Compliance to antibiotic guidelines leads to more appropriate use of antibiotics in skin and soft tissue infections in injecting drug users

Authors

Marit Nymoen Aasbrenn, MD

Department of Community Medicine, UiT The Arctic University of Norway, Tromsø, Norway

Ivar Skeie, MD PhD

Innlandet Hospital Trust, Gjøvik, Norway

The Norwegian Centre for Addiction Research, Faculty of Medicine, University of Oslo, Oslo, Norway

Dag Berild, MD Dr M Sci

Department of Infectious Diseases, Oslo University Hospital, Oslo Norway

Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway

Corresponding author complete information

Marit Nymoen Aasbrenn

marit.n.aasbrenn@uit.no

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Abstract

Background

Knowledge about treatment of skin and soft tissue infections in injecting drug users in countries with low prevalence of antibiotic resistance is limited. We investigated bacterial antibiotic resistance and treatment of skin and soft tissue infections in Norwegian drug users.

Methods

We performed a two year clinical cross-sectional observational study in a Norwegian hospital. Data was collected retrospectively from hospital records. We examined bacteriological findings and antibiotic resistance and evaluated compliance to treatment guidelines and appropriateness of empirical antibiotic therapy relative to results of cultures and susceptibility testing. Descriptive and univariate analyses were performed.

Results

135 injecting drug users were admitted with skin and soft tissue infection in the study period. Cultures were obtained from 103 (77%) abscesses and eight (24%) erysipelas and cellulitis, with bacterial growth in 80 (78%) and five (63%) respectively. Streptococci and staphylococci were the most prevalent bacteria, but methicillin resistant Staphylococcus aureus was found in only one patient. Compliance to hospital antibiotic guidelines was 70%. 91% of patients in the compliant and 79% in the non-compliant group were given effective empirical antibiotics ($p=0,334$). In the non-compliant group, significantly more patients received broad-spectrum empirical antibiotics ($p<0,001$). In 30 cases where adjustment of antibiotic therapy was possible according to susceptibility testing, this was performed in only 14 cases.

Conclusions

Bacteria and resistance patterns did not differ significantly from skin and soft tissue infections in the general population in Norway. Compliance to antibiotic guidelines led to significantly less use of broad-spectrum antibiotics and to good bacterial coverage. General guidelines for treatment should be applied to injecting drug users with skin and soft tissue infections.

Key words

Skin and soft tissue infections; abscess; drug users; people who inject drugs; antibiotics; compliance to guidelines

Introduction

Skin- and soft tissue infections (SSTIs) are prevalent in people who inject drugs (PWID) [1-5], and constitute a substantial burden to the public health system [1, 2, 5, 6].

The bacteria causing SSTIs are introduced from the commensal skin and oral flora and from contaminated drugs and injection paraphernalia [3, 5, 7-9]. In PWID, the dominating etiology is staphylococci and streptococci [2, 3, 5, 10-15]. Some studies, mainly from urban USA, show a high incidence of infections caused by methicillin resistant Staphylococcus aureus (MRSA) [3, 7, 10, 14-19]. Northern European studies have not reproduced these findings, except in isolated outbreaks [2, 13, 16, 20]. Mixed infections with gram-negative rods and/or anaerobes are commonly seen [2, 3, 5, 10-13, 15, 19]. Outbreaks of infections with Clostridium and Bacillus species have been described [3, 5, 8, 9, 21, 22].

Studies show regional variations in antibiotic resistance over time [3, 9, 16]. We have limited information about the special features of SSTIs in PWID in areas with low-prevalence of resistant bacteria, and no recent studies have investigated the microbiology in SSTI in PWID in Norway.

Our hypothesis was that, assuming differences between PWID and the common population in the distribution of bacteria causing SSTIs, PWID would be at risk of receiving inappropriate antibiotics if treated according to the general guidelines. We aimed to investigate the following issues:

(1) Which bacteria and resistance patterns are found in SSTIs in an unselected hospitalized PWID population?

(2)

(A) Is treatment in compliance with Norwegian guidelines?

(B) Is empirical antibiotic therapy appropriate relative to results of bacteriological cultures and susceptibility testing, and do cases receiving treatment with and without compliance to guidelines differ in this regard?

(C) Is antibiotic therapy adjusted according to culture results and susceptibility testing?

Material and methods

Design

The study was retrospective with an observational cross-sectional design.

Sample, setting and observation period

Oslo University Hospital Aker is a 323-bed tertiary care hospital serving unselected patients from a catchment area of 180.000 people. All patients admitted during 2009 and 2010 with the following primary or secondary ICD-10-diagnosis were identified: L02 Cutaneous abscess, furuncle and carbuncle, L03 Cellulitis, L04 Acute lymphadenitis, L05 Pilonidal cyst, L08 Other local infections of skin and subcutaneous tissue and A46 Erysipelas. Data was collected retrospectively from hospital records. Patients with no record of injecting drug use during the last month were excluded as were patients admitted and discharged the same day. Each admission was considered separately, but two or more subsequent admissions with an interval up to 14 days, identical foci and compatible culture results, were defined as one single incident. 184 episodes of SSTI in 135 PWID were identified. Only the first episode of infection in each patient was included in the statistical analyses. There was no follow-up after discharge.

Measures

Demographic and clinical data, bacterial culture results, including dates for sampling and reporting, and antibiotic treatment, were registered. Antibiotics prescribed before culture results were available were recorded as empirical.

SSTIs were categorized as either abscess or erysipelas/cellulitis. The data did not enable us to distinguish erysipelas from cellulitis. Identification of bacterial species was performed by Gram stain and Vitek 2. Disk diffusion, E-test and Vitek 2 were used for susceptibility testing and susceptibility tests were interpreted according to EUCAST [23]. Cultures were obtained on clinical indication, set by the doctor who treated the patient. Additional foci were identified in order to avoid biasing of the evaluation of antibiotic therapy. We defined sepsis as systemic inflammatory response syndrome (SIRS) or SIRS and bacteremia. We noted sepsis or bacteraemia only if it affected choice of antibiotics. Blood cultures were not obtained from all patients.

Guidelines for SSTI therapy

In Aker Hospital guidelines, which are in accordance with national guidelines, penicillin is the drug of choice for erysipelas and dicloxacillin or cloxacillin for cellulitis. In patients with allergy to penicillins, erythromycin, cefalotin/cefalexin or clindamycin are antibiotics of choice. The guidelines emphasize that therapy should be adjusted according to culture and susceptibility results. The guidelines give no antibiotic recommendations regarding abscesses, but consensus is established that simple incision and drainage is the standard treatment. If antibiotics are indicated, dicloxacillin or cloxacillin are preferred and metronidazole might be added if anaerobic pathogens are suspected.

Evaluation of antibiotic treatment

Appropriateness of antibiotic treatment was evaluated for episodes in which empiric antibiotics were prescribed and positive culture results were achieved. Episodes with additional foci other than SSTI were excluded. Treatment was regarded as non-appropriate if isolated bacteria were of intermediate susceptibility or resistant, if an antibiotic with a lower minimum inhibitory concentration (MIC) could have been prescribed, or if treatment had unnecessarily broad spectrum. In most cases, evaluation was non-controversial, but some cases required consideration as follows.

Against streptococci, penicillin was the drug of choice. Clindamycin prescribed to non-allergic patients was regarded non-appropriate due to unnecessarily broad spectrum, unless clindamycin was started empirically and continued after testing reported clindamycin sensitive streptococci. These cases were analyzed regarding empirical therapy, but excluded from analysis of adjusted therapy, as this was too controversial to judge in retrospect. Dicloxacillin and cloxacillin were regarded non-appropriate against streptococci, due to a higher MIC than penicillin.

Against staphylococci, dicloxacillin or cloxacillin was the drug of choice. Although controversial, we regarded clindamycin appropriate if the staphylococci were susceptible, in order to give a conservative estimate of the proportion of non-appropriate treatment. Penicillin was regarded as appropriate if the staphylococci were susceptible.

In cases with single isolates of streptococci or staphylococci, a combination of dicloxacillin or cloxacillin and penicillin was regarded non-appropriate due to unnecessary combination therapy and thus broad spectrum. In infections with isolation of both streptococci and staphylococci, the combination was regarded as appropriate, as was penicillin monotherapy, if the isolates were susceptible.

In anaerobic infections, we regarded metronidazole or penicillin as single therapy as appropriate, if isolates were susceptible. Other culture results were considered individually.

Adjustment of antibiotic therapy was considered possible when results of cultures and susceptibility testing indicated this was an option.

Statistics

Descriptive and univariate statistics were used. 95% confidence intervals were calculated using estimated standard error. For bivariate analysis of categorical variables we used chi-square-test or Fisher´s exact test. P values < 0,05 were considered statistically significant. SPSS versions 22 and 25 were used.

Ethics

The study was approved by the Regional Ethics Committee of South-East Norway and the Data Protection Officer for Research at Aker Hospital. We were granted exception from requiring informed consent in order to minimize the risk of selection bias, because the study population of PWID are often difficult to reach and have high mortality subsequently to discharge from hospital and our data were collected retrospectively [2].

Results

During the two year study period 135 PWID were admitted with SSTI. 72% were men, and the mean age was 41,2 years. They constituted 21% of in-patient days for all SSTIs and 31% of abscesses, and 0,5% of all patients admitted. Many patients had more than one infection focus, maximum four. In all there were 170 SSTI foci, of which 133 (78%) were abscesses. 19 patients

(14%) had additional foci, and 11 of these had bacteraemia or sepsis, of which eight had bacteremia verified by blood culture.

Bacteria and resistance patterns

Cultures were obtained from 103 (77%) abscesses, with bacterial growth in 80 (78% of those cultured). In patients with erysipelas and cellulitis, eight cultures (24%) were obtained and five (63% of those cultured) had bacterial growth. Staphylococci and streptococci were the most prevalent bacteria. MRSA was found in only one patient. Ten isolates of Gram-negative rods and ten anaerobes, one of those Clostridium perfringens, were found [Table I]. In 16 foci, there were mixed cultures, with a maximum of four bacterial strains.

All streptococci and 15% of staphylococci were susceptible to penicillin, while 90% of streptococci and 90% (CI 80-100%) of S. aureus were susceptible to clindamycin.

Antibiotic therapy

Antibiotics were prescribed to 91% of patients with abscesses and to 88% with erysipelas/cellulitis. 90% of abscess cases were treated surgically, 7% with surgery only.

There was compliance to guidelines in 59 (70%) patients with abscesses and in 12 (71%) patients with erysipelas/cellulitis. Antibiotics prescribed in the compliant and the non-compliant group are shown in Figure I.

Further evaluation of erysipelas/cellulitis cases was restricted by sparse data. Regarding abscesses [Table II], antibiotic therapy in compliance to guidelines was appropriate in 11 (32%) cases, compared to two (13%) cases with non-compliant therapy (p=0,293). In the compliant group there was resistance to given antibiotics in three (9%) cases and in the non-compliant group in three (21%). Hence, effective empirical antibiotics were given to 91% in the compliant group and 79% in the non-compliant group (p=0,334). Only 6% in the compliant group received broad spectrum empirical antibiotics in contrast to 87% in non-compliant cases (p<0,001). In the compliant group 53% received a second choice agent as empirical antibiotic compared to 13% in the non-compliant group (p=0,014).

In 37 cases where adjustment of antibiotic therapy was possible, including six cases with resistance to initial therapy, adjustment was performed in only 14 cases (38%). In seven cases we identified practical obstacles such as discharge from hospital before culture results were reported. In none of the cases with resistance was therapy adjusted [Table III].

Discussion

Main findings

As expected, staphylococci and streptococci were the most frequently isolated species.

Resistance

Bacteria and resistance patterns did not differ significantly from cases with SSTI in the general Norwegian population. In accordance with studies from Switzerland and Sweden, MRSA was rarely isolated [2, 24]. There was a higher prevalence of S. aureus resistant to clindamycin than the 2,3% reported from the total Norwegian population [25]. Our results may indicate a specific feature regarding clindamycin resistant bacteria in the PWID population in Oslo. Emergence of resistance to clindamycin and tetracyclines has been observed in some communities, and awareness of regional susceptibility patterns is thus necessary [26].

Antibiotic treatment

When compliant to guidelines, empiric antibiotic treatment was more often in accordance with culture results, as unnecessarily broad spectrum treatment was significantly more often prescribed in the non-compliant group. A substantial number of patients in the compliant group received second choice agents, as they were prescribed dicloxacillin or cloxacillin against streptococcal infections. This is an acceptable effect of covering empirically for possible staphylococcal infections.

Adjustment of antibiotic therapy was done in only half of the cases where it was possible, and in none of the cases with resistance to initial treatment. This might indicate an adequate effect of surgery alone, as all these patients were treated surgically. Other studies in hospitalized patients have shown that adequately drained abscesses have high healing rates, also when patients are treated with non-effective antibiotics [27-29]. Only 7% of abscesses in our study were treated with incision and drainage alone. This might suggest overtreatment of abscesses with antibiotics, but it may also indicate that SSTIs in PWID are more severe than in other patients or that the patients were hospitalized due to more serious infections.

There was no support for our hypothesis that PWID would receive inappropriate therapy if treated according to general guidelines. On the contrary, compliance to antibiotic guidelines led to significantly less use of broad-spectrum antibiotics and to good empirical coverage of bacteria. Our study revealed that there is still room for improvement of antibiotic therapy in this group of patients.

Implications for surveillance

The data in this study dates back to 2009/2010. There is no more recent corresponding data from Norway. It is important to monitor trends in pathogens and antibiotic resistance in PWID with SSTIs and compare to the general population.

As expected we found a low prevalence of MRSA, but further surveillance is needed, as outbreaks have been seen in other countries.

Public health

The PWID population in Oslo constitutes less than 1% of the total adult population. Nevertheless, one fifth of all inpatient days due to SSTIs and one third of those due to abscesses occurred among PWID. In this study none of the patients died, which may be due to comprehensive hospital treatment. Since these infections seldom are lethal, their importance may be underestimated [2]. A Norwegian study found an incidence of local bacterial infections of 8,5 hospital treatment contacts per 100 patient-years among PWID [30]. This underlines the vulnerability of PWIDs to such infections and the magnitude of drug injecting as a public health problem.

Strengths and limitations

This study refers to hospitalized patients and we do not know to what extent the findings are representative of SSTIs among non-hospitalized PWID. In comparison with PWID population statistics from the Norwegian Institute for Alcohol and Drug Research (SIRUS), the sample was representative of PWID in

Oslo regarding gender and substances used, but had a higher mean age of 41,2 years compared to 32-38 years in SIRUS materials [31]. It is probable that SSTIs resulting in hospitalization are more severe than average SSTIs within the PWID population with a greater proportion of infections where antibiotic treatment is indicated. Relevant characteristics of bacteria and antibiotic resistance unique to the PWID population would therefore likely be recognized in this sample. The observation period was two years and included patients from both surgical and medical wards. Hence, our observations regarding bacteria and antibiotic resistance are most likely representative of PWIDs in Oslo 2009/2010.

Our data is limited by retrospective collection from hospital records. Data was, furthermore, collected some time ago. We did not include a control group. With a control group, we could to a larger extent have been able to distinguish factors related to the patient population of PWID from other factors such as regional factors and demographic factors. We did not investigate subgroups of PWID in terms of abused drug preference. We have no information about the patients after discharge from hospital.

Conclusion

Bacteria and antibiotic resistance patterns did not differ significantly from SSTIs in the general population in Norway.

Compliance to antibiotic guidelines led to significantly less use of broad-spectrum antibiotics and to good coverage of bacteria. General treatment guidelines should be applied to PWIDs with SSTIs.

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intravenous drug use in Norway. SIRUS-report nr 5/2006]. Oslo2006.

Tables and figures

Table I: 112 isolated strains; 102 from abscesses, six from erysipelas/cellulitis, four from foci unclear whether abscess or erysipelas/cellulitis

Table II: Evaluation of empiric antibiotic treatment relative to culture results in cases where empirical antibiotics were prescribed and positive culture results were achieved

Table III: Isolated bacteria and initial antibiotic choice in six episodes with resistance to empirical antibiotic therapy

Figure I: Antibiotics prescribed in 71 treatment episodes with compliance to guidelines and 30 treatment episodes with non-compliance

Table I
112 isolated strains; 102 from abscesses, six from erysipelas/cellulitis, four from foci unclear whether abscess or erysipelas/cellulitis

Number (%, 95% confidence interval)

	Abscess	Erysipelas/ cellulitis	Total
Staphylococci	35 (34, 25-43)	5 (83, 52-100)	42 (38, 29-47)
Staphylococcus aureus, MSSA	*35*	*3*	*40*[a]
Staphylococcus aureus, MRSA	*0*	*2*[b]	*2*
Streptococci	44 (43, 33-53)	1 (17, 0-48)	46 (41, 32-50)
Streptococci, Milleri-group	*25*	*0*	*25*
Streptococci gr A, beta-hemolytic	*15*	*1*	*16*
Streptococci gr B, beta-hemolytic	*1*	*0*	*1*
Streptococci gr G, beta-hemolytic	*1*	*0*	*2*[a]
Streptococci, alpha-hemolytic	*1*	*0*	*1*
Streptococci, non-specified	*1*	*0*	*1*
Anaerobe bacteria	10 (10, 4-16)	0	10 (9, 4-14)
Prevotella divines	*1*	*0*	*1*
Clostridium perfringens	*1*	*0*	*1*
Bacterioides fragilis	*1*	*0*	*1*
Peptostreptococci	*1*	*0*	*1*
Anaerobe bacteria, non-specified	*6*	*0*	*6*
Gram negative rods	10 (10, 4-16)	0	11 (10,4-16)
Escherichia coli	*4*	*0*	*4*
Citrobacter species, non-specified	*2*	*0*	*2*
Enterobacteriaceae, non-specified	*1*	*0*	*1*
Pseudomonas aeruginosa	*0*	*0*	*1*[a]
Gram negative rods, non-specified	*3*	*0*	*3*
Other	3 (3, 0-6)	0	3 (3, 0-6)
Enterococcus faecalis	*2*	*0*	*2*
Gram positive rods, non-specified	*1*	*0*	*1*

[a] Cultured from foci, where it was unclear whether there was abscess or erysipelas/cellulitis.
[b] Two strains of MRSA found in one infectious episode, cultured from two different foci.

Table II
Evaluation of empiric antibiotic treatment relative to culture results in cases where empirical antibiotics were prescribed and positive culture results were achieved

Number (%)

Appropriateness of treatment of 34 abscess cases with compliance and 15 without compliance to guidelines

	Appropriate[a]	Non-appropriate[a]	p-value[b]
Compliance	*11 (32)*	*23 (66)*[b]	*p=0,293*
Non-compliance	*2 (13)*	*13 (87)*[b]	
Total	13	36	

Resistance to the prescribed antibiotics, comparing 33 abscess cases with compliance and 14 without compliance to guidelines

	Resistance	No resistance	p-value[b]
Compliance[c]	*3 (9)*	*30 (91)*	*p=0,334*
Non-compliance[d]	*3 (21)*	*11 (79)*	
Total	6	41	

Prescribing of broad-spectrum empirical antibiotics, comparing 34 abscess cases with compliance and 15 without compliance to guidelines

	Yes	No	p-value[b]
Compliance	*2 (6)*	*32 (94)*	*p=<0,001*
Non-compliance	*13 (87)*	*2 (13)*	
Total	15	34	

Use of a second choice agent as empirical antibiotic, comparing 34 abscess cases with compliance and 15 without compliance to guidelines

	Yes	No	p-value[b]
Compliance	*18 (53)*	*16 (47)*	*p=0,014*
Non-compliance	*2 (13)*	*13 (87)*	
Total	20	29	

[a] Treatment was regarded as non-appropriate if the isolated bacteria showed intermediate susceptibility or total resistance, if an antibiotic with a lower minimum inhibitory concentration (MIC) could have been prescribed, or if the treatment was unnecessarily broad spectrum.

[b] Fisher´s exact test

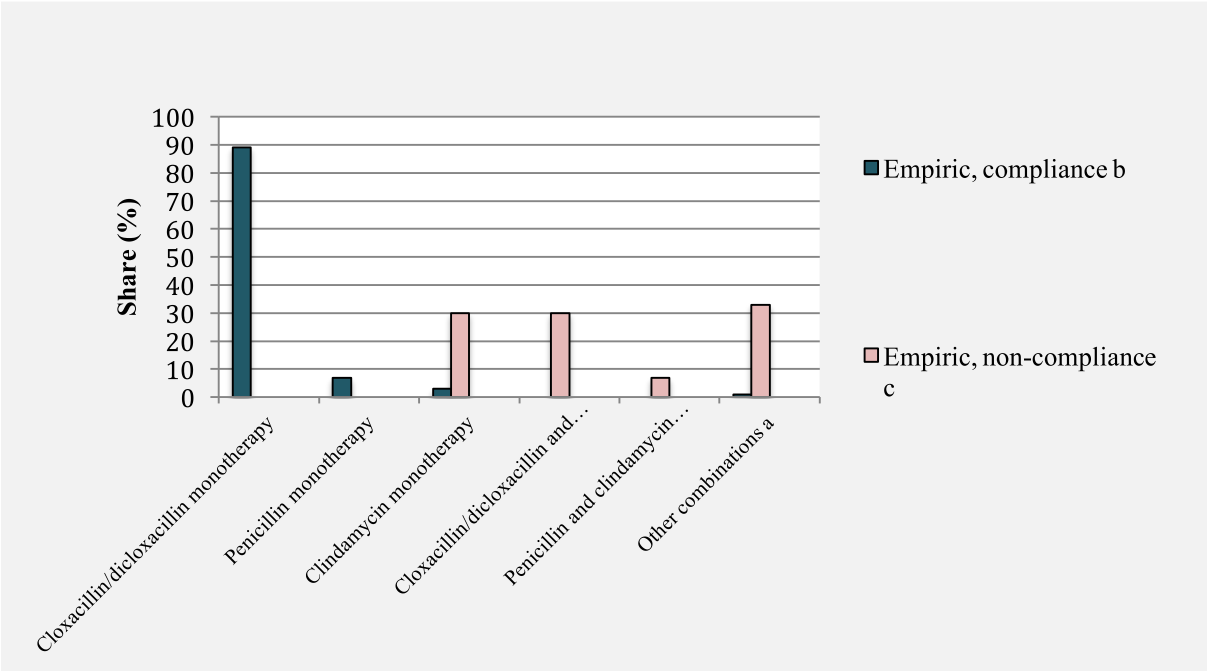
[c] In one treatment episode with compliance to guidelines, resistance could not be adequately assessed, but treatment was non-appropriate due to use of second choice agent

[d] In one treatment episode without compliance to guidelines, resistance could not be adequately assessed, but treatment was non-appropriate due to use of broad spectrum antibiotics

Table III
Isolated bacteria and initial antibiotic choice in six episodes with resistance to empirical antibiotic therapy

Type of focus	Compliance to guidelines	Empirical antibiotics	Surgery	Culture result	Adjusted
Abscess	Yes	Dicloxacillin	Yes	E. coli and anaerobes	No[a]
Abscess	Yes	Dicloxacillin	Yes	E. coli	No
Abscess	Yes	Dicloxacillin	Yes	Citrobacter sp.	No
Abscess	No	Penicillin and metronidazol	Yes	S. aureus	No
Abscess	No	Clindamycin	Yes	S. milleri	No[a]
Abscess	No	Penicillin and dicloxacillin	Yes	S. aureus[b]	No[a]

[a] Culture result after discharge from hospital
[b] Resistant to penicillin, sensitive to dicloxacillin



[a] In the compliance group one patient was prescribed a combination of dicloxacillin and metronidazol. In the non-compliance group 10 patients were prescribed combinations of dicloxacillin, penicillin, ampicillin, amoxicillin, ciprofloxacin, cefalexin, clindamycin, metronidazol or gentamycin.

[b] One treatment episode with bacteremia that did not interfere with treatment

[c] No treatment episodes with foci other than SSTI

Figure I
Antibiotics prescribed in 71 treatment episodes with compliance to guidelines and 30 treatment episodes with non-compliance