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Inappropriate initial treatment of secondary intra-abdominal infections leads to increased risk of clinical failure and costs

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Aims
The objective of this population-based, retrospective cohort study was to investigate the incidence and initial antibiotic treatment of secondary intra-abdominal infections (sIAI) and to assess whether inappropriate initial antibiotic therapy affects patient outcomes.

Methods
All patients hospitalized for sIAI (1995–1998) were identified in the PHARMO Record Linkage System, a patient-centric database including pharmacy dispensing records from community pharmacies linked to hospitalization records in the Netherlands. Complementary in-hospital antibiotic drug use was obtained from the computerized inpatient pharmacy files. The patient outcomes considered were switch to second-line antibiotic treatment, re-operation, and death. In addition, a composite variable clinical failure was constructed based on the above-mentioned outcomes. Furthermore, the effect of clinical failure on length of hospital stay and costs of hospitalization was assessed. Associations between appropriateness of initial antibiotic treatment and outcomes were estimated using multivariate logistic and linear regression models.

Results
In the source population of 228 000 persons, 175 cases were classified as sIAI (mean age 49.3 ± 24.5, 50.9% male) resulting in an incidence of 2.3/10 000 person-years [95% confidence interval (CI) 2.0, 2.7]. Initial antibiotic treatment was appropriate for 84% of the cases. The risk of clinical failure was 17.1%. Inappropriate initial antibiotic treatment increased the risk of clinical failure 3.4-fold (95% CI 1.3, 9.1). Length of hospital stay and costs of hospitalization were significantly increased for patients with clinical failure.

Conclusions
Inappropriate choice of initial antibiotic therapy in sIAI patients leads to more clinical failure resulting in a longer hospital stay and higher costs of hospitalization compared with appropriate initial antibiotic therapy.

Introduction

Secondary intra-abdominal infection (sIAI) describes peritoneal infection with an obvious cause based on intra-abdominal catastrophes such as bowel perforation (60–80% of all cases), bowel necrosis, nonbacterial peritonitis, or penetrating infectious processes [1]. The peritonitis develops when bacteria contaminate the peritoneum. The organisms most frequently cultured are mixed flora in which Gram-negative bacilli and anaerobes predominate, especially when originating from the colon. Existing estimates of the incidence of sIAI use the number of patients who are admitted to an intensive care unit or who undergo laparotomies as denominator, but there is a general lack of insight into the population-based incidence of sIAI [1].

Antibiotic therapy is an important aspect of the treatment of sIAI. The Surgical Infection Society has developed and presented guidelines for use of anti-infective agents in sIAI [2]. Acceptable antimicrobial regimens include single drugs such as cefotetan or ertapenem or combination therapy with antianaerobe drugs such as clindamycin and metronidazole with an aminoglycoside, cephalosporine or monobactam [2–4]. Antimicrobial agents with little or no activity against facultative anaerobic or anaerobic Gram-negative rods are considered not appropriate [2]. However, there are indications that these infections are not always treated according to these guidelines, which may lead to significant treatment failure in daily practice.

The objective of this population-based study was to investigate the incidence and initial antibiotic treatment of sIAI and to assess whether inappropriate initial antibiotic therapy affects patient outcomes.

Methods

Setting

We conducted a retrospective cohort study using data from the PHARMO Record Linkage System (http://www.pharmo.nl) that was complemented with *ad hoc* collected data from computerized inpatient pharmacy files. The PHARMO database includes pharmacy dispensing records from community pharmacies linked to hospital discharge records of more than two million community-dwelling residents of 40 population-defined areas in the Netherlands from 1985 onwards [5]. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification [6]. The hospital discharge records are obtained from PRISMANT (http://www.prismant.nl), previously known as the Dutch Centre for Healthcare Information (LMR database), an institute that collates nationwide all hospital discharge records in the Netherlands since the 1960s into a standardized format. These records include detailed information concerning the primary and secondary discharge diagnoses, diagnostic, surgical and treatment procedures, type and frequency of consultations with medical specialists and dates of hospital admission and discharge. All diagnoses are coded according to the International Classification of Diseases, 9th edition (ICD-9-CM). For this study, PHARMO data were linked to in-hospital drug use data and hospital discharge letters available for four hospitals that covered an area of 228 000 inhabitants. In these hospitals drugs were dispended and registered on a named patient basis. The inpatient drug file always comprised the minimal identification information on the patient (anonymous), name of the active compound and day of dispensing.

Case definition

IAI cases were defined as patients who acquired one of the following sIAI during the study period from 1 January 1995 to 1 January 1999: cholecystitis with rupture; diverticular abscess; appendiceal perforation and periappendiceal abscess; acute gastric and duodenal perforation operated within 24 h; perforation of intestines; traumatic perforation of the intestines; and intra-abdominal abscess.

To obtain the sIAI cases we used a two-step approach, starting out with a broad search to identify potential cases followed by a validation step. Potential cases of sIAI were identified from the computerized hospitalization records on the basis of a primary discharge diagnosis with one of the following International Classification of Diseases, ninth revision (ICD-9-CM) codes: 475, 540–543, 562, 567, 569, 574–577, 614.5, 997.4, 998.2, E8782, E8783. Subsequently, all potential cases that did not receive an intra-abdominal surgical intervention to establish the diagnosis sIAI or antibiotic treatment during their hospital admission were excluded. For all remaining potential sIAI cases hospital discharge letters were independently validated by a clinician and an epidemiologist on meeting our case definition.

Inappropriate antibiotic therapy

Initial antibiotic therapy was considered inappropriate if it did not cover facultative and aerobic Gram-negative bacteria plus anaerobic microorganisms [2, 4]. Thus, inappropriate therapies comprised single therapies and/or combination regimens that failed to cover β-lactamase producing Gram-negative bacilli.

Outcome parameters

For outcome assessment all patients were followed from the day of hospitalization until discharge. As study out-

comes we considered switch to second-line antibiotic treatment, re-operation, and death [7]. We also constructed a composite variable of clinical failure that comprised switch to second-line therapy, re-operation or death [7]. Absence of clinical failure was defined clinical success. Furthermore, the effect of clinical failure on length of hospital stay, and direct medical costs of hospitalization (from the perspective of third-party payer) was assessed.

Co-variates

Relevant clinical characteristics and risk factors for the various outcomes were obtained from the PHARMO database and comprised: age, gender, antibiotic therapy during the 30 days prior to hospitalization and comorbidity predictive of preoperative organ impairment, which included cerebrovascular disease within 1 month of admission, cardiovascular disease (ischaemic disease, congestive heart failure), pulmonary disease (respiratory underlying disease: asthma/chronic obstructive pulmonary disease, cystic fibrosis), cancer, endocrinological disease (insulin-dependent diabetes mellitus), thyroid disease, renal disorders, liver disease, and use of corticosteroids or immunomodulants. As measure of chronic comorbidity the updated chronic disease score (CDS) was calculated [9]. The CDS is based on use of drugs as a proxy for long-term diseases [8]. The continuous score was categorized into four classes: no comorbidity (CDS = 0), mild (CDS 1–3), moderate (CDS 4–6) and severe comorbidity (CDS > 6).

The anatomical origin of infection was obtained from the hospital discharge letter and categorized on the basis of type and load of bacterial contamination as either upper gastrointestinal (GI), appendix, lower GI, or other.

Analysis

The incidence rate of sIAI was calculated by dividing the number of cases by the number of person-years in the source population. Incidence calculations were based on information from three out of four hospitals, for which we captured more than 90% of sIAI. Poisson regression was used to calculate the 95% confidence interval (CI) of the incidence rate.

The association between appropriateness of initial antibiotic treatment, covariates and outcome parameters was analysed using multivariate logistic regression analyses.

The effect of clinical failure on length of hospital stay and costs of hospitalization [excluding Intensive Care Unit (ICU) costs] was explored using general linear models.

The costs of hospitalization were estimated for each patient based on charges to third-party payers and expressed in Euro values at the time they were incurred (1995–1998 values). Costs attributable to inappropriate antibiotic treatment were estimated by multiplying the attributable risk fraction [AR = (OR − 1)/OR] that was obtained from the association between inappropriate antibiotic treatment and clinical failure by the cost difference among patients with and without clinical failure. All analyses were conducted with SPSS PC version 10 (SPSS Inc., Chicago, IL, USA) and SAS PC version 6.2 (SAS Institute Inc., Cary, NC, USA).

Results

Study population

Within the source population of 228 000 persons we identified 569 potential cases of sIAI who received both surgery and antibiotics. For 58 potential cases (10.2%) the correct discharge letter could not be retrieved, and 336 potential cases (65.9% of validated discharge letters) did not meet our definition of sIAI cases. Our final study population comprised 175 cases with sIAI (median age 53 years, 50.9% male) (Table 1). The most frequent cause of sIAI was a perforated appendicitis (49.7% of 175). Only 10.9% of the cases had been treated with oral antibiotics in the month prior to hospitalization (mostly doxycycline, amoxicillin and trime-

Table 1
Clinical characteristics of cases of secondary intra-abdominal infection

Characteristic	*N*	%
Age (median, IQR)	53	(29–69)
Male	89	50.9
Comorbidity (based on CDS)		
No comorbidity	96	54.9
Light comorbidity	36	20.6
Moderate comorbidity	33	18.9
Severe comorbidity	10	5.7
Prior treatment (last month) with antibiotics	19	10.9
Origin of infection		
Upper gastrointestinal tract	39	22.3
Appendix	87	49.7
Lower gastrointestinal tract	47	26.9
Other	2	1.1
Operation		
Within 1 day	156	89.1
After more than 1 day	19	10.8
Total	175	100.0

thoprim). Surgery was conducted within 1 day in 90% of the patients. The prevalence of preoperative organ impairment was 25.7%, the most frequent concomitant diseases were cardiovascular, pulmonary and immunomodulatory. The population-based incidence rate of sIAI was 2.3/10 000 persons-years (95% CI 2.0, 2.7).

Initial antibiotic treatment and outcomes

The first antibiotic regimen was considered appropriate in 84% of the patients (Table 2).

A total of 11 patients needed to change to second-line antibiotic therapy during hospitalization (6.3%). Change to second-line antibiotic therapy occurred significantly more among patients who initially started with inappropriate therapy (32.1%, 95% CI 17.9, 50.7) compared with patients who started appropriate initial treatment (1.4%, 95% CI 0.04, 4.8) (Table 2). Re-operation had to be conducted in 15 patients (8.6%) in total. The risk of re-operation was highest in patients with a lower GI origin of infection ($P = 0.010$), but neither appropriateness of initial antibiotic therapy nor other covariates was associated with re-operation. Ten persons in total died during hospitalization for sIAI, leading to a fatality rate of 5.7% (95% CI 3.1, 10.2). Mortality was associated with increasing age (all deaths were of those >65 years old, $P < 0.001$), cardiovascular comorbidity ($P = 0.013$), endocrinological comorbidity ($P = 0.003$), and origin of infection (highest risk for upper GI tract origin 15.4%, 6.4% for lower GI and 1.1% for appendix as origin, $P = 0.016$). Although not statistically significant, we observed a higher fatality rate among patients with inappropriate treatment (10.7% *vs.* 4.8%).

The overall risk for the composite variable clinical failure during hospitalization for sIAI was 17.1% (95% CI 12.2, 23.4) (Table 2). Risk factors for clinical failure were age ($P = 0.002$), inappropriateness of initial therapy ($P = 0.004$) and origin of infection ($P = 0.003$) (Table 3). Inappropriateness of initial antibiotic therapy remained the only independent predictor (OR = 3.4, 95% CI 1.3, 9.1) of clinical failure in a multivariate logistic regression model that included age, origin of infection and initial antibiotic therapy (Table 3).

The median length of hospital stay for all sIAI patients was 10 days (range 3–133 days, interquartile range 7–16 days). The median length of hospital stay for patients without clinical failure was 9 days compared with 16.5 days for patients with clinical failure ($P < 0.001$). In a multivariate general linear model, ori-

Table 2
Initial antibiotic regimens and patients' outcomes

Type of first treatment	*N*	Change to second-line therapy	Re-operation	Death	Clinical failure
Appropriate therapy[1]	147 (84.0%)	2 (1.4%)	14 (9.5%)	7 (4.8%)	20 (13.6%)
Amoxicillin +clavulanic, metronidazole	2				
Cefazolin, metronidazole	5				
Cefotaxime, clindamycine	2				
Cefotaxime, metronidazole	43	2	8	3	10
Cefuroxime, metronidazole	95		6	4	10
Inappropriate therapy[1]	28 (16.0%)	9 (32.1%)	1 (3.4%)	3 (10.7%)	10 (35.7%)
Piperacillin	1	1			1
Piperacillin, gentamicin	1	1			1
Amoxicillin	2			1	1
Ceftazidime or cefotaxime or cefuroxime	8				
Flucoxacillin	1	1	1		1
Gentamicin	1				
Metronidazole	8	3		2	3
Norfloxacin or ofloxacin	6	3			3
Total	175	11 (6.3%)	15 (8.6%)	10 (5.7%)	30 (17.1%)

[1]*Classification according to Surgical Infection Society Policy Statement [2]. Metronidazole, cefotaxime, cefuroxime, and the aminoglycosides were all administered as intravenous (i.v.) therapy.*

Table 3
Associations between initial antibiotic regimen, selected covariates[1] and the composite outcome clinical failure

Characteristic	*N*	Risk of failure within stratum	*P*-value[2]	OR[3]	95% CI
Initial antibiotic regimen					
Inappropriate	10	35.7%	0.004	3.4	1.3, 9.1
Appropriate	20	13.6%		Ref.	
Age, years					
<65	12	10.6%	0.002	Ref.	
>65	18	29.0%		2.3	0.90, 5.7
Department of admission					
Surgical	23	15.5%			
Nonsurgical	7	25.9%	0.19		
Operation delay					
Within 1 day	26	16.6%			
After more than 1 day	4	21.0%	0.63		
Origin of infection					
Upper gastrointestinal tract	9	23.1%	0.003	0.77	0.28, 2.1
Appendix	6	6.9%		0.27	0.09, 0.84
Lower gastrointestinal tract	14	29.8%		Ref.	
Other	1	50.0%		NA	
Total	30	17.1%			

[1]*Comorbidity, CDS and treatment with antibiotics in the 30 days prior to hospitalization were also analysed, but no association with clinical failure was found.* [2]*Pearson's* χ^2. [3]*Odds ratio following multivariate logistic regression with age, origin of infection, and initial antibiotic regimen.*

gin of intra-abdominal infection (especially lower GI origin, $P = 0.0001$) and clinical failure ($P = 0.0001$) remained independent predictors for an increased length of hospital stay.

The total costs of sIAI amounted to €1076 024 for all cases or mean costs of €6150 per person per hospitalization. Without ICU costs (extrapolated from a sample of 61 patients among whom the ICU admission rate was 13.1%, with mean ICU costs of €1055 per person) the mean costs were €6011 per person per hospitalization (median €4131). In a multivariate model only the origin of infection and clinical failure remained independent predictors of costs. The difference in costs between patients with and without clinical failure amounted to €6287. Of these costs, 70.5% (€4438) could be attributed to inappropriate initial antibiotic therapy among those who received inappropriate antibiotic therapy.

Discussion

The results of this study show that sIAI requiring prompt surgical intervention and antibiotic treatment is a rare condition (2.3 cases per 10 000 person-years). To our knowledge, there is no information on the population-based incidence of sIAI. Our incidence estimate depends on our definition of sIAI and will certainly be underestimated due to the strict criteria of intervention and antibiotic treatment, incomplete retrieval of discharge letters (10.2%) and hospitalizations of patients outside of the region (less than 10%).

The most frequent anatomical origin of infection in our case series was the appendix, which is consistent with other case series [1, 9]. The fatality rate was low in our study, but may be explained by the high proportion of low-mortality infections such as acute appendicitis, which has reported fatality rates of 0–2% [3].

Our clinical failure rate is in line with rates from trials that showed failure rates between 1.7 and 37% [3, 7, 9], depending on the type of antibiotics used, severity and type of sIAI included and definition of clinical failure. In our study, inappropriate antibiotic treatment increased the risk of clinical failure 3.4-fold. Clinical failure itself was associated with a longer length of hospital stay and higher costs of hospitalizations per patient. Among patients with clinical failure, 35.7% had received inappropriate antibiotic treatment, and for those patients 70.5% of the extra costs could be attrib-

uted to inappropriate antibiotic treatment. Our results are comparable to a recently published study performed in Germany which showed a significant association between appropriateness of initial antibiotic therapy and clinical failure in patients with community-acquired sIAI [9]. Clinical failure was a composite of three different outcomes: requirement for second-line treatment, re-operation and death [7]. This measure has been proposed and accepted as a measure for evaluation of drug effectiveness in clinical trials. However, in our study the association between inappropriate antibiotic treatment and clinical failure was driven by switches to second-line antibiotic treatment rather than re-operation or death, which may be considered less relevant from a clinical perspective, where more value is given to re-operation and death and less value to the requirement for second-line treatment. Unfortunately, the number of cases was too small to study second-line treatment, re-operation and death, separately.

The association between inappropriateness of antibiotic treatment and clinical failure or the association between clinical failure and length of hospital stay or costs may be slightly confounded by the lack of data on prognostic scores such as APACHE II, the Mannheim peritonitis index or other scores that have been evaluated to be associated with mortality [10–13]. Lack of adjustment for these factors may have resulted in an underestimation of the effect of inappropriate antibiotic therapy, since inappropriate initial antibiotic therapy is likely to be negatively associated with initial severity. As a consequence, our estimate of attributable risk and costs due to inappropriate antibiotic treatment is conservative. Although we adjusted for the origin of infection, we cannot exclude heterogeneity and therefore residual confounding due to the broad classes. However, stratification for origin of infection showed that the association between inappropriateness of initial therapy and clinical failure was rather homogeneous, which strengthens our conclusions.

In conclusion, we showed that the incidence of sIAI requiring surgical intervention and antibiotic treatment is low. An inappropriate choice of initial antibiotic therapy in sIAI patients leads to more clinical failure resulting in a longer hospital stay and higher costs of hospitalization compared with appropriate initial antibiotic therapy.

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