРСКА МЕДИЦИНСКА ЛИТЕРАТУРА

Детски и инфекц. бол.
Detski i Infects. bol.

Год. VI **2014** **Брой 2**

АВТОРСКИ СТАТИИ

ВЪТРЕБОЛНИЧНИТЕ ИНФЕКЦИИ В Р. БЪЛГАРИЯ, 1999-2011 Г. – ПЪРВА ЧАСТ

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NOSOCOMIAL INFECTIONS IN BULGARIA, 1999-2011 – PART ONE

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Резюме. Вътреболничните инфекции (ВБИ) представляват сериозен проблем за общественото здравеопазване, тъй като се характеризират с удължен болничен престой, затруднено лечение поради множествена резистентност на причинителите, висока смъртност, повишени разходи за лечебното заведение, пациентите и техните семейства. Обикновено засягат критично болни пациенти, с нарушен имунен статус, чието лечение може да включва инвазивни процедури или оперативни интервенции. Проучването представя анализ в две части на официално регистрираните ВБИ в страната чрез компютъризираната система (АИС-ВБИ) в течение на 13-годишен период (1999-2011 г.). Системата работи с два вида показатели – за честота (заболяемост, преизчислена на 1000 изписани болни в проучването), и относителен дял, т.е. структура по видове инфекции и микробни причинители. Отразена е последната актуализация от 2011 г., отнасяща се до регистрация на пневмония, свързана с изкуствена белодробна вентилация, т.нар. вентилационна пневмония (ВАП), и включването на допълнителни отделения специална хирургия. Първата част обсъжда общата структура на ВБИ в страната и заболяемостта по категории болници и отделения с акцент върху педиатрични и реанимационни отделения. Средната заболяемост е 10‰ при следната структура: ВАП – 5%, инфекции на хирургичното място (ИХМ) и белодробни (бронхит, бронхиолит, пневмония, несвързана с процедура на командно дишане) – по 16-18%; уроинфекции – 13-15%; сепсис – 4-5%, чревни, кожни, инфекции на сетивните органи, интраабдоминални и инфекции на сърдечно-съдовата система – по 2%; ендометрит и други гинекологични – 1%; мастит при родилки – 0,1%. Микробиологично диагностицирани са 50-60% от инфекциите и в 40-50% – сборно непотвърдени микробиологично и неизследвани. Най-чести причинители са E. coli и S. aureus (1/3 от инфекциите) и редица опортюнистични бактерии, известни с множествена резистентност към антибактериални средства: Klebsiella spp., Pseudomonas spp., Acinetobacter spp. и др. Честотата на инфекциите е в ниски граници – например белодробни – педиатрични отделения – до 3‰; VAP/белодробни инфекции – реанимация (ОАРИЛ) 15/19‰, интензивна терапия (ОИТ) 5/8‰; уроинфекции – реанимация, урология – 13‰; инфекции на хирургичното място – изгаряния – 38‰, гнойно-септична хирургия – 23‰, съдова хирургия – 11‰; сепсис – изгаряния – 22‰, ОАРИЛ – 8‰, кардиохирургия – 6‰, ОИТ – 5‰.

Ключови думи: вътреболнични инфекции, автоматизирана информационна система, вентилационна пневмония, белодробни инфекции, инфекции на хирургичното място, уроинфекции, сепсис, отделения по анестезиология, реанимация и интензивно лечение, отделения за интензивна терапия

Summary. Nosocomial infections (NI) represent a serious public health problem because they are characterized by a prolonged hospital stay, difficult treatment due to the multidrug resistance of etiological agents, high mortality, and increased costs for hospital, patients and their families. Usually they affect critically ill patients, with impaired immunity, whose treatment may require invasive procedures or operation. The study presents an analysis in two parts of the officially registered NI in the country by the computerized

Ulutas Med J 2016;2(1):20-26
DOI: 10.5455/umj.20160210060327

ORIGINAL ARTICLE OPEN ACCESS

Efficacy of Local *Lactobacillus Casei Var Rhamnosus Döderlein* Monotherapy for Bacterial Vaginosis

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Abstract

Introduction: The objective of this study was to establish the efficacy of local probiotic monotherapy for the treatment of bacterial vaginosis.

Method: A total of 141 women with bacterial vaginosis, randomized into two groups, were examined. In the first group, 85 women were treated with local probiotic medicine (QD for 10 days) containing Lactobacillus casei var rhamnosus Döderlein (Lcr35®). In the second group, 56 patients received the same local probiotic treatment as those in the first group, in addition to treatment with an oral administration of metronidazol (500 mg tablet BID for 7 days). The efficacy of the monotherapeutic scheme was evaluated by comparing the number of clinical complaints and the results of clinical examinations and microbiological tests in the two groups.

Results: One month after the probiotic monotherapy in the first group, the clinical efficacy was 47.1% and the microbiological efficacy was 41.1%. The combined treatment in the second group was more efficacious (clinical efficacy: 89.3%; microbiological efficacy: 76.7%).

Conclusion: Our results indicate that local probiotic monotherapy is less effective than combined metronidazole/probiotic scheme for the treatment of bacterial vaginosis.

Keywords: Lactobacilli, monotherapy, probiotic, vaginal flora

Introduction

The use of probiotics to restore and maintain normal vaginal flora represents a promising alternative or addition to conventional therapy for the treatment of bacterial vaginosis (BV) (1, 2, 3). Probiotics can be used independently or in addition to the primary therapy for BV and clinical trials have been conducted for both monotherapy and combined therapy (1, 2, 3). These studies administered specific strains of lactobacilli orally or locally and tracked their ability to colonize the vagina of patients with symptomatic and asymptomatic BV. The ability of the strains to reduce the colonization and symptoms of pathogens was also assessed. The results of these studies indicate that the use of probiotics in treatment of BV is a promising alternative to conventional therapy (1, 2, 3).

The aim of our study was to establish the clinical and microbiological efficacy of local probiotic *Lactobacillus casei var rhamnosus Döderlein* monotherapy of BV and its effect on the vaginal flora.

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Received: Jan 31, 2016 **Accepted:** Feb 28, 2016
Published: March 30, 2016

The European Centre for Disease Prevention and Control (ECDC) pilot point prevalence survey of healthcare-associated infections and antimicrobial use

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Citation style for this article:
Zarb P, Coignard B, Griskeviciene J, Muller A, Vankerckhoven V, Weist K, Goossens MM, Vaerenberg S, Hopkins S, Catry B, Monnet DL, Goossens H, Suetens C, National Contact Points for the ECDC pilot point prevalence survey, Hospital Contact Points for the ECDC pilot point prevalence survey. The European Centre for Disease Prevention and Control (ECDC) pilot point prevalence survey of healthcare-associated infections and antimicrobial use. Euro Surveill. 2012;17(46):pii=20316. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20316

Article submitted on 15 May 2012 / published on 15 November 2012

A standardised methodology for a combined point prevalence survey (PPS) on healthcare-associated infections (HAIs) and antimicrobial use in European acute care hospitals developed by the European Centre for Disease Prevention and Control was piloted across Europe. Variables were collected at national, hospital and patient level in 66 hospitals from 23 countries. A patient-based and a unit-based protocol were available. Feasibility was assessed via national and hospital questionnaires. Of 19,888 surveyed patients, 7.1% had an HAI and 34.6% were receiving at least one antimicrobial agent. Prevalence results were highest in intensive care units, with 28.1% patients with HAI, and 61.4% patients with antimicrobial use. Pneumonia and other lower respiratory tract infections (2.0% of patients; 95% confidence interval (CI): 1.8–2.2%) represented the most common type (25.7%) of HAI. Surgical prophylaxis was the indication for 17.3% of used antimicrobials and exceeded one day in 60.7% of cases. Risk factors in the patient-based protocol were provided for 98% or more of the included patients and all were independently associated with both presence of HAI and receiving an antimicrobial agent. The patient-based protocol required more work than the unit-based protocol, but allowed collecting detailed data and analysis of risk factors for HAI and antimicrobial use.

Introduction

Healthcare-associated infections (HAIs) and antimicrobial resistance are well known major public health threats. The European Centre for Disease Prevention and Control (ECDC) proposed in 2008 that the total burden of HAIs should be measured regularly and in a standardised manner throughout the European Union (EU) [1]. The initial steps towards standardisation of surveillance of HAIs in Europe had been carried out on surgical site infections and infections in intensive care units by the 'Hospitals in Europe Link for Infection Control through Surveillance (HELICS)' project, from 2000 to 2003 [2-6].

Subsequently, HELICS implemented standardised surveillance of HAIs in 2004 and 2005, and later as part of the 'Improving Patient Safety in Europe (IPSE)' network from 2005 to 2008 [7] which was transferred to ECDC in July 2008. Continuous surveillance, especially prospective active surveillance, is the gold standard [8]. However, repeated point prevalence surveys (PPSs) represent a more feasible alternative for hospital-wide surveillance of all HAIs, while still allowing the estimation of disease burden by HAIs in acute hospitals, and helping to prioritise areas requiring interventions [9]. Based on a review of 30 national or multicentre PPSs in 19 countries that had been carried out between 1996 and 2007 and included a total of 837,450 patients, ECDC estimated in 2008 the prevalence of HAIs in EU acute care hospitals to be on average of 7.1% [1].

However, major methodological differences between these PPSs made comparison between countries impossible [1,10-13]. When coordination of the IPSE network was transferred to ECDC in July 2008, ECDC recommended that surveillance in the EU should include all types of HAIs. Subsequently, the ECDC prepared a protocol for a PPS of HAIs in acute care hospitals, which was finalised in March 2011 [14].

Although most antimicrobials are prescribed in the community [15], the selective pressure they exert is

Healthcare-associated infections in European long-term care facilities: how big is the challenge?

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Citation style for this article:
Suetens C. Healthcare-associated infections in European long-term care facilities: how big is the challenge?. Euro Surveill. 2012;17(35):pii=20259. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20259

Article submitted on 30 August 2012 / published on 30 August 2012

Europe is aging. The percentage of the population in the European Union (EU) aged 65 years and over increased from 9.6% in 1960 to 16.0% in 2010, and is projected to increase to 29.3% (152.6 million) in 2060 [1,2]. The population aged 80 years and over is projected to increase from 16.8 million (4.1%) in 2010 to 43.3 million (11.5%) in 2060, almost as many as the expected percentage of children (0–14 years, 15%) in 2060 [2,3]. At the same time, healthcare systems are striving for cost optimisation, which results, among other things, in shorter hospital stays and early discharge. These two factors combined have led to a rapid rise in the demand for nursing homes and other social and healthcare services for the elderly such as long-term care facilities (LTCFs), residential homes and home care. The Organisation for Economic Co-operation and Development (OECD) estimated that across OECD countries (these include 22 countries of the EU and European Economic Area (EEA)), about 12% of the population aged 65 years and older received some form of long-term care service in 2009 , either at home (64.5% of the services) or in institutions (35.5%) [3]. Based on these figures, the European Centre for Disease Prevention and Control (ECDC) estimates the number of residents in LTCFs in the EU at approximately 3.7 million in 2010, a number that will certainly increase in the coming decades.

Because of age-related dysfunctions of the immune system and physiological changes, the elderly are more sensitive to infection and therefore predisposed to the most frequent infections occurring in nursing homes: urinary tract infections, pneumonia, skin and soft tissue infections and gastro-intestinal infections, in particular those for which previous antibiotic use is a risk factor, such as *Clostridium difficile* infection [4]. Healthcare-associated infections in LTCFs are also associated with severe consequences including debilitation, hospital admission and sometimes death [5]. Because of the ageing population, the frequent transfer of patients from LTCFs to hospitals and back to LTCFs, the increasing prevalence of multidrug-resistant micro-organisms such as meticillin-resistant Staphylococcus aureus (MRSA), extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae and vancomycin-resistant Enterococcus spp. (VRE), and the low availability of infection control resources in these facilities [6,7], prevention and control of healthcare-associated infections in European LTCFs is becoming an increasing challenge.

The number of patients acquiring a healthcare-associated infection in acute care hospitals in the EU has previously been estimated at 4.1 million each year [6], but there is no similar estimate for LTCFS. Facing the lack of EU-wide data on healthcare-associated infections in LTCFs, ECDC provided funding for the Healthcare Associated infections in Long-Term care facilities (HALT) project from December 2008 to May 2011.

The project's aims were to support prevention of healthcare-associated-infections and antimicrobial resistance in European LTCFs and to provide a tool for the assessment of the prevalence of healthcare-associated infections, antimicrobial use as well as performance indicators for infection prevention and control practices and antimicrobial stewardship in LTCFs. A methodology for repeated point prevalence surveys tailored to the LTCF/nursing home setting was developed by HALT and implemented in a Europe-wide network of LTCFs.

The HALT project estimated that there were at least 62,000 LTCFs in the EU in 2010, with a capacity of approximately 3.1 million beds, 58% of which were located in general nursing homes (residents needing 24-hour medical or highly skilled nursing supervision), 32% in residential homes (residents needing 24-hour supervision of daily activities) and 10% in mixed facilities. Even though these figures are probably an underestimate because of the difficulty to collect precise data in several countries, in particular on privately owned LTCFs, the estimated number of long-term care beds was of the same order of magnitude as the above-mentioned estimate of residents in European LTCFs.

After a pilot survey in 2009 [8], a first EU-wide point prevalence survey was performed from May to September 2010, including a total of 64,007 residents surveyed in 722 LTCFs in 25 countries (Austria, Belgium, Bulgaria, Croatia, Cyprus, the Czech Republic,

A pilot validation in 10 European Union Member States of a point prevalence survey of healthcare-associated infections and antimicrobial use in acute hospitals in Europe, 2011

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Citation style for this article:
Reilly JS, Price L, Godwin J, Cairns S, Hopkins S, Cookson B, Malcolm W, Hughes G, Lyytikaïnen O, Coignard B, Hansen S, Suetens C, National Participants in the ECDC pilot validation study. A pilot validation in 10 European Union Member States of a point prevalence survey of healthcare-associated infections and antimicrobial use in acute hospitals in Europe, 2011. Euro Surveill. 2015;20(8):pii=21045. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=21045

Article submitted on 03 July 2014 / published on 26 February 2015

We present a pilot validation study performed on 10 European Union (EU) Member States, of a point prevalence survey (PPS) of healthcare-associated infections (HAIs) and antimicrobial use in Europe in 2011 involving 29 EU/European Economic Area (EEA) countries and Croatia. A total of 20 acute hospitals and 1,950 patient records were included in the pilot study, which consisted of validation and inter-rater reliability (IRR) testing using an in-hospital observation approach. In the validation, a sensitivity of 83% (95% confidence interval (CI): 79–87%) and a specificity of 98% (95% CI: 98–99%) were found for HAIs. The level of agreement between the primary PPS and validation results were very good for HAIs overall (Cohen's kappa (κ): 0.81) and across all the types of HAIs (range: 0.83 for bloodstream infections to 1.00 for lower respiratory tract infections). Antimicrobial use had a sensitivity of 94% (95% CI: 93–95%) and specificity of 97% (95% CI: 96–98%) with a very good level of agreement (κ: 0.91). Agreement on other demographic items ranged from moderate to very good (κ: 0.57–0.95): age (κ: 0.95), sex (κ: 0.93), specialty of physician (κ: 0.87) and McCabe score (κ: 0.57). IRR showed a very good level of agreement (κ: 0.92) for both the presence of HAIs and antimicrobial use. This pilot study suggested valid and reliable reporting of HAIs and antimicrobial use in the PPS dataset. The lower level of sensitivity with respect to reporting of HAIs reinforces the importance of training data collectors and including validation studies as part of a PPS in order for the burden of HAIs to be better estimated.

Introduction

In 2011, the European Centre for Disease Prevention and Control (ECDC) initiated the first European point prevalence survey (PPS) of HAIs and antimicrobial use in acute care hospitals [1] involving 29 European Union (EU)/ European Economic Area (EEA) countries and Croatia. The objective was to estimate the total burden (prevalence) of HAIs and antimicrobial use in European acute care hospitals.

A pilot validation study was undertaken in the first phase of this PPS in 2011 with two major objectives: (i) to test the sensitivity and specificity of reporting HAIs and antimicrobial use and the level of agreement between primary and validation data collectors, whereby this constituted the validation component of the study; (ii) to test the inter-rater reliability (IRR) of hospital data collectors across Europe.

This paper focuses on the aggregated results for several EU Member States of this pilot validation study. Ten EU Member States took part in the validation component (Bulgaria, Finland, Germany, Hungary, Italy, Latvia, Lithuania, Poland, Spain, United Kingdom) and eight of these countries in the IRR component (Bulgaria, Finland, Germany, Italy, Lithuania, Poland, Spain, United Kingdom).

Method

The sample size for the pilot study was calculated to produce validation results overall for the European PPS rather than at individual country specific level. A pilot ECDC PPS had indicated a prevalence of 7.1% and

Standardised surveillance of *Clostridium difficile* infection in European acute care hospitals: a pilot study, 2013

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Citation style for this article:
van Dorp SM, Kinross P, Gastmeier P, Behnke M, Kola A, Delmée M, Pavelkovich A, Mentula S, Barbut F, Hajdu A, Ingebretsen A, Pituch H, Macovei IS, Jovanović M, Wiuff C, Schmid D, Olsen KE, Wilcox MH, Suetens C, Kuijper EJ, for the European Clostridium difficile Infection Surveillance Network (ECDIS-Net) on behalf of all participants. Standardised surveillance of Clostridium difficile infection in European acute care hospitals: a pilot study, 2013. Euro Surveill. 2016;21(29):pii=30293. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.29.30293

Article submitted on 21 January 2016 / accepted on 00 March 2016 / published on 21 July 2016

Clostridium difficile infection (CDI) remains poorly controlled in many European countries, of which several have not yet implemented national CDI surveillance. In 2013, experts from the European CDI Surveillance Network project and from the European Centre for Disease Prevention and Control developed a protocol with three options of CDI surveillance for acute care hospitals: a 'minimal' option (aggregated hospital data), a 'light' option (including patient data for CDI cases) and an 'enhanced' option (including microbiological data on the first 10 CDI episodes per hospital). A total of 37 hospitals in 14 European countries tested these options for a three-month period (between 13 May and 1 November 2013). All 37 hospitals successfully completed the minimal surveillance option (for 1,152 patients). Clinical data were submitted for 94% (1,078/1,152) of the patients in the light option; information on CDI origin and outcome was complete for 94% (1,016/1,078) and 98% (294/300) of the patients in the light and enhanced options, respectively. The workload of the options was 1.1, 2.0 and 3.0 person-days per 10,000 hospital discharges, respectively. Enhanced surveillance was tested and was successful in 32 of the hospitals, showing that *C. difficile* PCR ribotype 027 was predominant (30% (79/267)). This study showed that standardised multicountry surveillance, with the option of integrating clinical and molecular data, is a feasible strategy for monitoring CDI in Europe.

Introduction

After recognition of European outbreaks of *Clostridium difficile* infections (CDIs) associated with the emergence of PCR ribotype 027/NAP1 in 2005, CDI surveillance at country level was encouraged by the European Centre for Disease Prevention and Control (ECDC) [1]. In 2008, an ECDC-supported European CDI survey (ECDIS) identified large intercountry variations in incidence rates and distribution of prevalent PCR ribotypes, with the outbreak-related PCR ribotype 027 being detected in 5% (range: 0–26) of the characterised isolates [2]. The surveillance period was limited to one month and the representation of European hospitals was incomplete; however, this has been the only European (comprising European Union (EU)/European

Health-care-associated infections in neonates, children, and adolescents: an analysis of paediatric data from the European Centre for Disease Prevention and Control point-prevalence survey

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Keywords: prevalence survey, children, neonates, infants, paediatrics, health-care-associated infections, nosocomial infection, Europe, European Centre for Disease Prevention and Control, ECDC, bloodstream infection

Published edited version:
Lancet Infect Dis 2017. Published Online January 12, 2017. http://dx.doi.org/10.1016/S1473-3099(16)30517-5
See Online/Comment http://dx.doi.org/10.1016/S1473-3099(17)30026-9

Clinical Microbiology and Infection 24 (2018) 469–475

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Narrative review

How to: Surveillance of *Clostridium difficile* infections

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ARTICLE INFO

Article history:
Received 29 September 2017
Received in revised form
9 December 2017
Accepted 13 December 2017
Available online 20 December 2017

Editor: L. Leibovici

Keywords:
Clostridium difficile
Clostridium difficile typing
Clostridium difficile infection
Clostridium difficile infection epidemiology
Healthcare-associated infection

ABSTRACT

Background: The increasing incidence of *Clostridium difficile* infections (CDI) in healthcare settings in Europe since 2003 has affected both patients and healthcare systems. The implementation of effective CDI surveillance is key to enable monitoring of the occurrence and spread of *C. difficile* in healthcare and the timely detection of outbreaks.
Aims: The aim of this review is to provide a summary of key components of effective CDI surveillance and to provide some practical recommendations. We also summarize the recent and current national CDI surveillance activities, to illustrate strengths and weaknesses of CDI surveillance in Europe.
Sources: For the definition of key components of CDI surveillance, we consulted the current European Society of Clinical Microbiology and Infectious Diseases (ESCMID) CDI-related guidance documents and the European Centre for Disease Prevention and Control (ECDC) protocol for CDI surveillance in acute care hospitals. To summarize the recent and current national CDI surveillance activities, we discussed international multicentre CDI surveillance studies performed in 2005–13. In 2017, we also performed a new survey of existing CDI surveillance systems in 33 European countries.
Content: Key components for CDI surveillance are appropriate case definitions of CDI, standardized CDI diagnostics, agreement on CDI case origin definition, and the presentation of CDI rates with well-defined numerators and denominators. Incorporation of microbiological data is required to provide information on prevailing PCR ribotypes and antimicrobial susceptibility to first-line CDI treatment drugs. In 2017, 20 European countries had a national CDI surveillance system and 21 countries participated in ECDC-coordinated CDI surveillance. Since 2014, the number of centres with capacity for *C. difficile* typing has increased to 35 reference or central laboratories in 26 European countries.
Implications: Incidence rates of CDI, obtained from a standardized CDI surveillance system, can be used as an important quality indicator of healthcare at hospital as well as country level. **M. Krutova, Clin Microbiol Infect 2018;24:469**

Background

Clostridium difficile, recently reclassified as *Clostridioides difficile*, is a Gram-positive spore-forming ubiquitous bacterium [1]. Toxigenic strains can cause *C. difficile* infection (CDI) with diverse clinical manifestations ranging from mild diarrhoea to life-threatening conditions. The most important modifiable risk factor for CDI is previous antibiotic treatment [2]. European data on CDI epidemiology in acute healthcare derive from a few limited studies with significant differences in their study design and number of participating healthcare facilities [3–7]. In response to an increased CDI incidence and spread of epidemic *C. difficile* strains belonging to ribotype (RT) 027 in Europe since 2003 [2–4], the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) published guidance documents for CDI diagnostics, treatment and infection control [8–10].

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https://doi.org/10.1016/j.cmi.2017.12.008
1198-743X/

BMJ Open

Analysis of the challenges in implementing guidelines to prevent the spread of multidrug-resistant gram-negatives in Europe

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To cite: Tacconelli E, Buhl M, Humphreys H, *et al*. Analysis of the challenges in implementing guidelines to prevent the spread of multidrug-resistant gram-negatives in Europe. *BMJ Open* 2019;**9**:e027683. doi:10.1136/bmjopen-2018-027683

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2018-027683).

Received 2 November 2018
Revised 11 February 2019
Accepted 5 April 2019

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ABSTRACT

Objective The main objective of the study was to investigate major differences among European countries in implementing infection prevention and control (IPC) measures and reasons for reduced compliance.

Design An online survey including experts in IPC and a gap analysis were conducted to identify major limitations in implementing IPC guidelines.

Setting Europe.

Main outcome measures Four areas were targeted: (1) healthcare structure, (2) finances, (3) culture and (4) education and awareness. Perceived compliance to IPC measures was classified as low (<50%), medium (50% to 80%) and high (>80%). Countries were classified in three regions: North-Western Europe (NWE), Eastern Europe (EE) and Southern Europe (SE).

Results In total, 482 respondents from 34 out of 44 (77.3%) European countries participated. Respondents reported availability of national guidelines to control multidrug-resistant Gram-negatives (MDR-GN) in 20 countries (58.0%). According to participants, compliance with IPC measures ranged from 17.8% (screening at discharge) to 96.0% (contact precautions). Overall, three areas were identified as critical for the compliance rate: (1) number of infection control staff, (2) IPC dedicated educational programmes and (3) number of clinical staff. Analysis of reasons for low compliance showed high heterogeneity among countries: participants from NWE and SE deemed the lack of educational programmes as the most important, while those from EE considered structural reasons, such as insufficient single bed rooms or lacking materials for isolation, as main contributors to the low compliance.

Conclusions Although national guidelines to reduce the spread of MDR-GN are reported in the majority of the European countries, low compliance with IPC measures was commonly reported. Reasons for the low compliance are multifactorial and vary from region to region. Cross-country actions to reduce the spread of MDR-GN have to consider structural and cultural differences in countries. Locally calibrated interventions may be fruitful in the future.

Strengths and limitations of this study

- By summarising the opinions of almost 500 experts, covering ~75% of all European countries, this analysis on the implementation of infection prevention and control (IPC) measures is the most comprehensive in Europe, even though some countries were over-represented.
- Combining open online survey, direct emailing and offering an open booth for attendees at the European Congress of Clinical Microbiology and Infectious Diseases conference, this study summarises the opinion of a large range of professionals in the field.
- The length of the survey may have been perceived as an obstacle by IPC professionals, and thus, decreased response rate potentially leading to a bias.

BACKGROUND

The global increase of healthcare-associated infections (HAI) presents a growing concern in healthcare worldwide. According to the European Centre for Disease Prevention and Control (ECDC), the annual number of HAI exceeds 2.6 million and produces the highest estimated amount of disability-adjusted-life-years, surpassing all other reported communicable diseases in the European Union and European Economic Area.[1] Multidrug-resistant Gram-negative (MDR-GN) bacteria have become increasingly common as a cause for HAI, such as central line-associated bloodstream infections, wound or surgical site infections and catheter-associated urinary tract infections.[2 3] The US National Healthcare Safety Network identified Gram-negative bacteria as the cause of more than 30% of HAI overall, with almost 70% of all infections due to Gram-negatives occurring in the intensive care setting.[4] These infections significantly increase the risk of short- and long-term mortality and hospital

JAMA Network Open

Original Investigation | Critical Care Medicine

Association of *Staphylococcus aureus* Colonization and Pneumonia in the Intensive Care Unit

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Abstract

IMPORTANCE Carriage of *Staphylococcus aureus* is associated with *S aureus* infection. However, associations between *S aureus* carriage and the development of *S aureus* intensive care unit (ICU) pneumonia (SAIP) have not been quantified accurately, and interpretation of available data is hampered because of variations in definitions.

OBJECTIVE To quantify associations of patient-related and contextual factors, including *S aureus* colonization status, with the occurrence of SAIP.

DESIGN, SETTING, AND PARTICIPANTS This cohort study was conducted in ICUs of 30 hospitals in 11 European countries, geographically spread across 4 regions. Among patients with an anticipated length of stay 48 hours or longer who were undergoing mechanical ventilation at ICU admission, *S aureus* colonization was ascertained in the nose and lower respiratory tract. From this group, *S aureus*–colonized and noncolonized patients were enrolled into the study cohort in a 1:1 ratio. Data analysis was performed from May to November 2019.

MAIN OUTCOMES AND MEASURES SAIP was defined as any pneumonia during the ICU stay developing 48 hours or more after ICU admission with *S aureus* isolated from lower respiratory tract specimens or blood samples. The incidence of SAIP was derived in the study cohort and estimated on the weighted incidence calculation for the originating overarching population, while taking competing events into account. Weighted risk factor analysis was performed using Cox multivariable regression.

RESULTS The study cohort consisted of 1933 patients (mean [SD] age, 62.0 [16.0] years); 1252 patients (64.8%) were men, and 950 patients (49.1%) were *S aureus* carriers at ICU admission. In all, 304 patients (15.7%) developed ICU-acquired pneumonia, of whom 131 patients (6.8%) had SAIP. Weighted SAIP incidences were 11.7 events per 1000 patient-days in the ICU for *S aureus*–colonized patients and 2.9 events per 1000 patient-days in the ICU for noncolonized patients (overall incidence, 4.9 events per 1000 patient-days in the ICU). The only factor independently associated with SAIP was *S aureus* colonization status at ICU admission (cause-specific hazard ratio, 3.6; 95% CI, 2.2-6.0; $P < .001$). There were marked regional differences in SAIP incidence and cause-specific hazard ratios for colonization status.

CONCLUSIONS AND RELEVANCE SAIP incidence was 4.9 events per 1000 ICU patient-days for patients undergoing mechanical ventilation at ICU admission (or shortly thereafter). The daily risk of SAIP was 3.6 times higher in patients colonized with *S aureus* at ICU admission compared with noncolonized patients.

JAMA Network Open. 2020;3(9):e2012741. doi:10.1001/jamanetworkopen.2020.12741

Key Points

Question What is the incidence density of *Staphylococcus aureus* intensive care unit pneumonia (SAIP) in Europe, and which factors are associated with the risk of SAIP?

Findings In this cohort study of 1933 participants, the weighted incidence density of SAIP was 4.9 events per 1000 intensive care unit patient-days, and *S aureus* colonization was the only factor independently associated with SAIP.

Meaning These findings suggest that SAIP incidence may be higher than initially perceived, and future interventions to prevent SAIP should focus on patients colonized with *S aureus* to achieve a higher efficacy.

+ Supplemental content

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Critical Care

RESEARCH

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Plasma protein biomarkers reflective of the host response in patients developing Intensive Care Unit-acquired pneumonia

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Abstract

Background Immune suppression has been implicated in the occurrence of pneumonia in critically ill patients. We tested the hypothesis that Intensive Care Unit (ICU)-acquired pneumonia is associated with broad host immune aberrations in the trajectory to pneumonia, encompassing inflammatory, endothelial and coagulation responses. We compared plasma protein biomarkers reflecting the systemic host response in critically ill patients who acquire a new pneumonia (cases) with those who do not (controls).

Methods We performed a nested case–control study in patients undergoing mechanical ventilation at ICU admission with an expected stay of at least 48 h enrolled in 30 hospitals in 11 European countries. Nineteen host response biomarkers reflective of key pathophysiological domains were measured in plasma obtained on study inclusion and day 7, and—in cases—on the day of pneumonia diagnosis.

Results Of 1997 patients, 316 developed pneumonia (15.8%) and 1681 did not (84.2%). Plasma protein biomarker analyses, performed in cases and a randomly selected subgroup of controls (1:2 ratio to cases, $n=632$), demonstrated considerable variation across time points and patient groups. Yet, cases showed biomarker concentrations suggestive of enhanced inflammation and a more disturbed endothelial barrier function, both at study enrollment (median 2 days after ICU admission) and in the path to pneumonia diagnosis (median 5 days after ICU admission). Baseline host response biomarker aberrations were most profound in patients who developed pneumonia either shortly (< 5 days, $n=105$) or late (> 10 days, $n=68$) after ICU admission.

Conclusions Critically ill patients who develop an ICU-acquired pneumonia, compared with those who do not, display alterations in plasma protein biomarker concentrations indicative of stronger proinflammatory, procoagulant and (injurious) endothelial cell responses.

Trial registration: ClinicalTrials.gov Identifier: NCT02413242, posted April 9th, 2015.

Keywords Critical care, Respiratory tract infections, Biomarkers

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