Rapid Increase in Multidrug-Resistant Enteric Bacilli Blood Stream Infection After Prostate Biopsy—A 10-Year Population-Based Cohort Study

Markus Aly,[1,2]* Robert Dyrdak,[3,4] Tobias Nordström,[1,2] Shah Jalal,[3,5] Caroline E. Weibull,[2] Christian G. Giske,[3,4] and Henrik Grönberg[2]

[1]*Department of Clinical Sciences, Danderyd Hospital, Karolinska Institute, Stockholm, Sweden*
[2]*Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden*
[3]*Department of Clinical Microbiology, Karolinska University Hospital, Stockholm, Sweden*
[4]*Department of Microbiology and Tumour and Cell Biology (MTC), Karolinska Institute, Stockholm, Sweden*
[5]*Department of Clinical Microbiology, Unilabs Stockholm, Stockholm, Sweden*

BACKGROUND. Bloodstream infection following a transrectal prostate biopsy is a well-known and feared complication. Previous studies have shown an increase in multi-resistant bacterial infections as a consequence of higher usage of antibiotics in investigated populations. Our aim was to analyze bacterial resistance patterns in positive blood cultures, after prostate biopsies in Stockholm, Sweden, where the use of antibiotics has been low and decreasing during the last 10 years.

METHODS. From the three pathology laboratories in Stockholm, reports of prostate examinations were retrieved (n = 56,076) from 2003 to 2012. By linking men to the National Patient Register all but prostate core biopsies were excluded (n = 12,024). Prostate biopsies in men younger than 30 years of age were excluded (n = 5) leaving 44,047 biopsies for analysis. From laboratory information systems data regarding blood cultures were retrieved. Proportions of blood cultures within 30 days by year were calculated. Crude and adjusted logistic regression models were used to estimate ORs.

RESULTS. In total, 44,047 prostate biopsies were performed in 32,916 men over 10 years. On 620 occasions a blood culture was drawn within 30 days of the biopsy; 266 of these were positive. The proportions with positive blood cultures in 2003 and 2012 were 0.38 and 1.14%, respectively. The proportion of multidrug-resistant bacteria increased significantly during the study. In the crude and the adjusted analysis, the year of biopsy and Charlson Comorbidity Index were associated with the risk of having a positive blood culture.

CONCLUSION. Multidrug-resistant enteric bacilli are becoming a problem in Sweden, despite low antimicrobial use. Men need to be informed about the increasing risks of infectious complications of transrectal prostate biopsy. One out of 50 men undergoing a prostate biopsy will develop symptoms suggestive of a bloodstream infection after the biopsy and one in 100 men will have a positive blood culture. *Prostate 75:947–956, 2015.*

Grant sponsor: Swedish Cancer Society; Grant sponsor: Swedish Research Council (CRisP); Grant sponsor: Jenny Hagstrand and Sigfrid Linners Memorial Fund.

*Correspondence to: Markus Aly, MD, Department of Clinical Sciences, Danderyd Hospital, Karolinska Institute, Stockholm, Sweden.
E-mail: markus.aly@ki.se
Received 11 December 2014; Accepted 16 January 2015
DOI 10.1002/pros.22979
Published online 23 March 2015 in Wiley Online Library
(wileyonlinelibrary.com).

KEY WORDS: **blood-stream infection; prostate; biopsy; complications; antimicrobial resistance**

INTRODUCTION

Bloodstream infection (BSI) following a transrectal prostate biopsy is a well-known and feared complication. In a Canadian study it was reported that the proportion of positive urine and blood cultures with ciprofloxacin-resistant, Gram-negative bacilli had doubled within the last 2 years of the study, at which point they were being detected in almost 1.4% of men undergoing a prostate biopsy [1]. Another Canadian study reports that in 18 cases with positive blood cultures, *Escherichia coli* was responsible for 14 cases, in whom 86% of these cultures featured ciprofloxacin-resistant strains [2]. Others report that where prophylactic antibiotics were not routinely used, 8% of the men undergoing a prostate biopsy suffered from infectious complications [3]. In a review article published in 2013, the infectious complication rate was reported to be between 0.5 and 4% [4]. A Swedish study, based on the National Prostate Cancer Register, indicated that 1% of all men diagnosed with prostate cancer at a prostate biopsy, were hospitalized due to infectious complications within 30 days of a prostate biopsy and almost 6% of men undergoing the procedure were prescribed antibiotics commonly used for treating urinary tract infections [5].

It has been shown that the prevalence of ciprofloxacin-resistant enteric bacilli is more common in countries with high use of fluoroquinolones and that the use of these antibiotics is a significant cause in the progression of fluoroquinolone resistance in bacteraemic *E. coli* [6,7]. Sweden has had a restriction policy on antimicrobial use. In terms of defined daily doses (DDDs) and packages per 1,000 inhabitants, Sweden is among the countries with the lowest use of antibiotics in an outpatient setting [8]. In terms of DDD/1,000/day, the use has decreased by 17–27% from 2007 to 2013 [9].

Our hypothesis was that severe infectious complications after prostate biopsies have increased during the last years. It is important to identify the rising problem of multidrug-resistant enteric bacilli in countries that have historically been able to avoid the worst of this clinical challenge.

METHODS

Data Sources and Study Population

This investigation is a retrospective population cohort study. Using data from all three pathology laboratories in Stockholm, the Karolinska University Laboratory (KUL), Aleris Medilab (AM) and Unilabs (UL), we identified histological examinations of the prostate from January 1, 2003 to December 31, 2012 (n = 56,076). By linking the men to the National Patient Register (NPR) we could exclude specimens retrieved by transurethral resection of the prostate (TURP) and other procedures (n = 12,024). We further excluded histological exams performed in men younger than 30 years old at the time of biopsy (n = 5) (Fig. 1).

The men were linked to the STHLM-0 database, which provides access to all prostate-specific antigen (PSA) test results in Stockholm County [10], and to the Swedish Cancer Register to confirm prostate cancer diagnoses. To define whether or not a prostate biopsy was positive for cancer or not, we used SNOMED codes (Supplementary Table S1). Thereafter the men were linked to data from the laboratory information systems of the two laboratories (KUL, UL) that perform all microbiological analyses of blood cultures in Stockholm to analyze all blood cultures drawn within 30 days of the prostate biopsy.

The cohort were again linked to the NPR to identify men who had been admitted to any hospital in Sweden within 30 days of the prostate biopsy. We identified infectious-related discharge codes using the International Classification of Diseases and Related Health Problems, 10th revision (ICD-10) (Supplementary Table S2). Only the first hospital admittance was included in the analyses. Using the Swedish Intensive Care Unit Register (www.icuregswe.org, accessed April 1, 2014), which was started in 2005 and received good coverage in 2009, we identified men who had been admitted to any intensive care unit (ICU) in Sweden within 30 days of the prostate biopsy. Further using the Swedish Cause of Death Register, we added information on death date and underlying cause of death to calculate the expected and observed mortality within 30 and 90 days.

The Charlson Comorbidity Index (CCI) score was calculated based on ICD-10 codes from the Patient Register in Sweden preceding the date of the prostate biopsy. Prostate cancer diagnosis at the time of the follow-up biopsy was excluded in the calculation of CCI scores.

Linkage between registers was achieved by utilizing Swedish personal identification numbers [11]. The final study population encompassed 32,916 men with a total of 44,047 prostate biopsies (Fig. 1). Background population mortality rate was acquired from www.mortality.org (accessed on September 1, 2014) using the rates for Swedish men.

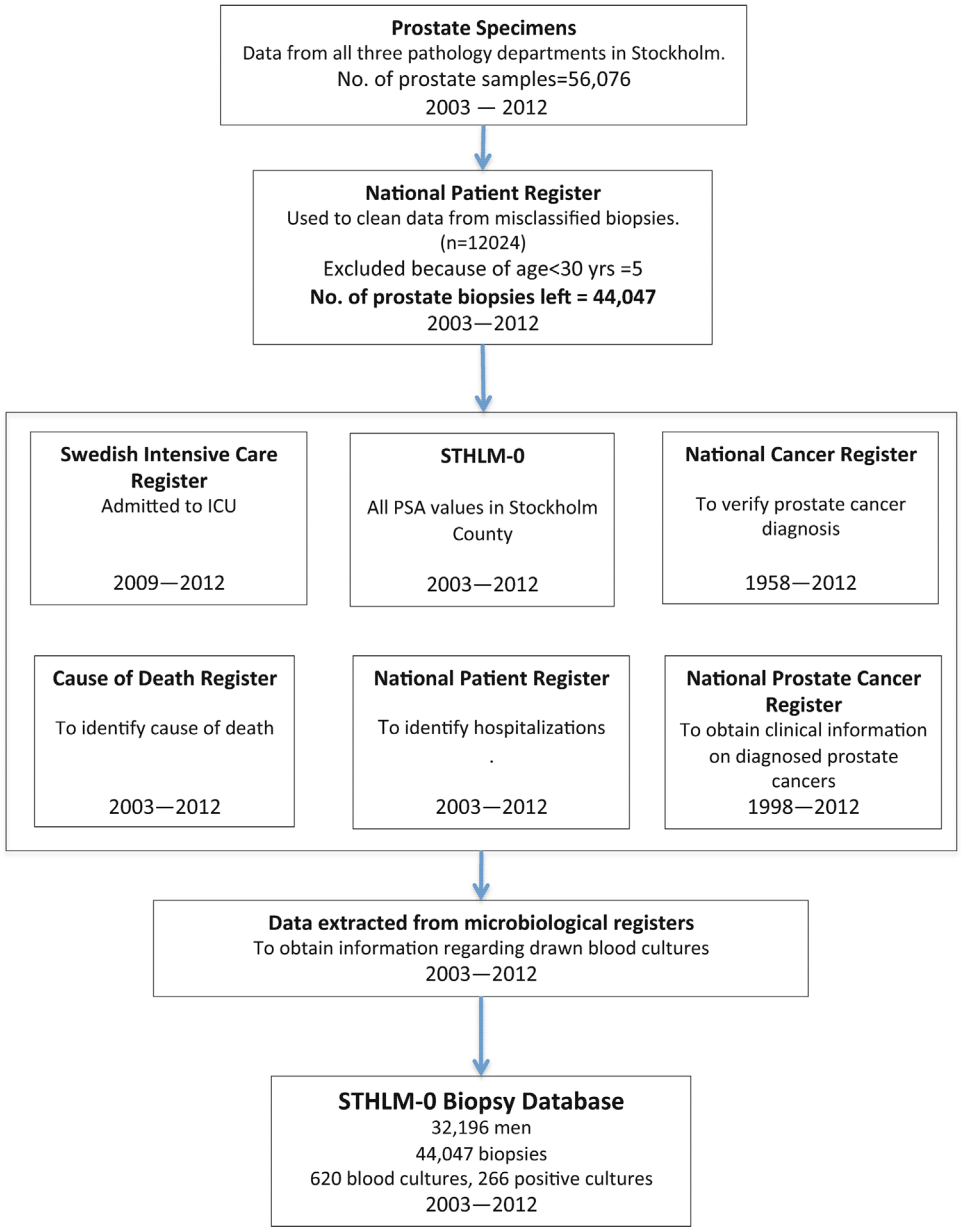

Fig. 1. Overview of the study population and data retrieval process.

Antimicrobial Resistance Patterns

For resistance patterns, the most common pathogens in our sample were selected, namely *E. coli, Enterococcus* spp., *Enterobacter* spp., *Klebsiella* spp., *Proteus* spp., *Staphylococcus* aureus,and coagulase--negative staphylococci (CoNS), as well as the fraction of Gram-negative enteric bacilli producing extended spectrum β-lactamase (ESBL). Antimicrobial resistance patterns for ciprofloxacin and trimethoprim–sulfametoxazole, were investigated. Cefotaxime and gentamicin were included since these antimicrobials are commonly used in hospital settings. A small fraction of the cultures had growth of more than one bacterium, but only the first reported bacterium was used in the calculations.

Prophylactic Antibiotics

In our study population during the years of the study, antibiotic prophylaxis was recommended for all patients undergoing a prostate biopsy. At first, either trimethoprim–sulfametoxazole or a fluoroquinolone was recommended administered before the prostate biopsy [12–14]. After a prospective trial in southern Sweden in 2006 the recommended antibiotic

was ciprofloxacin 750 mg, administered once in direct conjunction with the procedure for healthy men with no risk factors [15].

Statistical Analysis

Frequency and proportion of biopsies that were followed by a blood culture within 30 days were calculated, as was the proportion of positive cultures and bacteria findings.

Crude and adjusted logistic regression models were used to estimate odds ratios (ORs) with 95% confidence intervals (CIs) as measures of relative risk (RR) of having a positive blood culture. The variable of main interest was calendar year of biopsy. Other variables analyzed in the crude regression models were age (<50, 50–59, 60–69, 70–79, and ≥80 years), PSA value (<3, 3–10, 10–20, >20), cancer status at biopsy, CCI score (0, 1, ≥2) and number of previous biopsies. To assess possible linear trends, all variables in the adjusted model were also included, one at a time, as continuous. Linearity was tested using the Wald test.

The Cochrane–Armitage test for trend was used for significance in resistance patterns over time in supplemental data on overall BSIs in Sweden (supplementary Fig. S1).

All models were adjusted for the correlation between biopsies using the sandwich estimator of variance for clustered data (where biopsies from the same man were considered a cluster).

To evaluate whether men undergoing a prostate biopsy experience higher mortality, we compared the 30- and 90-days mortality rate in the study population with that in the general male population in Sweden, by calculating age-standardized mortality ratios (SMRs) a with 95% CIs.

All statistical analysis were done using Stata 11.2 for Mac (StataCorp, College Station, TX). The study was approved by the regional ethics committee at Karolinska Institute, Stockholm, Sweden (No. 2012/438–31/3, 2013/2088–32, 2014/460–32).

RESULTS

During 2003–2012, we found records on 44,047 prostate biopsies performed in 32,916 men. The total number of men undergoing at least one blood culture within 30 days of the prostate biopsy was 620 and the number of positive blood cultures was 266.

The total number of men admitted to hospital was 644, with 19 patients being treated at an ICU within 30 days of the prostate biopsy.

The proportion of men with a positive blood culture within 30 days of the biopsy increased from 0.38% in 2003 to 1.14% in 2012 (Table I). At the same time the proportion of men who underwent a blood culture increased from 1.15% in 2003 to 2.32% in 2012 (Fig. 2). The proportion of men admitted to hospital and discharged with an ICD-10 code related to an infectious complication also increased, from 1.26% to 1.85%, during this time period (Fig. 2). The odds of having a positive blood culture were more than three times higher in 2012 compared with 2003 (OR = 3.01; 95%CI 1.64–5.50) (Table I). This effect was still present in the adjusted analysis (OR = 3.64; 95%CI 1.64–8.07). Moreover, the test of linear trend for calendar year of biopsy was significant in the adjusted model ($P < 0.001$).

Men younger than 49 had an increased risk of a positive blood culture, as compared with men aged 60–69 at biopsy. The increased risk in younger men remained after adjusting the model for CCI score, number of previous biopsies, and PSA (OR = 2.79; 95%CI 1.54–5.05) (Table I). Level of PSA did not affect the risk of having a positive blood culture.

Men with a higher CCI score had increased risk of having a positive blood culture after a prostate biopsy. The results were robust in the adjusted model as well as the crude model (Table I).

A total of 266 positive blood cultures with antibiograms were available. *E. coli* was the most common pathogen found in cultures (n = 227), followed by *Klebsiella* spp. (n = 10), other Enterobacteriaceae (n = 7) and *S. aureus* (n = 7). In total twenty men had a culture showing growth of ESBL-producing enteric bacilli, in most cases *E. coli*. Ninety-seven cultures were ciprofloxacin-resistant and 95 were trimethoprim–sulfametoxazole-resistant. Altogether 43 cultures showed growth of bacteria resistant to gentamicin and 19 were resistant to cefotaxime (Supplementary Table S3). Both the total number and the proportion of resistant bacteria increased significantly (P for trend <0.05) over the years (Fig. 3).

In 2003–2010 there were only two detected cases among our study population, of ESBL-producing enteric bacilli. In 2011 and 2012, however, 18 patients had a positive blood culture with ESBL-producing enteric bacilli. The proportion of patients suffering from a BSI with a ciprofloxacin-resistant bacterial strain increased from 0% in 2003 to 19% in 2012, with total number of blood cultures analyzed as the denominator. The same pattern was seen for the other antibiotics tested (Fig. 3). Test of linear trend for increase in resistance, in relation to year of prostate biopsy, to cefotaxime (OR 1.44; 95%CI 1.12–1.86), ciprofloxacin (OR 1.15; 95%CI 1.05–1.26), and trimethoprim–sulfametoxazole (OR 1.16; 95%CI 1.06–1.27) was significant ($P < 0.05$), as was the OR for having ESBL-producing bacteria in relation to year of pros-

TABLE I. Frequency and Proportions of Blood Cultures Drawn Within 30 Days of Prostate Biopsies Performed Between 2003 and 2012 in Stockholm, Sweden, Showing Odds Ratios (ors) With 95% Confidence Intervals (cis) Calculated by Crude and Adjusted Logistic Regression Analysis

		No. of positive blood cultures		Crude model		Adjusted model		
		No	(%)	OR	95%CI	OR	95%CI	Total
		266	(0.60)					44,047
Age, years								
	≤49	15	(1.69)	2.91	1.70–4.97	2.79	1.54–5.05	888
	50–59	55	(0.60)	1.03	0.75–1.41	1.20	0.86–1.66	9,116
	60–69	125	(0.59)	1.00	ref	1.00	ref	21,282
	70–79	53	(0.53)	0.90	0.65–1.25	0.75	0.54–1.06	10,002
	≥80	18	(0.65)	1.11	0.68–1.83	0.79	0.46–1.37	2,759
PSA level, ng/ml								
	<3	31	(0.80)	1.29	0.88–1.90	1.12	0.76–1.66	3,852
	3–10	161	(0.62)	1.00	ref	1.00	ref	21,714
	10–20	29	(0.45)	0.72	0.49–1.08	0.79	0.53–1.18	6,208
	>20	27	(0.70)	1.12	0.74–1.68	1.02	0.65–1.59	4,076
	missing	18	(0.44)	–	–			4,091
Cancer status at biopsy								
	No cancer	148	(0.57)	1.00	ref	1.00	ref	25,926
	Cancer[a]	118	(0.65)	1.14	0.90–1.46	1.07	0.82–1.39	18,121
Year of biopsy								
	2003	13	(0.38)	1.00	ref	1.00	ref	3,405
	2004	16	(0.36)	0.95	0.45–1.98	1.24	0.50–3.1	4,394
	2005	16	(0.33)	0.88	0.41–1.86	0.95	0.36–2.51	4,784
	2006	16	(0.38)	0.99	0.47–2.05	1.19	0.48–2.97	4,248
	2007	19	(0.46)	1.21	0.60–2.44	1.30	0.54–3.15	4,130
	2008	22	(0.52)	1.37	0.69–2.73	1.63	0.69–3.86	4,199
	2009	32	(0.69)	1.82	0.95–3.48	2.27	0.99–5.18	4,616
	2010	36	(0.78)	2.06	1.09–3.88	2.54	1.12–5.76	4,604
	2011	40	(0.84)	2.22	1.18–4.15	2.61	1.16–5.89	4,749
	2012	56	(1.14)	3.01	1.64–5.50	3.64	1.64–8.07	4,918
Charlson Comorbidity Index score								
	0	145	(0.45)	1.00	ref	1.00	ref	32,153
	1	44	(0.82)	1.82	1.29–2.57	1.89	1.33–2.72	5,372
	2+	77	(1.18)	2.64	2.00–3.48	2.67	1.98–3.60	6,522
Number of previous biopsies								
	0	212	(0.64)	1.00	ref	1.00	ref	32,916
	1	41	(0.52)	0.81	0.58–1.14	0.81	0.57–1.14	7,817
	≥2	13	(0.39)	0.79	0.35–1.07	0.55	0.30–0.99	2,272

PSA, prostate-specific antigen.
[a]Cancer was defined as a cancer either detected at that biopsy or diagnosed at a previous biopsy.

tate biopsy (OR 1.55; 95%CI 1.13–2.14) (Supplementary Table S3).

Within 30 and 90 days, a total of 67 and 175 men, respectively, died, which corresponds to 0.15 and 0.40% of the total study population. Among men dying within 30 days of prostate biopsy, one man died of BSI; none due to UTIs; two men died following other infections such as pneumonia; and one man died following surgical procedures. The corresponding numbers after 90 days was five due to infectious causes and one due to surgical procedures (Table II).

The observed number of deaths in men >70 years of age in our study was in the same range as compared to the general male population, both within 30 (SMR = 0.99; 95%CI 0.76–1.30) and within 90 (SMR = 0.87; 95%CI 0.74–1.03) days of biopsy. For men <70 years at biopsy, the observed number of deaths was significantly lower than expected (SMR = 0.57; 95%CI

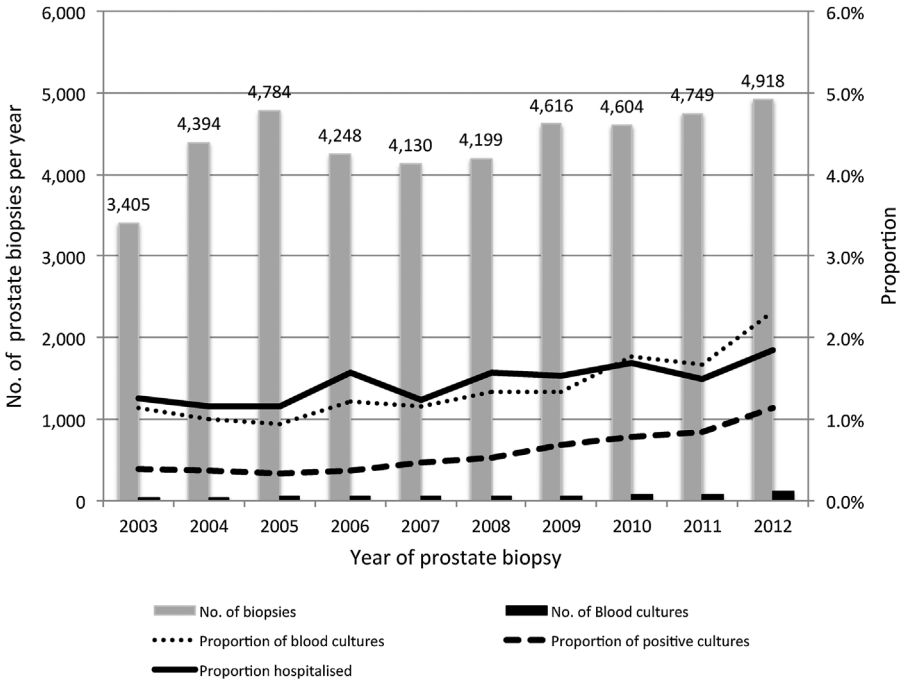

Fig. 2. Number of prostate biopsies, and blood cultures drawn in these patients, each year from 2003 to 2012. The graph also shows the proportion of men having a positive blood culture drawn within 30 days of biopsy, and the proportion of men being admitted to hospital within 30 days of biopsy (and discharged with an International Classification of Diseases and Related Health Problems (ICD) code related to an infection).

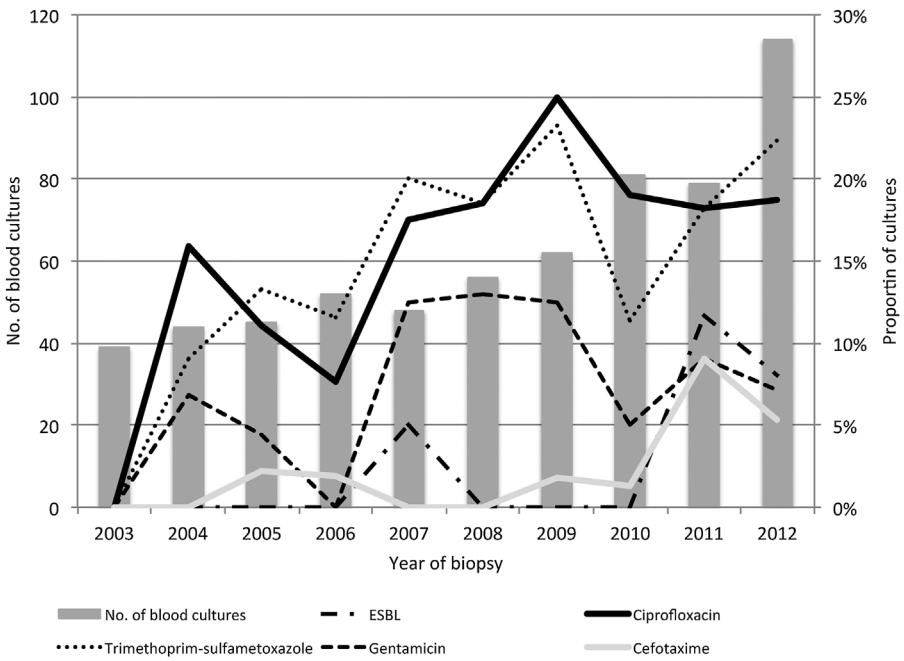

Fig. 3. Results from blood cultures with respect to resistance patterns. Lines refer to the proportion of cultures, which that are resistant to the tested antibiotic in relation to the total number of cultures. The tests for trend, using logistic regression, were significant for increase in resistance to extended spectrum β-lactamase (ESBL), ciprofloxacin, trimethoprim–sulfametoxazole, and cefotaxime, but not to gentamicin (Supplementary Table S1). Enterococcus was not included in the proportion calculated for resistance, nor was ESBL.

TABLE II. Cause of Death Within 30 and 90 Days Following Prostate Biopsy in Men Undergoing the Procedure in Stockholm, Sweden, 2003–2012

	Within 30 days		Within 90 days	
Cause of death	No. of deaths	No. of blood cultures drawn	No. of deaths	No. of blood cultures drawn
Bloodstream infection (septicaemia)	1	1	1	1
Urinary tract infection	0	0	2	0
Other infections	2	0	2	0
Prostate cancer	27	7	51	11
Other (not prostate) cancer	19	6	57	14
Coronary/arterial/pulmonary	11	1	39	2
Gastrointestinal causes–not cancer	0	0	4	0
Surgical procedures	1	1	1	1
Other	6	2	18	3
Total No. of deaths	67	18	175	32
Proportion	**0.15%**		**0.40%**	

0.34–0.94 for within 30 days, and SMR = 0.51; 95%CI 0.38–0.70 for within 90 days) (Table III).

DISCUSSION

The proportion of men with a positive blood culture within 30 days of biopsy increased from 0.38% in 2003 to 1.14% in 2012. During this time no known change was introduced in the handling of patients, concerning either patients with a suspected BSI or the handling of blood culture specimens. The increase in the proportion of positive cultures is likely explained by a change in virulence of the bacteria causing the infection. Carignan and co-authors report that 2.15% of men undergoing a prostate biopsy in 2010–2011 experienced symptoms of infection within 30 days. Of men with infectious symptoms, 42% had a positive blood culture [1]. In our study the proportion of men undergoing a blood culture in 2012 was 2.32%, and more than half of these blood cultures were positive (52%). The figures presented by Carignan et al. in their nested case-control study are based on a wider definition of infectious symptoms than used in our study, suggesting that the problem with severe complications is greater than earlier reported.

The proportion of positive cultures with a bacterium resistant to ciprofloxacin and to trimethoprim–sulfametoxazole during 2012 was 36 and 42%, respectively. This implies that these antibiotics should not be used as empirical treatment for men hospitalized due to an infection after a prostate biopsy.

Year of prostate biopsy was highly associated with the risk of a positive blood culture. This trend was strong and it is expected that the risk will increase over the forthcoming years. When looking at available risk factors for a positive blood culture we found that the CCI score was highly associated with the outcome. This emphasizes the fact that men with several comorbidities are at greater risk of post-biopsy infection, which should be recognized when deciding on a prostate biopsy.

Younger men also seemed to have an increased risk compared with older men, when adjusting for CCI. This suggests that elevated PSA levels indicating the need for a prostate biopsy in younger men may be elevated for reasons other than prostate cancer, such

TABLE III. Age-standardized Mortality Ratios (smrs) With 95% Confidence Intervals (cis) Comparing 30- and 90-Days Mortality Between Men With a Prostate Biopsy and the General Swedish Male Population

	Age at biopsy, yrs	Observed	Expected	SMR	95%CI	
30-days mortality	<70	15	26.6	0.57	0.34	0.94
	≥70	52	52.3	0.99	0.76	1.30
	Total	67	78.9			
90-days mortality	<70	40	78.3	0.51	0.38	0.70
	≥70	135	154.7	0.87	0.74	1.03
	Total	175	233			

as infections. Overall, the PSA level did not seem to affect the risk of having a positive blood culture.

There was no obvious association between the number of previous biopsy sessions and the risk of having a positive blood culture, although there was a tendency in the adjusted model that men with more than two previous biopsies had a slightly lower risk of having a positive blood culture. The reason behind this is unknown but a partial explanation might be that the physician performing the biopsy is aware of the previous biopsies and uses another prophylactic regimen.

In our cohort only two cases of ESBL-producing enteric bacilli caused an infection before 2010, while 18 cases were detected post-2010. During the last years a statistically significant increase in these bacteria has been seen in general in Sweden (supplementary data Fig. S1), although a decrease in the prescription rate of several antibiotics, including fluoroquinolones, has been observed [9]. It has been shown in a British study that men traveling abroad not long before a prostate biopsy have higher risk (RR = 2.7) of infectious complications compared with men who have not been abroad [16]. Foreign travel appears to be a risk factor for acquiring multi-resistant Enterobacteriacea [17,18]. Part of the explanation that the rates of resistant bacteria increase in Sweden might be related to the travel habits of Swedes. In 2012 there were >1,100,000 travels from Sweden to countries known to have a high prevalence of multi--resistant bacteria, such as Thailand, India, Turkey, and Egypt [19]. It has been shown that 24% of people traveling outside northern Europe are asymptomatic carriers of ESBL-producing *E. coli* upon arrival in Sweden, and such strains very often carry resistance to other drug classes, such as fluoroquinolones [20]. After a clinical infection with ESBL-producing enteric bacilli, a Swedish study found that 43% of patients still had positive faecal cultures up to 1 year after the infection [21]. It is unclear how long asymptomatic persons carry ESBL-producing bacteria. Such strains are known to be frequently resistant to fluoroquinolones, trimethoprim–sulfametoxazole, cephalosporins, and aminoglycosides [20]. This risk factor could not be assessed in our study, but it should be emphasized that taking a careful history of the patient with regard to recent travels could influence the choice of prophylactic antibiotics.

Previous studies have discussed a more individualized prophylactic regimen based on risk factors or rectal swabs [1,22,23]. Although this would likely help the individual patient, it does not solve the larger problem regarding the amounts of antibiotics used and the fear that enteric bacilli will eventually develop resistance to these antibiotics as well. A transperineal approach could lower the risk of infections [24]. However, this route to obtain prostate tissue for histological examination is a more complex, expensive and time-consuming procedure, which would have large effects on the health care system.

The risk of serious complications after a prostate biopsy is increasing. However, the mortality rate from complications in this population is lower compared with mortality in the general population. Our numbers are in line with the findings in the Swedish part of the European Randomized Study of Screening for Prostate Cancer [25]. Care has to be taken when interpreting the lower number of deaths in our study since this most likely could be attributed to a selection bias at the time of the biopsy.

Study limitations include the retrospective design and the lack of information on individual prophylaxis used at the time of biopsy. The number of men being treated at ICU is an underestimation, as this register did not have an acceptable coverage until 2009.

Objections could be raised against using Swedish men as the standard population when calculating SMRs. One could argue for use of a population more comparable to our cohort, such as men undergoing PSA tests. However, since this test has been taken in >75% of the male adult population of Stockholm [10], it is our belief that this would not affect the analysis and that using the background rate for Sweden is adequate.

The results of this study reflect the situation in an area with a history of low rates of multidrug resistant bacteria, low antibiotic use in the population, with low numbers of loss of follow-up. Antibiotic use and microbiological resistance patterns are different in different populations thus making generalizations to other populations difficult; we believe that this study reflects the situation in a population where large efforts have been taken to reduce unnecessary antibiotic use in general and despite this a rapid increase is seen.

CONCLUSION

Multidrug-resistant enteric bacilli are becoming a problem in Sweden, despite low antibiotic use in the Swedish population. Men need to be informed about the increasing risks of infectious complications of transrectal prostate biopsy. One out of 50 men undergoing a prostate biopsy will have symptoms suggestive of a BSI within 30 days of the biopsy and one in 100 men will have a positive blood culture.

ACKNOWLEDGEMENTS

We wish to express our gratitude to Mariam Lashkariani and Astrid Björklund for excellent

management of our databases. We would also like to express our thanks to Aleris Medilab, Karolinska University Laboratory and Unilabs for excellent collaboration. Thanks go to the Swedish Intensive Care Register for their cooperation. Appreciation is also expressed to The National of Board of Health and Welfare for their help in retrieving data. Finally, we would like to thank the staff working at the National Prostate Cancer Register for their cooperation.

Author Contribution

MA, RD, CG, CW, and HG conceived and designed the study. MA, TN, RD, SJ, and CG acquired the data. MA and CW analyzed the data and performed the statistical analysis. All authors interpreted the data. MA drafted the manuscript. All authors critically revised the manuscript and approved the submitted version. HG, MA, and TN were involved obtained funding. MA had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Competing Interests

All authors have completed the ICMJE uniform disclosure form and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

REFERENCES

1. Carignan A, Roussy J-F, Lapointe V, Valiquette L, Sabbagh R, Pépin J. Increasing risk of infectious complications after transrectal ultrasound-guided prostate biopsies: Time to reassess antimicrobial prophylaxis? Eur Urol 2012;62(3):453–459.
2. Rudzinski JK, Kawakami J. Incidence of, infectious complications, following transrectal ultrasound-guided prostate biopsy in Calgary Alberta, Canada: A retrospective population-based analysis. Can Urol Assoc 2014;8(5–6):E301–E305.
3. Aron M, Rajeev TP, Gupta NP. Antibiotic prophylaxis for transrectal needle biopsy of the prostate: a randomized controlled study. BJU Int 2000;85(6):682–685.
4. Loeb S, Vellekoop A, Ahmed HU, Catto J, Emberton M, Nam R, Rosario DJ, Scattoni V, Lotan Y. Systematic review of complications of prostate biopsy. Eur Urol 2013;64(6):876–892.
5. Lundström K-J, Drevin L, Carlsson S, Garmo H, Loeb S, Stattin P, Bill-Axelson A. Nationwide Population Based Study of Infections after Transrectal Ultrasound Guided Prostate Biopsy. J Urol 2014;192(4):116–122.
6. Cuevas O, Oteo J, Lázaro E, Aracil B, de Abajo F, García-Cobos S, Ortega A, Campos J. Spanish EARS-Net Study Group. Significant ecological impact on the progression of fluoroquinolone resistance in Escherichia coli with increased community use of moxifloxacin, levofloxacin and amoxicillin/clavulanic acid. J Antimicrob Chemother 2011;66(3):664–669.
7. van de Sande-Bruinsma N, Grundmann H, Verloo D, Tiemersma E, Monen J, Goossens H, Ferech M. European Antimicrobial Resistance Surveillance System Group, European Surveillance of Antimicrobial Consumption Project Group. Antimicrobial drug use and resistance in Europe. Emerg Infect Dis 2008;14(11):1722–1730.
8. Adriaenssens N, Coenen S, Versporten A, Muller A, Minalu G, Faes C, Vankerckhoven V, Aerts M, Hens N, Molenberghs G, Goossens H, ESAC Project Group. European Surveillance of Antimicrobial Consumption (ESAC): Outpatient antibiotic use in Europe (1997–2009). J Antimicrob Chemother 2011;66(suppl 6):vi3–v12.
9. Hellman J, Aspevall O, Bengtsson B, Greko C. editors. SWEDRES SVARM [Internet]. Public Health Agency of Sweden and National Veterinary Institute, 2013; Available from: www.folkhalsomyndigheten.se/publicerat-material/.
10. Nordström T, Aly M, Clements MS, Weibull CE, Adolfsson J, Grönberg H. Prostate-specific antigen (PSA) testing is prevalent and increasing in Stockholm County, Sweden, despite no recommendations for PSA screening: Results from a population-based study, 2003–2011. Eur Urol 2013;63(3):419–425.
11. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol 2009; 24(11):659–67.
12. Vårdprogram 2007 Prostatacancer [Internet]. 2007 [cited 2014 Sep 30]. Available from: http://www.karolinska.se/upload/Onkologiskt%20centrum/RegionalVardprogram/Prostata2007.pdf
13. Vårdprogram för prostatacancer 2004. ISBN 91-85738-61-1
14. Vårdprogram för Prostatacancer 2008. ISBN 91 85738 79 4
15. Lindstedt S, Lindström U, Ljunggren E, Wullt B, Grabe M. Single-dose antibiotic prophylaxis in core prostate biopsy: Impact of timing and identification of risk factors. Eur Urol 2006;50(4):832–837.
16. Patel U, Dasgupta P, Amoroso P, Challacombe B, Pilcher J, Kirby R. Infection after transrectal ultrasonography-guided prostate biopsy: Increased relative risks after recent international travel or antibiotic use. BJU Int 2012;109(12):1781–1785.
17. Lausch KR, Fuursted K, Larsen CS, Storgaard M. Colonisation with multi-resistant Enterobacteriaceae in hospitalised Danish patients with a history of recent travel: A cross-sectional study. Travel Med Infect Dis 2013; 11(5):320–323.
18. Peirano G, Laupland KB, Gregson DB, Pitout JDD. Colonization of returning travelers with CTX-M-producing Escherichia coli. J Travel Med 2011; 18(5):299–303.
19. Andersson P, Remvig H. Så reser svenskarna [Internet]. 2013 [cited 2014 Sep 29]. Available from: http://www.vagabond.se/artiklar/nyheter/20130528/sa-reser-svenskarna.
20. Tängdén T, Cars O, Melhus A, Löwdin E. Foreign travel is a major risk factor for colonization with Escherichia coli producing CTX-M-type extended-spectrum beta-lactamases: A prospective study with Swedish volunteers. Antimicrob Agents Chemother. Am Soc Microbiol 2010; 54(9):3564–3568.
21. Titelman E, Hasan CM, Iversen A, Nauclér P, Kais M, Kalin M, Giske CG. Faecal carriage of extended-spectrum β-lactamase--producing Enterobacteriaceae is common 12 months after infection and is related to strain factors. Clin Microbiol Infect. 2014; 20(8):O508–O515.

22. Batura D, Rao GG, Nielsen PB. Prevalence of antimicrobial resistance in intestinal flora of patients undergoing prostatic biopsy: implications for prophylaxis and treatment of infections after biopsy. BJU Int 2010;106(7):1017–1020.

23. Park DS, Hwang JH, Choi DK, Gong IH, Hong YK, Park S. Oh JJ. Control of infective complications of transrectal prostate biopsy. Surg Infect (Larchmt) 2014;15(4):431–436.

24. Grummet JP, Weerakoon M, Huang S, Lawrentschuk N, Frydenberg M, Moon DA, O'Reilly M, Murphy D. Sepsis and "superbugs": Should we favour the transperineal over the transrectal approach for prostate biopsy. BJU Int. 2014;114(3): 384–388.

25. Carlsson SV, Holmberg E, Moss SM, Roobol MJ, Schröder FH, Tammela TLJ, Aus G, Auvinen AP, Hugosson J. No excess mortality after prostate biopsy: Results from the European Randomized Study of Screening for Prostate Cancer. BJU Int 2011;107(12):1912–1917.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.