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Nontraditional Anti - Infectious Agents in Hemodialysis

Martin Sedlacek
Dartmouth Hitchcock Medical Center, One Medical Center Drive
Lebanon

1. Introduction

The distinction between antibiotic and non antibiotic medications is in fact quite arbitrary as drugs against bacteria can have unpredictable side effects in man and drugs developed for use in humans can affect microbes. It would be extremely surprising if it was otherwise, as eukaryotes and prokaryotes are related by evolution and share conserved molecular mechanisms. Many antibiotic and non antibiotic medications have closely related chemistries and share the same historic roots.

For example, both antimicrobial activity and an affinity for brain tissue of the phenothiazine compound methylene blue were described by Paul Ehrlich in the 19th century. Early uses of phenothiazines included treatment of urinary tract infection and postoperative analgesia. As a positive effect on psychotic patients was discovered, phenothiazines became with the development of chlorpromazine an important tool in psychiatry (Williams, 1995). With the discovery of penicillin the antimicrobial activities of phenothiazines and other earlier compounds fell into the background, but with the emergent problem of antibiotic resistance in more recent years there was new interest. Phenothiazines have activity against multidrug resistant *Staphylococcus aureus* and *Enterococcus faecalis*, presumably through the inhibition of bacterial efflux pumps (Kristiansen J.E. et al., 2007).

As a routine, antibiotic medications are tested for their effects on the eukaryotic host as these constitute potential side effects. While the ideal antibiotic would have no side effects at all, the discovery of unexpected side effects has lead to important drug developments. For instance, the clinical observation of a hypoglycemic effect of sulfonamide antibiotics led to the development of sulfonylureas for the treatment of diabetes. Likewise the observation that Sulfanilamide causes hens to lay eggs without shells because of alkaline diuresis led to the development of acetazolamide and ultimately the thiazide diuretics. The initial observation derived from the similarity between the sulfonamide ion and the bicarbonate ion. The antiviral amantadine was found to be useful in the treatment of Parkinson's disease and motility agents to treat gastroparesis are derived from the observation of the bothersome gastrointestinal side effects of erythromycin. As described below, even Lipitor, the "best selling drug in the world" with $11 Billion of annual sales according to Forbes magazine, was developed from a compound initially discovered as an antibiotic originating from a fungal broth.

On the other hand side, the efforts to look into the unintended effects on microbes of non antibiotic medications have been less systematic. Non antibiotic medications can affect

microbes in various ways: Compounds may have direct anti microbial effects in vitro, similar to traditional antibiotics. However, to be clinically useful the drug level to achieve minimum inhibitory concentration has to be within a range that is achievable and tolerable in humans. Compounds can exert an antimicrobial effect by inhibition of bacterial pumps. A well known example is the potentiation of antibiotic treatment against *Helicobacter pylori* through omeprazole. Many psychotropic medications including the phenothiazines fall into this category. Aspirin appears to modulate the expression of genes that are important for Staphylococcal virulence and the statins appear to have immune modulatory effects. Both medications are discussed in more detail below.
This chapter deals with the anti microbial effects of medications that are not traditionally regarded as antibiotics with regards to dialysis.

2. A combination of unfortunate events: infection in dialysis

The current epidemic of obesity and, as a complication, diabetic nephropathy associated to type 2 diabetes mellitus has fueled the spectacular growth of hemodialysis into an industry that is dominated by a handful of large companies. Infection is a leading cause of morbidity and mortality in dialysis patients and the annual mortality rate caused by sepsis is several hundred folds higher in patients with end stage renal disease than in the general population (Laupland et al., 2004). The incidence of bacteremia has increased in hemodialysis patients over the years, mainly because of increased rates of serious *Staphylococcus aureus* infection in this population (Foley at al., 2004). *S. aureus* has its name from a gold coloured caroten virulence factor called staphyloxanthin which allows the bacteria to survive oxidative bursts of neutrophils (Liu G.Y. & Nizet V., 2009). *S.aureus* produces a battery of surface proteins, enzymes and toxins which enable the bacteria to both persist in intracellular locations and in biofilms for long periods of time, and to rapidly disseminate in the host in an opportunistic fashion which makes it one of the most dangerous and pathogenic bacteria in humans.
The use of dialysis catheters is a major risk factor for developing *S.aureus* infection because of disruption of the normal skin barrier, thus forming a gateway for bacterial entry into the blood stream (Vandecasteele S.J. et al., 2009). Despite Kidney Disease Outcomes Quality Initiative clinical practice guidelines recommending the use of auto logos arterio-venous fistulae as dialysis access and other efforts, the overall prevalence of hemodialysis catheter use has been increasing, approaching 30% in the United States (Rayner et al., 2004). Humans are the main natural reservoir for *S.aureus* which can colonize skin, gastrointestinal and urogenital tracts. The most frequent site of colonization is the anterior nose and longitudinal studies have shown that there are three types of *S.aureus* nasal carriage in healthy adults: fifty percent are persistent non carriers, thirty percent are intermittent carriers and twenty percent are persistent carriers (VandenBergh et al., 1999). Hands are the main vector of transmission and in the majority of cases the same strain that is found in the bloodstream is also found on the hands and in the nose (von Eiff C. et al., 2001). It follows that rigorous hand washing is extremely important to prevent infection in the dialysis units as it is elsewhere in the medical setting. The majority of *S.aureus* infections has its source in the endogenous reservoir in the nose of the same person and can thus be considered an "autoinfection" (Boelart et al., 1995 as quoted in Vandecasteele et al., 2009). Consistent with this view is that in prospective studies the interval between catheter placement and staphylococcemia can be very short, with 23% of episodes occurring less than one week after catheter insertion (Little M.A. et al., 2001). *S.aureus* bacteremia is associated frequently with

metastatic infection such as endocarditis, osteoarticular infection, septic pulmonary embolism and epidural abscess and carries a mortality that is higher than with other pathogens. While the original observation by Fleming that led to the discovery of penicillin involved the accidental overgrowth of an *S.aureus* culture with fungus, staphylococcal resistance to penicillin has since become very frequent both in community and hospital acquired infections. A recent study in the US found that methicillin resistant *S.aureus* accounted for 65% of isolates from the nose in hospitalized dialysis patients (Johnson L.B. et al., 2009). As with methicillin sensive *S.aureus*, colonization seems to precede clinical infection. A scheme of three times a week nasal mupirocin ointment can decrease nasal carriage but is cumbersome, the rate of recurrence is high and rapid development of resistance has been observed (Vandecasteele et al., 2009).

3. Salicylic acid

Salicylic acid, the active ingredient of willow bark, is one of the oldest medicines still in use, in the buffered form of aspirin. The beneficial effect on fever, pain and inflammation were already described by Hippocrates. Fallen out of favour because of other non steroidal anti inflammatory drugs with more favorable side effects profiles aspirin has made a spectacular come back fifty years ago as the antiplatelet effects of aspirin were discovered. Since then aspirin has found widespread therapeutic use in the treatment of cardiovascular disease. Chronic treatment with Aspirin may prevent colorectal cancer, presumably by inhibition of cyclooxygenase 2 (COX-2) which is expressed in large amounts in adenocarcinoma (Ruder E.H. et al., 2011). Salicylic acid is ubiquitous in plants as a phytohormone. It is part of the innate immune system of plants, involved in local resistance to pathogens and in systemic acquired resistance (SAR), where a pathogenic attack one part of a plant induces resistance in other parts. Depending on the amount of fruit and vegetables in the diet humans have detectable serum levels of salicylic acid. It has been hypothesized that diet derived salicylic acid could in part account for the observed link between diet and colorectal cancer (Paterson J.R.& Lawrence J.R., 2001) and this might possibly apply to the relation between diet and cardiovascular disease as well. Salicylic acid is used as a food preservative and an antiseptic in toothpaste. Aspirin is thus not only one of the oldest but also one of the most versatile and successful drugs known.

3.1 Laboratory evidence for an anti staphylococcal effect of salicylic acid

Early studies in the rabbit endocarditis model showed that platelets provide a nidus for bacteria and that aspirin can decrease vegetation size (Pujadas et al., 1988). The observation was made that aspirin can reduce not only the weight of vegetations in a rabbit model of *S.aureus* endocarditis but also bacterial density although neither aspirin nor salicylic acid have known antibacterial effects at the low concentrations employed (Nicolau D.P. et al., 1993). This benefit was seen if aspirin was given together with antibiotics but also if aspirin was provided prior to the infectious challenge with which endocarditis was induced (Nicolau D.P. et al., 1995). Even more puzzling in this study was that vegetation weight and bacterial density were higher if higher doses of aspirin were administered while the optimum beneficial effect was seen at a lower dose, suggesting that serum levels may be very important. Subsequently this observation has been called the "Goldilocks effect" in which too little and too much aspirin may cause paradoxically diminished effects on outcome parameters in the infectious endocarditis model (Eisen et al., 2008). The beneficial

effects of aspirin in the rabbit model of endocarditis have been recapitulated with salicylic acid, its major biometabolite (Kupferwasser et al., 1999). As salicylic acid has no anti-platelet properties, this indicates that platelet independent mechanisms are likely to have a more significant role in the action of aspirin on *S.aureus* endocarditis that the platelet dependant effects. Further experimental work in vivo in animal models of infectious *S.aureus* endocarditis showed that aspirin reduced a multitude of measurable parameters of the severity of the infection and metastasis such as vegetation weight and the bacterial density in vegetations and the number of renal emboli and these effects were dose dependant, more pronounced at lower rather than higher doses (Kupferwasser et al., 1999). In vitro studies showed that salicylic acid inhibits the expression of two key virulence genes in *S. aureus* that are involved in endovascular pathogenesis: alpha-toxin [hla] and fibronectin-binding adhesion [fnbA], through activation of genetic pathways involving the major stress response operon, sigma factor B (Kupferwasser et al., 2003). These aspirin mediated effects on sigma factor B were observed at serum concentrations that are achieved by usual clinical dosages of aspirin in humans (Kupferwasser et al., 2003). On the other hand side, it has been shown that the presence of salicylic acid decreases expression of capsular polysaccharides. It has been hypothesized that the loss of these capsular virulence factors could lead to an increased capacity of *S.aureus* to invade epithelial cells and that chronic treatment with aspirin could potentially lead to more persistent or recurrent infection (Alvarez C.P. et al., 2010).
In conclusion a significant body of in vitro and in vivo evidence indicates that aspirin may have the potential to be useful in the treatment of *S.aureus* infection by down modulating key regulator and structural genes resulting in the abrogation of virulent phenotypes but it has to be noted that important questions remain.

3.2 Clinical evidence for a beneficial effect of aspirin in *S.aureus* endocarditis

The earliest clinical observations of a potential salutatory role of aspirin come from the study of bacterial endocarditis. In a small retrospective study a decreased rate of embolic events was found in patients with native valve endocarditis who were on long term aspirin treatment (11% versus 47%), although the number of patients treated with aspirin was too small to be conclusive (Schunemann S. et al., 1997). A small preliminary prospective observational study conducted in 9 patients found adjunctive treatment of established endocarditis with aspirin beneficial (Taha et al., 1992).
Subsequently, a Canadian prospective multicenter study in 115 patients with endocarditis showed no benefit of the adjunctive treatment with a 325mg dose of aspirin (Chan et al., 2003). Despite its prospective design this study was criticized as patients on chronic aspirin treatment were excluded from this study although the greatest benefit might be expected in this population. Moreover, Aspirin was added only after an average of 35 days after onset of symptoms. Only 14 patients (25%) in the Aspirin treatment group had *Staphylococcus aureus* endocarditis while the majority had streptococcal endocarditis. As the putative mechanism of action of aspirin involves the inhibition of *S.aureus* virulence factors, the benefit of aspirin is likely greatest if it is used before infection occurs. The benefit of aspirin is also very likely to be limited to *S.aureus* as the mechanism seems to be specific to this pathogen. The same authors presented a post hoc analysis of their data in 2008, comparing 84 patients who had been excluded from their previous study because of long term aspirin treatment with 54 patients in the placebo arm and again found no significant clinical differences in the outcome between both groups (Chan et al., 2008). Only 29% of patients, 16 and 24 patients

respectively, in both arms had *S.aureus* endocarditis and thus the same concern that the study was underpowered to detect a difference was voiced for this study as well (Eisen D.P. & Bayer A.S., 2008).

A retrospective single center cohort study of 600 patients with infectious endocarditis, who were treated over a 18 year period at the Mayo Clinic, found that the odds of suffering symptomatic embolic events was decreased by 64% in patients who were treated with antiplatelet agents for at least 6 months prior to the diagnosis: Aspirin was the antiplatelet agent in 98% of cases and an 81mg daily dose was used in the majority of patients (Anavekar et al., 2007).

Eisen et al. used the International Collaboration on Endocarditis –Prospective Cohort Study (ICE-PCS) database to assess the influence of aspirin usage at the time of diagnosis on the outcome of definitive *S.aureus* endocarditis. A cohort of 670 patients had both information on prior aspirin use and *S.aureus* endocarditis. Aspirin use at the time of diagnosis in 132 patients was a predictor for a decreased risk of acute valve surgery, independent of methicillin resistance status. A statistically significant decrease in embolic events in aspirin users was found in a univariate analysis that became a trend in multivariate analysis. A comparison of groups with and without aspirin use among patients with Streptococcal endocarditis was made and no association of aspirin with improved outcomes was found (Eisen et al., 2009).

Thus the data on aspirin use in *S.aureus* endocarditis suggests that aspirin likely does alter the course of illness. The non dependence of the effect on methicillin resistance status and the absence of an observed effect of aspirin on other pathogens are consistent with the proposed specific mechanism of aspirin on staphylococcal virulence factors. It is also noteworthy that Staphylococcal endocarditis is rather difficult to study in adequate numbers as the population incidence is fortunately low.

3.3 Aspirin and *S.aureus* nasal carriage

Karabay et al. investigated the prevalence of *S.aureus* nasal carriage in an outpatient cardiology clinic. Of a total of 346 patients 199 were chronic aspirin user while 147 patients were not. The prevalence of *S.aureus* nasal carriage was 5% on patient treated chronically with aspirin versus 16% in those that did not take aspirin. Only aspirin was found to be associated with a decreased rate of nasal carriage in a multivariate analysis (Karabay et al., 2006). These findings are of obvious significance to hemodialysis patients as nasal colonization is considered the initiating event that leads to catheter associated staphylococcal bacteremia. If confirmed, aspirin could decrease nasal carriage at a fraction of the cost and effort of mupirocin ointment. Given the fact that aspirin is a very old drug the findings of Karabay et al. have another potential significance: If a clinical effect of aspirin on *S.aureus* can still be detected after decades of over-the-counter use it would be unlikely that *S.aureus* would develop resistance to this effect in the future. It is clear that the important findings of Karabay et al. merit further investigation both in hemodialysis and in the general population.

3.4 A potential beneficial effect of aspirin in hemodialysis patients

Patient undergoing hemodialysis treatments suffer staphylococcal infections with increased frequency because of a high prevalence of tunneled or non tunneled dialysis catheters. The hemodialysis setting is thus well suited to study the potential beneficial clinical anti staphylococcal effects of aspirin.

We conducted a single center retrospective study in 872 patients with tunneled catheters who dialyzed over a ten year time period from 1995 to 2005. During this time period our patients had 1853 tunneled dialysis catheters placed and accumulated more than 476 patient-catheter-years and had 4722 blood cultures performed. Temporary dialysis catheters were excluded because of the high variability in the circumstances of placement of temporay catheters and also greater difficulty in tracking them retrospectively. The overall incidence of bacteremia was 7.2 episodes per 100 patient-catheter-months and the incidence of *S.aureus* bacteremia was 2.1 episodes per 100 patient-catheter-months. The incidence of *S.aureus* endocarditis was 0.16 episodes per 100 patient-catheter-months. These numbers are within the range reported in the literature. Blood cultures were obtained at the discretion of the treating physician if infection was suspected. Tunneled catheters that were a suspected source of infection were usually removed and negative cultures were required before insertion of a new tunneled catheter. All tunneled catheters were placed and removed by the same interventional radiology service. Suspected infection was the principal reason for tunneled catheter removal (19%), followed by poor catheter blood flow (14%) and presence of a mature permanent vascular access (14%). Infection rates were compared by Poisson regression analysis. In this study catheter associated bacteremia was defined as one or more positive blood cultures in a patient with a tunneled catheter. In retrospect it was impossible to exclude other sources of infection and contamination and for this reason all positive blood culture results that were obtained in the presence of a tunneled catheter were included without discrimination. Blood cultures that were obtained after a tunneled catheter was removed were excluded per definition. Our institution is a tertiary care medical center that offered hemodialysis in two outpatient units, serving a population of about 400,000 people. Because of location in a rural area, limited availability of hemodialysis and other geographical factors limiting access to other institutions the long term follow up of patients was excellent. A proprietary medical record system integrated electronic inpatient and outpatient records with procedure notes and laboratory, radiological and microbiological test result and was ideally suited for a large retrospective study. As a result the fate of only 8 catheters (<0.5%) was unaccounted for.

The number of episodes and rates of catheter associated bacteria is shown in Table 1 which includes repeated episodes and polymicrobial infections with more than one bacterial isolate. As expected, Gram positive bacteria accounted for the majority of bacteremic episodes. When all bacteremic episodes were considered together, there was no difference between patients treated with aspirin or not. In fact, the only pathogen with a lower rate of catheter-associated bacteremia in patients treated with aspirin was *S.aureus* which caused only half as many episodes in the aspirin group compared to patients not treated with aspirin (0.17 versus 0.34 events/patient-catheter-years, p=0.003). In addition to blood cultures 369 catheter tip cultures were performed in the same time interval, albeit in a less systematic fashion. Of these 53 catheter tip cultures grew *S.aureus*. In such a case treatment is usually recommended because *S.aureus* bacteremia is considered more likely than contamination (Peacock et al., 1998). If these tip cultures were added to bona fide blood cultures in the analysis, the difference was statistically more significant: 83 instances (0.36 events per patient-catheter-year) of *S.aureus* in the non aspirin treated group versus 45 (0.18 event per patient-catheter-year) in the aspirin treated group (p=0.001).

Moreover, if we excluded repeated events in the same patient from our data and considered only first episodes of *S.aureus* bacteremia, the difference looked between the two groups looked even more impressive: 28 first episodes of *S.aureus* bacteremia in patients treated

with aspirin (0.23 events per patient-catheter year) versus more than double, 64 first episodes of *S.aureus* bacteremia (0.57 events per patient catheter year) in patient not treated with aspirin ($p<0.001$).

We explored the association between aspirin dose and rates of catheter associated *S.aureus* and *MRSA* bacteremia in table 2. There was a dose effect as only a 325mg dose of Aspirin, but not an 81mg dose (common formulations in the United States), was associated with a decreased rate of *Staphylococcus aureus* infection compared to patients not treated with aspirin. Importantly there was a significantly lower rates of *Methicillin resistant Staphylococcus aureus* bacteremia (*MRSA*) in patients treated with 325mg of aspirin a day.

	No Aspirin		**Aspirin**		***P***
	978 Catheters/227.4 Patient-Catheter-Years		**875 Catheters/ 249.3 Patient-Catheter-Years**		
	No.	**Rate (/patient-catheter-y)**	**No.**	**Rate (/patient-catheter-y)**	
All positive	232	1.02	207	0.83	0.30
Gram-positive					
Coagulase-negative *Staphylococcus*	96	0.42	93	0.37	0.85
S aureus	77	0.34	43	0.17	0.003*
MRSA	19	0.08	11	0.04	0.16
Enterococcus species	21	0.09	30	0.12	0.18
Corynebacterium species	7	0.03	6	0.02	0.82
Streptococcus species	4	0.02	7	0.03	0.34
Bacillus species	4	0.02	4	0.02	0.97
Gram-negative					
Enterobacter species	20	0.09	21	0.09	0.81
Pseudomonas species	11	0.05	13	0.05	0.64
Serratia species	12	0.05	9	0.04	0.55
Klebsiella species	9	0.04	10	0.04	0.77
Escherichia coli	7	0.03	4	0.02	0.39
Acinetobacter species	4	0.02	4	0.02	0.97
Bacteroides species	3	0.01	3	0.01	0.78

Note: Multiple bacterial isolates and repeated episodes were included in this table. Fungal isolates and bacterial species found fewer than 5 times during the 10-year study period were omitted.
*Significant difference by Poisson regression.

Table 1. Number of Episodes and Rates of Catheter-Associated Bacteremia in a 10-Year Period from 1995 to 2005
Reprinted from Sedlacek et al.: "Aspirin Treatment Is Associated With a Significantly Decreased Risk of Staphylococcus aureus bacteremia in Hemodialysis Patients With Tunneled Catheters", Am J Kidney Dis Vol49, pp401-408 with permission from Elsevier

	No Aspirin		81 mg Aspirin		325 mg Aspirin	
	978 Catheters/227.4 Patient-Catheter-Years		367 Catheters/116.2 Patient-Catheter-Years		508 Catheters/133.1 Patient-Catheter-Years	
	No.	Rate (/patient-catheter-y)	No.	Rate (/patient-catheter-y)	No.	Rate (/patient-catheter-y)
S aureus	77	0.34	26	0.22	17	0.13
		$P = 0.26$				
		$P < 0.001$*				
MRSA	19	0.08	10	0.09	1	0.01
		$P = 0.62$				
		$P = 0.001$*				

Table 2. Association between Aspirin Dose and Rates of Catether-Associated *S aureus* and MRSA Bacteremia
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We used Cox proportional hazard analysis to study risk factors for developing a first episode of *S.aureus* bacteremia. Table 3 shows the patient characteristics and distribution of covariates that were used for this analysis. Patient treated with aspirin were on average 10 years older and had a higher prevalence of coronary artery disease, peripheral vascular disease, history of stroke, hypertension and diabetes mellitus than patients not treated with aspirin.
Table 4 shows the result of the Cox proportional hazard analysis. Aspirin decreased the odds of developing a first episode of *S.aureus* bacteremia by 54% (with a confidence interval of 72% to 24%, p=0.002). No other cardiovascular medication and neither clopidogrel nor Warfarin had a similar effect. Also, no beneficial effect of statins on the odds of *S.aureus* bacteremia was observed in this study. On the opposite side, the presence of diabetes mellitus increased the risk of developing a first episode of catheter associated *S.aureus* bacteremia, as was previous recognized (Breen et al. 1995). COPD decreased the odds of a first episode *S.aureus* bacteremia in this study. A potential explanation for this observation could be more frequent antibiotic use in this condition which might reduce nasal carriage. A greater incidence of *S.aureus* bacteremia was reported in patients with cardiovascular disease (K/DOQI, 2005) but the opposite, lower numbers of *S.aureus* bacteremia was observed in this sicker patient population which may be taken as a sign of the potential clinical importance of the anti staphylococcal effects of aspirin. Similar results were obtained when multiple logistic regression analysis was used instead of Cox analysis.
Data on metastatic infection (endocarditis, osteomyelitis, septic arthritis) was analyzed as well. There were significantly less events in patients treated with aspirin compared with events in patients not treated with aspirin (3 versus 11 events, p=0.04).
A Kaplan-Meier plot of cumulative catheter failure associated with *S.aureus* bacteremia is shown in Figure 1. Grouping by aspirin treatment resulted in two divergent graphs with catheter failure caused by *S.aureus* infection significantly more frequent in the non aspirin group (p<0.001). The two graphs diverge very early which is consistent with the clinical observation that almost a quarter of *S.aureus* infection occur very early within a week after catheter insertion (Little M.A. et al., 2001). Figure 1 also illustrates another measure of the beneficial anti staphylococcal effect of aspirin: delayed onset of infection.

	No Aspirin (454 patients)	Aspirin (418 patients)	*P*
Age (y)	59 ± 19*	68 ± 13*	<0.0001
Time on dialysis (d)	362 ± 810	346 ± 542	0.73
Catheter no.	1.8 ± 1.8	1.9 ± 1.7	0.70
Female sex	194 (42)	186 (44)	0.54
Tobacco use	205 (45)*	225 (54)*	0.01
Diabetes mellitus	170 (38)*	236 (56)*	<0.0001
Hypertension	333 (74)*	364 (87)*	<0.0001
COPD	92 (20)*	117 (28)*	0.009
Coronary artery disease	159 (35)*	309 (79)*	<0.0001
Peripheral vascular disease	113 (25)*	200 (48)*	<0.0001
Stroke	66 (15)*	99 (24)*	0.007
Arthritis	141 (31)*	164 (39)*	0.01
Cancer	102 (23)	80 (19)	0.24
Previous transplant	50 (11)*	14 (3)*	<0.0001
Clopidogrel	12 (3)*	40 (10)*	<0.0001
Warfarin	61 (14)	60 (14)	0.77
Statin	69 (15)*	172 (41)*	<0.0001
B-Blocker	248 (55)*	315 (75)*	<0.0001
ACE inhibitor/ARB	136 (30)*	187 (45)*	<0.0001
Calcium channel blocker	216 (48)	216 (52)	0.28
Aspirin	0	418	<0.0001

Note: Values expressed as mean ± SD or number (percent).
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.
*Statistically significant difference between aspirin-treated and non–aspirin-treated groups by means of Fisher exact test or unpaired Student *t*-test, as appropriate.

Table 3. Patient Characteristic and Distribution of Covariates for the Cox Proportional Hazard Analysis
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A second study that addressed the anti staphylococcal effects of aspirin in hemodialysis patients was published in abstract form (Sedlacek et al., 2008). We performed a historical cohort study of the United States Renal Data System (USRDS) Dialysis Morbidity and Mortality Study (DMMS) Wave II data, linking medication data to mortality data from the core files. The updated USRDS Wave II data comprise 4024 patients, 16% of which were treated with Aspirin at study start date and 2776 of whom died. 54 of 2262 deaths (2.39%) in patients not treated with aspirin were attributed to septicemia due to vascular access either as primary or secondary cause, while there were only 4 of 510 deaths (0.78%) in patients treated with aspirin that were attributed to this cause ($p<0.02$, 2-tailed Fisher's Exact Test). Although anti platelet agents and other cardiovascular medications are underused in dialysis patients, we still find a strong negative association between aspirin treatment and

death from septicemia due to vascular access in USRDS data. These results provide a confirmation of a clinical anti-staphylococcal effect of aspirin in hemodialysis patient that is independent from the data pool used in our first study.

	Relative Risk (95% CI)	***P***
Age (y)	1.0 (1.0-1.0)	0.99
Time on dialysis (d)	1.0 (1.0-1.001)	0.88
Catheter no.	0.95 (0.83-1.09)	0.45
Female sex	1.19 (0.76-1.86)	0.45
Tobacco use	0.78 (0.49-1.24)	0.30
Diabetes mellitus	1.65 (1.02-2.67)	0.04*
Hypertension	1.36 (0.74-2.51)	0.33
COPD	0.49 (0.24-0.97)	0.04*
Coronary artery disease	0.80 (0.48-1.34)	0.40
Peripheral vascular disease	1.01 (0.62-1.65)	0.97
Stroke	1.11 (0.63-1.96)	0.72
Arthritis	1.22 (0.78-1.92)	0.39
Cancer	1.04 (0.59-1.83)	0.89
Previous transplant	1.19 (0.55-2.55)	0.66
Clopidogrel	1.06 (0.40-2.83)	0.91
Warfarin	1.79 (1.03-3.10)	0.04*
Statin	1.08 (0.63-1.85)	0.79
B-Blocker	1.13 (0.70-1.83)	0.62
ACE inhibitor/ARB	0.79 (0.50-1.25)	0.31
Calcium channel blocker	0.73 (0.46-1.15)	0.17
Aspirin	0.46 (0.28-0.76)	0.002*

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.
*Statistical significance in Cox proportional hazard model.

Table 4. Risk of First *S aureus* Bacteremia Episode in 872 Dialysis Patients with a Tunneled Catheter by using Cox Proportional Hazard Analysis
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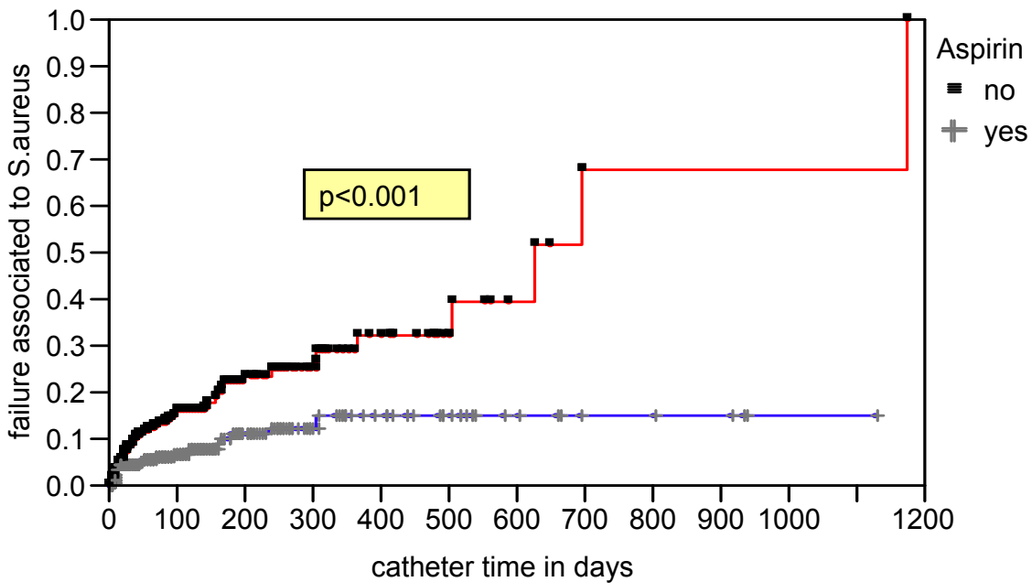
3.3 Concerns about aspirin use in hemodialysis patients

The abuse of non steroidal inflammatory drugs is a well described risk factor for upper gastrointestinal bleeding. The concern has been raised that the use of aspirin in dialysis patients could be harmful by causing bleeding (Chan et al., 2003 and 2008). As noted in a recent metanalysis the available data is conflicting for a variety of reasons such as selection bias, insufficient length of follow up and concomitant treatment with proton pump inhibitors (Hiremath et al., 2009). In the study of Chan et al a trend towards a higher incidence of bleeding was observed which did not reach statistical significance as both the initial study as well as the subsequent post hoc analysis was underpowered to either



patients at risk:

ASA	417	142	66	35	25	16	9	6	5
no ASA	452	118	61	37	22	11	6	3	2

Fig. 1. Cumulative plot of tunneled catheter failure associated with *S aureus* bacteremia. The failure plot was obtained using the Kaplan-Meier method. Tics represent censoring of catheter removal unrelated to *S aureus* bacteremia. Log-rank test was used to calculate *P*. Reprinted from Sedlacek et al.: "Aspirin Treatment Is Associated With a Significantly Decreased Risk of Staphylococcus aureus bacteremia in Hemodialysis Patients With Tunneled Catheters", Am J Kidney Dis Vol49, pp401-408 with permission from Elsevier

support or refute this hypothesis. In our own study no increased risk of bleeding was observed (unpublished data, Sedlacek et al., 2008). A study on aspirin use in 28320 patients from the Dialysis Outcomes and Practice Patterns Study I and II found neither a decreased cardiovascular risk nor an increase in the gastrointestinal bleeding with the use of aspirin (Ethier J et al., 2007). (Of note, no data on infectious complications was included in this manuscript which why it was not discussed in the above sections.)

While there is no unequivocal proof that aspirin increases the risk of upper gastrointestinal bleeding in dialysis patients, it must not be forgotten that upper gastrointestinal bleeding is a well documented part of the uremic syndrome and that anticoagulation is routinely used during the hemodialysis procedure. It would thus seem reasonable to adopt a similar approach to high risk dialysis patients as has been recommended in high risk cardiac patients who would benefit from aspirin. Patients can be screened and treated for *H.pylorii* and proton pump inhibitors may be considered. Lastly it has to be noted that upper gastrointestinal bleeding is more amenable to treatment and represents a lesser risk to a high risk dialysis patient than for example cardiac stent occlusion.

4. Statins

Statins are cholesterol reducing medications that similarly to aspirin have become a cornerstone in the prevention and treatment of cardiovascular disease. The antimicrobial

effects of statins have been known for a long time. In fact, statins were discovered by searching for compounds that would inhibit HMG-CoA reductase in microbes that require sterols or other isoprenoids, which are part of bacterial cytoskeleton, for growth. The first statins were described as antibiotics secreted by Penicillium species. The first statin compound, mevastatin, is derived from a culture of *Pythium ultimum* and *Penicillium citrinum* and under the name compactin the same compound was isolated from a culture of *Penicillium brevicompactum* (Endo et al., 1976). A mevastatin analog currently in use, lovastatin, was isolated from a culture of *Aspergillus terreus*. (Endo A., 1992). The antimicrobial effects of statins were rediscovered at a later time and it was noted that the minimum inhibitory concentration of simvastatin for *S.aureus* was much higher than the serum levels that can be achieved during routine treatment at recommended doses (Jerwood S. & Cohen J., 2008). Direct antimicrobial effects with potential clinical relevance have been postulated for HIV, CMV, HCV, Salmonella and yeast (Gupta et al., 2007) but are perhaps less relevant for dialysis catheter associated infection. Newer laboratory evidence shows that the interferon response to viral infection of the innate immune immune system is coupled to the mevalonate-isoprenoid arm of the sterol pathway. These findings may explain the observation that the CMV and HCV viruses are sensitive to statin administration and that treatment with interferon decreases plasma cholesterol levels similar to treatment with statins (Blanc M et al., 2011).

Several observational studies in patients with severe bacterial infections have reported improved survival in patients treated with statins (Bjoerkheim-Bergman et al., 2010). These beneficial effects appear to be greater than what might be expected with lipid lowering alone and are attributed to pleiotropic effects of statins. Such effects involve improving endothelial function, decreasing oxidative stress and inflammation and inhibiting the thrombogenic response (Liao J.K. & Laufs U., 2005).

The hypothesis that treatment with statins could have an influence on the rate of septic events in dialysis patients was investigated by Gupta et al in 2007. The authors used data from a prospective study to investigate choices and outcomes of dialysis care, which enrolled 1041 patients from 1995 to 1998, the majority of which dialyzed in units associated with Dialysis Clinic Inc in Nashville TN. These patient data were linked to United States Renal Data System administrative data which included hospitalizations and data from other treatment settings, including outpatient and skilled nursing facilities. Primary outcome were sepsis events but "only episodes in which the primary event was sepsis were included (…) to avoid including cases in which infection was acquired as a secondary phenomenon" (Correction by the same authors in JAMA Vol 299 P 765). The correction to their method section published later by the authors raises the possibility that their data analysis could come to a different conclusion if all episodes of sepsis were considered, not only the events that were considered"primary". The authors found that 143 patients (14%) received statin treatment compared with 898 patients (86%) who were not. Among all 1041 patients there were a total of 303 events of primary sepsis during a mean follow up of 3.4 years. The crude incidence rate of sepsis events was 63% lower in patients treated with statins compared with the control group (41 events per 1000 patient-years compared with 110 events per 1000 patient years) The authors found that the odds ratio for a primary septic event in statin users was 0.38 (95% CI 0.21-0.67) with adjustments for demographics, dialysis modality, comorbidities and laboratory values. In a propensity-matched subcohort analysis statin use was even more protective with an odds ratio of 0.24 (CI 0.11-0.49) (Gupta et al., 2007). In

contrast to the results of this study no difference in the rate of death from fatal infection with the use of atorvastatin was found in the 4D study (Wanner et al., 2005).
An interesting question that is raised by the study by Gupta et al. is whether the observed benefit could be due to concomitant treatment with aspirin (Gupta et al., 2007). Both statins and aspirin are used for the treatment of coronary artery disease and a head to head comparison would be instructive. Our aspirin study did not find a beneficial effect of statins on the risk of septic events (Sedlacek et al., 2007) and the study by Gupta et al. did not control for aspirin use.
It has to be noted that the relation between lipid parameters and mortality in dialysis patients is complex, confounded by the fact that elevated serum cholesterol levels are paradoxically protective in this population, probably because they are a marker for the absence of malnutrition and inflammation. In practical terms it is advised to use low doses of statins to reduce side effects and to avoid the concomittant administration of other drugs metabolized by the cytochrome P-450 system such as cyclosporine, azole antifungals and fibrates (Olyaei et al., 2011).

5. Effects of other drugs used on dialysis

Several other drugs that are frequently used on dialysis have known interactions with microbes. Heparin is used frequently to block dialysis catheters when not in use to preserve their patency. Unfortunately, heparin has been found to promote growth of bacterial biofilm in dialysis catheters (Shanks et al., 2005). Citrate has been used as an alternative to heparin to block catheters and was found to have inhibitory effects on biofilms at elevated concentration. Reminiscent of the "Goldilocks effect" observed with aspirin, citrate stimulates biofilm formation at sub inhibitory concentrations, an effect which might have clinical relevance at catheter tips (Shanks et al., 2006). EDTA also has an inhibitory effect on biofilm. The mechanism for both EDTA and citrate is thought to be through chelation of divalent ions essential to the extracellular matrix structure of biofilm (Percival et al., 2005).
Diltiazem, Amlodipine and the angiotension converting enzyme inhibitor Zofenopril have modest in vitro antimicrobial activity against S.aureus. Most of these effects are bacteriostatic and occur at higher drug concentrations in vitro than the therapeutic concentrations that are usually achieved during therapy in vivo. It has to be noted however, that drug concentration can vary considerably throughout different organs and body compartments. In the case of Amiloride it has been determined that urine concentrations achieved in patients are not sufficient to replicate the antibacterial effects that are observed in vivo (Cederlund et al., 1993). The relevance of these observations probably concerns more microbial purity testing of drugs during the fabrication process rather than clinical effects.
Emla cream, a mixture of lidocaine, prilocaine and preservatives, which is used for topical anesthesia at the site of dialysis fistula puncture, has no effect on microbial growth (Kruszewska et al., 2010). Other drugs relevant to ESRD that have been tested and were found to be devoid of antimicrobial effects are the loop diuretics furosemide and bumetanide.
The antihistaminic drug diphenhydramine has been reported to be synergistic with the penicillins (Kristiansen, 1992) and amiloride reportedly enhances uptake of tobramycin in pseudomonas aeruginosa (Cederlund et al., 1993).

6. Last but not least: Honey

Honey has been used for the treatment of wounds since ancient times and its medicinal use is sanctioned by the Bible, Torah and Koran (Namias N., 2003). Johnson et al. conducted a prospective trial of topical honey versus topical Mupirocin ointment for the prevention of dialysis catheter associated infection. In a two year study period the authors enrolled 101 patients with tunneled dialysis catheters in their hospital based dialysis unit. Honey was applied three times a week to the dialysis catheter exit site in 51 patients while mupirocin ointment was used in 50 patients. No exit site infections were observed in either group and no difference in the rate of catheter associated bacteremia could be demonstrated. The cost of the Australian grown medicinal honey that the authors used was equivalent to mupirocin. As the authors noted, it is interesting that at the time of the study about 2% of staphylococcal isolates in their hospital were resistant to mupirocin while no bacterial resistance to honey has yet been reported despite millennia of being around (Johnson D.W. et al., 2005).

7. Conclusion

In summary, a couple of observational studies have shown that both aspirin and statins might have significant salutatory effects on infectious complications in hemodialysis patients. Of note, aspirin does not have growth inhibitory or bactericidal activity at pharmacologically relevant concentrations and thus may be less likely to promote bacterial resistance as traditional antimicrobials do (Eisen et al., 2009). The same might apply for statins as well (Jerwood & Cohen, 2008). However, retrospective and observational studies are prone to multiple sources of bias that are unquantifiable and of indeterminate direction. Thus, randomized prospective trials are needed to further investigate this exciting new approach to the prevention of infectious complications in dialysis patients.

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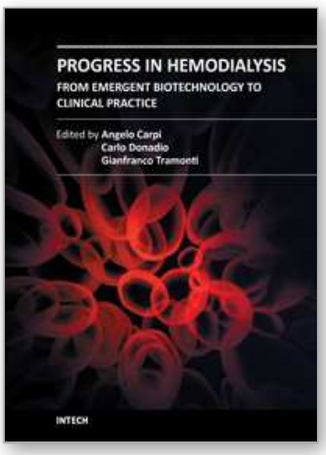

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Hemodialysis (HD) represents the first successful long-term substitutive therapy with an artificial organ for severe failure of a vital organ. Because HD was started many decades ago, a book on HD may not appear to be up-to-date. Indeed, HD covers many basic and clinical aspects and this book reflects the rapid expansion of new and controversial aspects either in the biotechnological or in the clinical field. This book revises new technologies and therapeutic options to improve dialysis treatment of uremic patients. This book consists of three parts: modeling, methods and technique, prognosis and complications.

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Slavka Krautzeka 83/A
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Phone: +385 (51) 770 447
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Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
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