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Antimicrobial Stewardship: Integrating Theory, Practice, and Technology

ABSTRACT BOOKLET

October 19th 2023, Brussels

ID 1

REDUCING RESIDUAL VOLUME BY FLUSHING: REQUIRED FLUSHING VOLUME-EFFICIENCY, USER-FRIENDLINESS, COST EFFICIENCY AND SAFETY

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Introduction and Objectives: it's been known for many years that with the administration of intravenous medication a rather significant part of the planned to be administered infusion solution, the residual volume (the volume that remains in the IV line and or infusion bag), does not reach the patient and is wasted. This could result in underdosage and diminished therapeutic effect. Despite the important impact on the patient, the reduction of residual volume lacks attention. An optimized and cleary stated protocol concerning the reduction of residual volume in a IV line is necessary for each hospital. The required flushing volume was determined and effectiveness, user-friendliness, cost efficiency and safety of the different flushing techniques were compared and a new developed experimental technique was described.

Material and Methods: in laboratory research possible flush methods aiming to reduce the residual volume were measured. Furthermore a self-developed experimental method was added to the study. The current flush methods and the self-developed method were compared to each other based on cost efficiency, user-friendliness and safety.

Results: the residual volumes were measured and laboratory research showed that if flushing was done with minimally 1 time equivalent the residual volume, 95 percent of glucose would be flushed through. Based on comparison it became clear that flushing by use of a pre-filled syringe would be the most cost efficient, user-friendly and safest method. According to the laboratory research, the self-developed experimental method is feasible and has the advantage that the remaining fraction of the medication can be administrated to the patient in unchanged concentration without dilution. Furthermore this technique can be applied regardless the level of the residual volume.

Conclusion and Recommendations: it's recommendable to revise the current infusion systems and flushing methods in most hospitals in Europe. Aside from education of the hospital staff and alignment on a uniform substantiated protocol, an optimized and clear policy on the reduction of residual volume is necessary in each hospital. It's recommended to flush all standard IV lines with rinsing fluid with at least the equivalent volume of the residual volume. Further laboratory and clinical research for the self-developed experimental method is needed before this method can be implemented clinically in a broader setting.

ID 2

ANTIMYCOTIC AND ANTIFUNGAL PRESCRIBING PATTERNS IN BELGIUM. RESULTS FROM THE GLOBAL POINT PREVALENCE SURVEY ON ANTIMICROBIAL CONSUMPTION AND RESISTANCE

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Background: In response to the WHO fungal priority pathogens list published in October 2022, and considering the unmet research needs regarding invasive fungal infections associated with significant morbidity and mortality, we aimed to describe patterns of antimycotics (J02) and antifungals (D01B) for systemic use in Belgian hospitals.

Methods: We analysed validated 2015-2022 Global-PPS and 2017 ECDC-PPS data from 404 surveys of 140 hospital sites.

Results: Out of 33,841 antimicrobials, antimycotics and antifungals comprised 1270 (3.75%; 1.2% in paediatric hospitals to 52.0% in secondary care hospitals) and 17 prescriptions (0.05%), respectively. Out of 1270 antimycotics, 1209 (95.2%) were prescribed for adults (mainly medical wards (34.2%), haematology-oncology wards (28.5%), intensive care units (16.0%)) and 61 (4.8%) for children (mainly haematology-oncology wards (37.7%) and paediatric medical wards (18.0%)). Triazole derivatives made up 1056 (87.3%) of prescriptions in adults, mainly fluconazole (n=814; 77.1% of which 26.3% for prophylactic and 7.6% for unknown use), voriconazole (n=117; 11.1% of which 98.3% for therapeutic use) and posaconazole (n=82; 7.8% of which 87.8% for prophylactic use). Other antimycotics represented 8.8% (n=106), mainly caspofungin (67.9%) and anidulafungin (28.6%). Triazole derivatives made up 50 (82.0%) prescriptions in children, mainly fluconazole (n=47; 94.0%) with 50.0% reported as prophylaxis; and 6 caspofungin prescriptions (9.8%), all for therapeutic use. Among adults, antimycotics for therapeutic use were mainly prescribed for pneumonia (n=169, 20.5%; mainly fluconazole (n=65; 38.5%) and voriconazole (n=59; 34.9%)), gastro-intestinal and intra-abdominal infections (n=156; 18.9%, mainly fluconazole (n=130; 83.3%), anidulafungin (n=11; 7.1%) and caspofungin (n=11; 7.1%)); and ear/nose/throat infections (n=101; 12.2%), mainly fluconazole (n=94; 93.1%)). Among adults, parenteral use was 41.3%; targeted prescribing 58.0%. Overall, the indication

was unknown in 6.4% of prescriptions, guidelines were absent in 10.2% of prescriptions; guideline compliance was 86.1%. The reason was documented in 72.5% of prescriptions; a stop/review date in 36.6%.

Conclusion: Predominantly fluconazole was prescribed. High prophylactic use warrants broadening and strengthening of stewardship interventions for antimycotic treatment, given its cost, toxicity and emerging antifungal resistance. Recommendations for antimicrobial stewardship interventions include development or review of existing guidelines; monitoring of the implementation of guidelines; improving documentation of the reason and a stop/review date for the prescription.

ID 3

BROAD SPECTRUM AZOLES AND FLUCLOXACILLIN: A DANGEROUS MATCH

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Objectives: Voriconazole and high dose flucloxacillin are standard first line treatments for invasive fungal infection with Aspergillus fumigatus and bloodstream infection with methicillin-susceptible Staphylococcus aureus (MSSA) respectively. When both co-occur, an underestimated risk of a significant interaction needs to be taken into consideration.

Methods: Description of a significant interaction in 2 critically ill patients.

Results: *Case 1:* in a 72 year old Caucasian female with chronic lymphatic leukemia, admitted to the ICU for severe SARS-CoV-2 pneumonia with respiratory failure, BAL growth of Aspergillus fumigatus prompted voriconazole therapy (6 mg/kg bid loading and 4 mg/kg bid maintenance dosing). Three days later, high dose flucloxacillin was initiated because of positive MSSA blood cultures. The voriconazole level on day 10 of the combination therapy, indicated a subtherapeutic level (< 0.2µg/mL), triggering doubling of voriconazole dosing (8mg/kg bid), whereas flucloxacillin therapy was discontinued because of a positive clinical and biochemical evolution. A second subtherapeutic voriconazole level (< 0.2µg/mL) was reported 2 days after flucloxacillin interruption, subsequently rising to a therapeutic level (3 µg/mL) after 3 days.

Case 2: A 79 year old men, with cardiac history, was admitted to the ICU for SARS-CoV-2 pneumonia with respiratory failure. A classic loading and maintenance voriconazole therapy was started and resulted in a therapeutic level (3.5µg/mL). After three days, high dose flucloxacillin was initiated because of positive MSSA blood cultures. Two voriconazole levels were undetectable (< 0.5µg/mL). After 7 days, flucloxacillin was stopped. Two days after discontinuation of the flucloxacillin, the voriconazole level was still subtherapeutic because of the persistent effect of flucloxacillin, leading to a dose increase (6mg/kg bid) and subsequent therapeutic voriconazole level (4.2µg/mL), further increasing to a toxic level (15.1µg/mL). The voriconazole therapy was continued intravenously at a maintenance dose of 4 mg/kg bid, which resulted in a therapeutic level (3.2µg/mL).

Conclusions: Subtherapeutic voriconazole levels may be caused by co-administration of high dose flucloxacillin. The need for therapeutic drug monitoring is well established because of non-linear voriconazole pharmacokinetics, narrow therapeutic-toxic margin, inter-individual variability of the expression of cytochrome enzymes. We must also take into account the sustained effect of induction after discontinuation of the therapy that induced CYP enzymes.

ID 4

COVID-19 IN THREE WAVES IN A TERTIARY REFERRAL HOSPITAL IN BELGIUM: A COMPARISON OF PATIENT CHARACTERISTICS, MANAGEMENT, AND OUTCOME

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Objective: In this study, we describe patient characteristics, treatment, and outcome of patients admitted for COVID-19 in the University Hospital of Antwerp over the first three epidemic waves of (2020-2021) and we quantified the effect of different risk factors.

Methods: Retrospective observational study of COVID-19 patients in a single Belgian tertiary referral hospital. All adult patients with COVID-19, hospitalized between February 29, 2020, and June 30, 2021, were included. Standardized routine clinical data was collected from patient records. Risk factors were assessed with multivariable logistic regression.

Results: We included 722 patients, during the first (n=179), second (n=347) and third (n=194) wave respectively. Of those, 31% required admission to the intensive care unit, of which 73% required invasive ventilation. Overall, 107 patients, or 15% died. We observed the lowest disease severity at admission during the first wave, and more elderly and comorbid patients during the second wave. Throughout the subsequent waves we observed more interhospital transfers mostly to the intensive care unit (85 of 116 transfers), an increasing use of corticosteroids and high-flow oxygen therapy. In spite of increasing number of complications throughout the subsequent waves, mortality did not increase (16.6%,15.6% 11.9% in 1st, 2nd and 3rd wave respectively). C-reactive protein above 150mg/L was predictive of the need for intensive care unit admission (odds ratio (OR) 3.77, 95% confidence interval (CI) 2.32-6.15). A Charlson comorbidity index ≥ 5 (OR 5.68, 95% CI 2.54-12.70) and interhospital transfers (OR 3.78, 95% CI 2.05-6.98) were associated with a higher mortality. For patients presenting with COVID at the emergency department we observed a decrease in antibiotic prescriptions at hospital admission from 55% (94/171) during the first wave to less than 30% (44/153) during the third wave.

Conclusions: We observed a reduction in mortality each subsequent wave, despite increasing comorbidity. Evolutions in patient management such as high-flow oxygen therapy on regular wards and corticosteroid use may explain this positive evolution. In addition, we noted a decrease in antibiotic prescriptions at hospital admission over time, possibly related to antibiotic stewardship efforts, incorporating the increasing evidence for the low incidence of early bacterial co- or superinfections.

ID 4: FIGURE AND TABLE

FIGURE 1. Epidemiologic situation in Belgium during the observation period

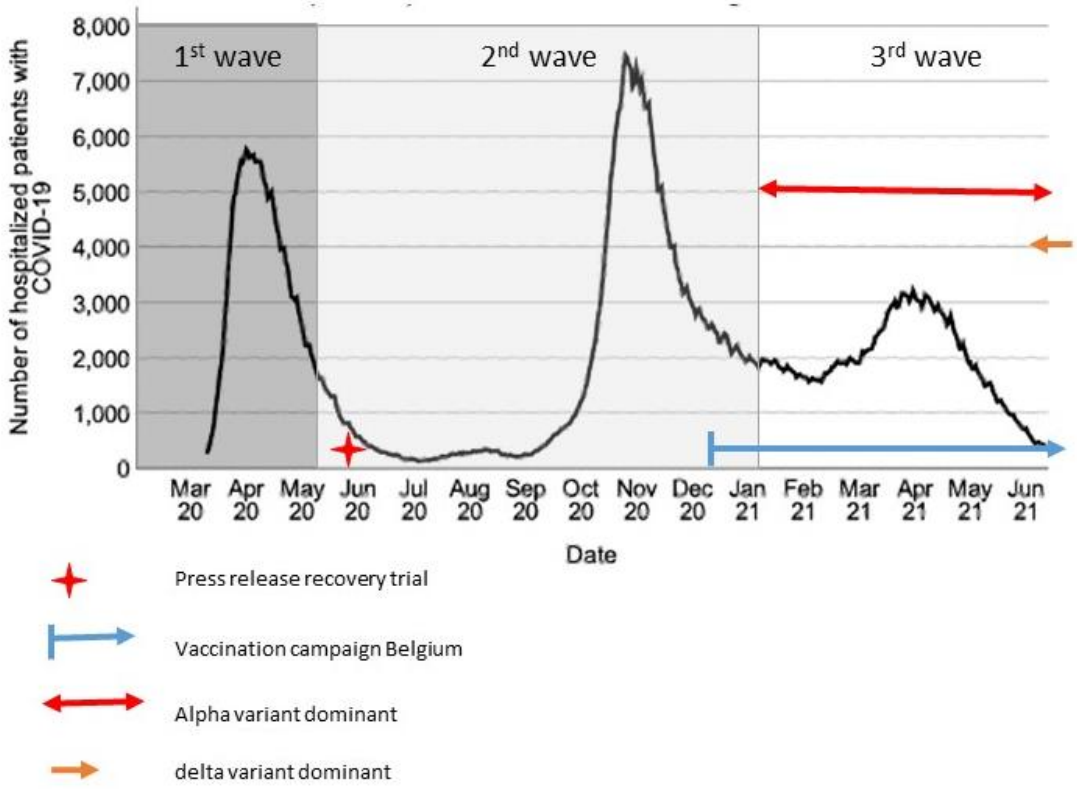

TABLE 1. Antibiotic use

Antibiotic use in non-transferred patients	All patients (	First wave (N = 171)	Second wave (N = 280)	Third wave (N = 153)	p
	n (%)	n (%)	n (%)	n (%)	
Antibiotic start at hospital admission	238 (39.4%)	94 (55.0%)	100 (35.7%)	44 (28.8%)	<0.001
Product					0.027
Amoxicillin-clavulanic acid	190 (79.8%)	69 (73.4%)	86 (86.0%)	35 (79.5%)	
Piperacillin-tazobactam	22 (9.2%)	12 (12.8%)	3 (3.0%)	7 (15.9%)	
Other	26 (10.9%)	13 (13.8%)	11 (11.0%)	2 (4.5%)	

ID 5

ANTIMICROBIAL STEWARDSHIP AS PART OF THE HOST NETWORK PROJECT: HOW TO FIND THE (COMMON) WAY TO GO?

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Background & aim: The Hospital Outbreak Support Team (HOST) is a federal project for hospital networks. Its main objective is to focus on inter- and transmural cooperation regarding antimicrobial stewardship (AMS) and infection prevention & control (IPC). The Hospital Network of Ghent consist of four hospitals. Members of each local AMS team are represented in the "HOST AMS working group". The aim is to explore and define the priorities in the next three years with focus on AMS within the HOST AMS working group.

Methods: Based on a literature review 23 AMS related quality indicators were identified by a panel of three clinical pharmacists. Each local AMS team scored the indicators on relevance using Likert scale 1-9. Furthermore each hospitals listed the top-5 indicators based on priority. The list consisted of process indicators in three main categories: diagnostics, antimicrobial therapy (indication/choice of antimicrobial agent, dosing, timing, administration route, duration, stop/de-escalation, TDM, feedback/follow-up) and some specific indicators (e.g. surgical prophylaxis, *Staphylococcus aureus* bacteremia).

Results: Each hospital prioritized different AMS quality indicators. The highest scores and priorities were given to indicators in the categories: stop/de-escalation, indication/choice of antimicrobial agent, stop/de-escalation and diagnostics.

Discussion and conclusion: Since each hospital has a different focus, the feasibility of initiating network-wide projects could be low. However, HOST can act as a central partner to share information between network hospitals. In the future, we will select and work on specific topics based on these priority scores. The best practices of a specific topic can be identified for each hospital, followed by sharing expertise and experience in the HOST AMS working group. Joint projects can be initiated in the future but are no longer the main purpose.

ID 6

RECURRENT AORTIC VALVE ENDOCARDITIS COMPLICATED BY BASILAR ARTERY THROMBOSIS DUE TO A DELAYED DIAGNOSIS OF CHRONIC Q-FEVER

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Background: Q-fever is a zoonosis caused by the intracellular pathogen *Coxiella burnetii*. Coxiellosis is widespread throughout the world with an extensive animal reservoir. Q-fever can manifest itself in both an acute and a chronic form. Acute Q-fever can cause a self-limited flu-like illness, but also pneumonia and hepatitis, although symptoms only occur in less than 50% of infected patients. Chronic Q-fever is often associated with cardiovascular complications, mostly endocarditis, but also aortic aneurysm or graft infection, osteomyelitis and osteoarthritis.

Case presentation: We present the case of a 62-year-old Dutch woman with a history of recurrent aortic valve endocarditis. The patient's first diagnosis of *S. hominis* endocarditis was in 2021. In addition to antibiotic treatment with flucloxacillin, bioprosthetic aortic valve replacement was performed. However, fever persisted after initial treatment. In June 2023, a second episode of aortic valve endocarditis was diagnosed by PET-CT scan and positive blood cultures for *S. epidermidis* (methicillin-susceptible - 1/6 bottles). No abnormalities were found on echocardiogram (TEE). Antibiotic treatment with flucloxacillin was continued for 6 weeks. Surgery was not performed. In August 2023, two weeks after discontinuation of antibiotics, the patient presented with persistent fever. Blood cultures turned positive for *S. epidermidis* (methicillin-resistant - 1/4 bottles). During hospitalisation she experienced an acute onset of left-sided hemiparesis caused by a basilar artery thrombosis. Emergency thrombectomy was successful with complete recovery of neurological symptoms. A subsequent TEE showed thickening of the aortic valve leaflets and the presence of a vegetation. In view of the multiple endocarditis episodes without convincing microbiological evidence, additional testing for culture-negative endocarditis was performed, with the detection of high *C. burnetiid* serology titres (IgG I > 1/8192, IgG II = 1/8192, IgM II = 3,89) suggestive of chronic Q-fever. Aortic valve *C. burnetii* PCR-testing is currently pending. Treatment with doxycycline and hydroxychloroquine was started for an 18-month period.

Discussion: In the absence of a convincing microbiological diagnosis of endocarditis or fever of unknown origin, Q-fever should be considered in the differential diagnosis with implementation of targeted diagnostics.

ID 7

A SYSTEMATIC REVIEW ON PHARMACOKINETICS AND TARGET ATTAINMENT OF ß-LACTAM ANTIBIOTICS IN OLDER PEOPLE

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Background: Older patients are characterized by various (patho)physiological changes that may influence the pharmacokinetics (PK) and target attainment of ß-lactam antibiotics using standard dosing regimens. This systematic review collects all current knowledge on PK and target attainment of ß-lactam antibiotics in older people, in order to identify priorities for dose optimization.

Methods: Relevant articles, published prior to the 1st of December 2021, were identified by searching the databases PubMed and EMBASE. All articles had to contain data on PK of ß-lactam antibiotics in adults ≥65 years. Extracted information included: reported PK parameters (volume of distribution, clearance, elimination rate constant, intercompartmental clearance, elimination half-life, area-under-the-concentration time curve, maximum and trough concentration), covariates on PK parameters, target attainment rate and dosing recommendations. Quality of the included articles was assessed using the clinPK scoring tool.

Results: This review includes 91 articles. The majority of articles was ruled to be of moderate to excellent quality. The main four ß-lactam subclasses were represented: 59.3% on cephalosporins + cephamycins, 25.3% on penicillins, 15.4% on carbapenems and 3.3% on monobactams. 65.9% of articles involved intravenous administration, 16.5% mixed administration routes, 12.1% oral administration and 5.5% intramuscular administration. In this review, volume of distribution was similar between the younger and older population. Older people were mainly characterized by a decreased clearance (CL) and a prolonged half-life compared to young subjects. Renal function was mostly identified as the contributing factor to altered drug CL. Target attainment was described in 30.8% of the articles and seemed to be suboptimal in 35.7% of these articles. Dosing recommendations were made in 87.9% of the articles.

Conclusions: Evidence-based dosing recommendations for the heterogeneous older population are currently sparse. There is an urgent need for more research on (patho)physiological changes in older people and PK studies that provide evidence-based dosing recommendation. This review revealed knowledge gaps and set priorities for further research.

ID 8

PK/PD TARGET ATTAINMENT OF AMOXICILLIN-CLAVULANATE AND PIPERACILLIN-TAZOBACTAM IN HOSPITALIZED OLDER PATIENTS USING CURRENT DOSING REGIMENS

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Background: (Patho)physiological changes in older people may influence the pharmacokinetics (PK) and consequently the PK/PD target attainment of ß-lactam antibiotics using standard dosing regimens. This pilot study studied PK/PD target attainment using current amoxicillin-clavulanic acid (AMOX/CLAV) and piperacillin-tazobactam (PIP/TAZ) dosing regimens in older patients.

Methods: Prospective, monocentric, observational PK study in patients over 75 years of age. 64 hospitalized patients on a geriatric ward unit treated with intravenous AMOX/CLAV (1G/0.2G QID as a 30 minutes infusion) or PIP/TAZ (4G/0.5G QID as a 3 h infusion) were included. Mid-dose blood samples were collected in first dose and/or in steady state conditions (day 1-3 after treatment). PK/PD target attainment for AMOX and PIP was defined as being 50% ƒT>MIC of 8 mg per L and 16 mg per L, according to EUCAST clinical breakpoints for Enterobacterales and Pseudomonas spp. respectively. Target attainment for CLAV respectively TAZ was defined as 50% *ƒ*T>threshold concentration of 2 mg per L and 4 mg per L.

Results: 52 patients were included for AMOX/CLAV (median age (IQR): 87 years (83-91)) and 12 patients were included for PIP/TAZ (median age (IQR): 85 years (80-90)). After the first dose, target attainment was achieved by 62.5% and 50% of patients for AMOX and CLAV respectively. In steady state conditions, target attainment was achieved by 80.6% and 58.1% of patients for AMOX and CLAV respectively. Target attainment for PIP and TAZ was achieved in all patients, both in first dose and steady state conditions.

Conclusions: This interim analysis of an ongoing antibiotic PK study shows that the current AMOX/CLAV dosing regimen requires optimization, especially in the first hours of treatment. More study is required within geriatric subpopulations to identify predictors for subtherapeutic concentrations.

ID 9

TO COVER OR NOT TO COVER NON-TYPHOIDAL SALMONELLA BLOODSTREAM INFECTION IN CHILDREN: DEVELOPING A CLINICAL DECISION SUPPORT MODEL FOR EMPIRICAL ANTIBIOTIC TREATMENT IN MALARIA ENDEMIC SETTINGS

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Introduction: Non-typhoidal *Salmonella* (NTS) frequently cause bloodstream infection in children under-five in sub-Saharan Africa and are often not covered by standard-of-care empirical antibiotics for severe febrile illness. We developed a clinical prediction model to help clinicians decide if empirical antibiotics should be modified to cover NTS in a drug-resistant NTS endemic setting.

Methods: Data were collected during a prospective cohort study in children (>28 days - <5 years) admitted with severe febrile illness to Kisantu district hospital, DR Congo. Predictors were selected *a priori* based on systematic literature review. The model was developed with multivariable logistic regression and a simplified model formatted as scoring system was derived. Internal validation to estimate optimism-corrected performance was performed using bootstrapping.

Results: In 12.7% (295/2327) of enrolled children, NTS bloodstream infection was diagnosed (Figure 1). The DeNTS prediction model and scoring system are described in Table 1 and Table 2, respectively. The area under the curve (AUC) was 0.79 (95%CI: 0.76-0.82) for the DeNTS prediction model, and 0.78 (0.85-0.80) for the DeNTS scoring system. The estimated calibration slopes were 0.95 (prediction model) and 0.91 (scoring system). At a decision threshold of 20% NTS risk, the prediction model and scoring system had 57% and 53% sensitivity, and 85% specificity (Figure 2). The net benefit suggested clinical utility, in particular when decision thresholds <30% are acceptable.

Conclusion: The model predicts NTS bloodstream infection and may support clinicians to initiate modified empirical antibiotics to cover drug-resistant NTS, in particular for decision thresholds <30%. External validation studies are needed to investigate generalizability.

ID 9: FIGURES AND TABLES

FIGURE 1. Flowchart of screening and enrollment of study participants. Legend: CFR = Case Fatality Ratio, NTS = Non-typhoidal *Salmonella*, *Pf* = *Plasmodium falciparum*; *: 2 children could not be subcategorized due to missing data on malaria status

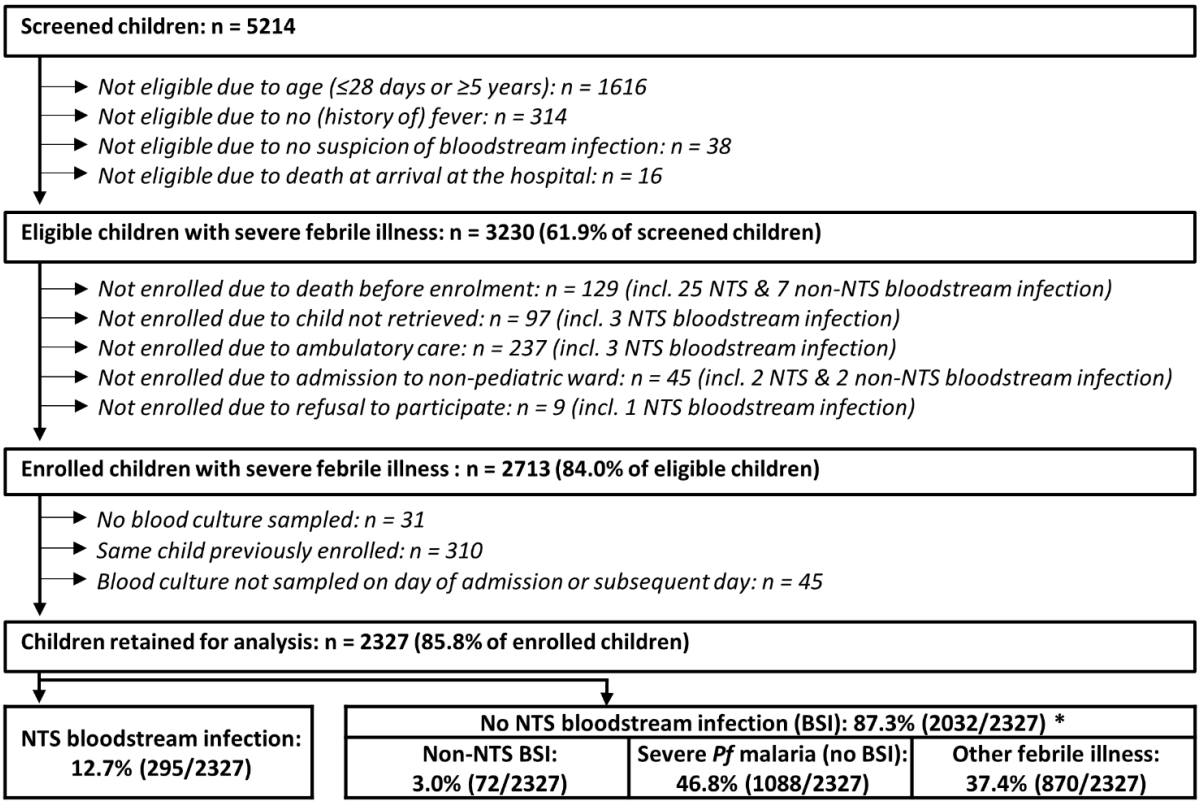
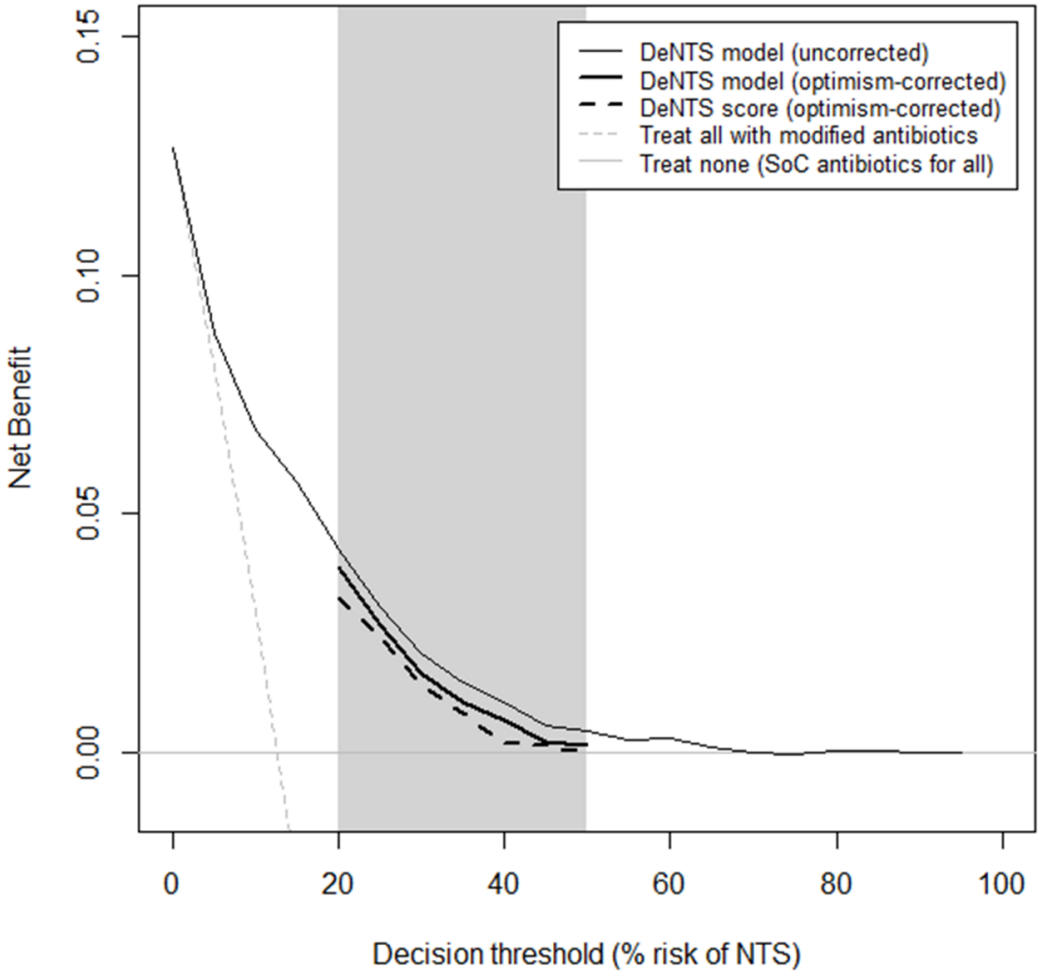


FIGURE 2. Decision curve displaying the net benefit of initiating the modified empirical antibiotic regimen to cover NTS bloodstream infections in a drug-resistant NTS endemic setting. The exact values of net benefit, and sensitivities and specificities corresponding to a range of clinically-relevant risk thresholds are displayed in the table below. Data are presented for the apparent DeNTS prediction model (uncorrected for optimism, thin black line) and, across the range of relevant risk thresholds (grey zone), for the optimism-corrected DeNTS prediction model (thick black line) and scoring system (dashed black line). The grey lines represent treating everybody with the modified empirical antibiotic regimen (dashed grey line) or treating nobody with the modified empirical antibiotic regimen (Standard of Care (SoC) empirical antibiotics for all; full grey line).



Decision threshold (estimated risk of NTS)	DeNTS prediction model			DeNTS scoring system		
	Sensitivity (95% CI)	Specificity (95% CI)	Net Benefit (per 100 children)	Sensitivity (95% CI)	Specificity (95% CI)	Net Benefit (per 100 children)
20%	57% (51-63)	85% (84-87)	3.9	53% (48-59)	85% (83-87)	3.2
25%	47% (41-53)	89% (88-91)	2.7	48% (42-53)	88% (87-90)	2.4
30%	38% (33-44)	92% (91-93)	1.7	38% (33-44)	92% (90-93)	1.4
35%	29% (24-35)	95% (94-96)	1.1	31% (26-37)	94% (93-95)	0.8
40%	24% (19-29)	96% (95-97)	0.7	22% (18-27)	96% (95-97)	0.2
45%	17% (13-21)	98% (97-98)	0.2	15% (11-20)	98% (97-99)	0.1
50%	13% (9-17)	99% (98-99)	0.1	10% (7-14)	99% (98-99)	0.01

TABLE 1. The DeNTS prediction model obtain by multivariable logistic regression with Firth's correction. Predictors retained in the DeNTS prediction model are marked in grey. The risk of NTS bloodstream infection can be calculated by the application of the coefficients in a logistic regression formula. This formula has been pre-programmed in Google spreadsheet and is freely accessible via https://tinyurl.com/dentsprediction.

Predictor	Beta-coefficients (standard error)
Intercept	-3.4509 (0.492)
Age at admission (per month)	-0.01614 (0.00576)
Admitted during rainy season	0.4998 (0.177)
Fever duration on admission (per doubling days)	0.4589 (0.0954)
Diarrhea	0.4793 (0.156)
Respiratory rate (per breath/min)	0.02296 (0.00501)
Hepato- or splenomegaly	0.5337 (0.144)
Moderate vs no malnutrition	0.4547 (0.189)
Severe vs no malnutrition	0.5419 (0.213)
Recent vs no *Plasmodium falciparum* malaria	0.7496 (0.189)
Current vs no *Plasmodium falciparum* malaria	-1.158 (0.201)
Hemoglobin (per g/dl)	-0.09086 (0.0312)

TABLE 2. Simplified DeNTS prediction model formatted as scoring system. The points per predictor were derived from the coefficients in a refitted DeNTS prediction model with categorization of continuous predictors. The sum of all points assigned to a child based on the presence of the clinical predictor variables is the total score. The estimated risks per total score value are displayed on the right. The last column lists the number of children in the dataset for each value of the total points. Color coding was applied as follows: red if the estimated risks were lower than the prevalence of non-typhoidal *Salmonella* (NTS) bloodstream infection in the dataset, yellow if higher than the prevalence of NTS bloodstream infection in the dataset but lower than the range of decision thresholds, green if within or higher than the range of clinically relevant decision thresholds.

Predictors	**Points per predictor**	**Assigned points**
Age on admission		
1-11 months	0	*Score child*
12-23 months	-1	
24-35 months	-2	
36-47 months	-3	
48-59 months	-4	
Fever duration on admission		
0 days	0	*Score child*
1 day	2	
2-3 days	3	
4-10 days	5	
>10 days	7	
Admitted during rainy season		
Yes	2	*Score child*
Diarrhea		
Yes	2	*Score child*
Moderate or severe acute malnutrition		
Yes	2	*Score child*
Fast breathing		
Yes	2	*Score child*
Hepato- or splenomegaly		
Yes	2	*Score child*
Malaria status		
Recent *Pf* malaria	3	*Score child*
Current *Pf* malaria	-4	
Moderate or severe anemia		
Yes	2	*Score child*
TOTAL SCORE		*Sum of all scores*

Total score	**Estimated risk**	**N in original dataset**
-8	0.2%	1
-7	0.3%	0
-6	0.4%	0
-5	0.5%	2
-4	0.7%	14
-3	0.9%	19
-2	1.2%	23
-1	1.5%	67
0	1.9%	75
1	2.5%	145
2	3.2%	165
3	4.1%	233
4	5.3%	225
5	6.8%	260
6	8.6%	187
7	11%	185
8	14%	139
9	17%	113
10	21%	86
11	26%	90
12	31%	71
13	37%	68
14	43%	63
15	50%	33
16	56%	27
17	62%	17
18	68%	9
19	74%	5
20	78%	0
21	82%	0
22	86%	1

ID 10

EFFECT OF ANTIBIOTICS ON CATHETER ASSOCIATED URINARY TRACT INFECTIONS IN THE ICU: A NON-INFERIORITY RETROSPECTIVE TRIAL

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Introduction: Catheter-associated urinary tract infections (CAUTI) are frequent nosocomial infections, although rarely severe. The benefit/risk ratio of antibiotic therapy is unclear since overconsumption leads to antimicrobial resistance. Catheter-associated asymptomatic bacteriuria should not be treated but distinction between asymptomatic bacteriuria and urinary infection is difficult in ICU patients. We therefore hypothesized that abstention of treatment of positive urine cultures associated with systemic signs of inflammation is not related with an increased sepsis occurrence in the following 7 days.

Methods: Comparative retrospective monocentric study with a non-inferiority design. Patients hospitalized between 2012 and 2018 for at least 48h in the ICU, with a bladder catheter and a positive urinary culture presenting fever(>38°C) or CRP level above 100mg/l were included. Exclusion criteria were pregnancy, kidney transplant recipients, planned urological surgery, neutropenia, bacteriemic urinary tract infection the day of inclusion, other source of infection requiring antibiotics for which the urinary bacteria was susceptible or septic shock. Based on a previous study we expected a sepsis occurrence of 10%. To provide a power of 80% with a non-inferiority margin of 10% we planned to include 112 patients in each group.

Results: Among 222 included patients, 100(45%) received antimicrobial therapy and 122(55%) did not. Groups were comparable in terms of age, sex, SAPS II score and co-morbidities. SOFA score the day of inclusion was higher in the groups who received antibiotics (median 4 versus 3 p=0,004). *Escherichia Coli* (50,4%), was the most frequent bacteria identified. Amoxicillin-clavulanic acid (42%), piperacillin/tazobactam (19%) and ciprofloxacin (16%) were the most prescribed antibiotics with a median duration of 5 days. Sepsis occurrence 7 days after the positive urinary culture were similar between the two groups (treated: 7% no treatment : 1,6% p=0,089). Moreover we found no difference between groups in terms of mortality (6% versus 1,6% p=0,08) or bacteremia (2% versus 2,4%p=0,671).

Conclusion : Absence of antibiotic treatment for urinary catheter associated positive culture and inflammatory syndrome in ICU patients was not associated with an increase in sepsis occurrence the next 7 days following the urinary culture. Further studies are needed to better define indication of antibiotic treatment for CAUTI in ICU setting.

ID 11

CLINICAL OUTCOMES OF THIRD-GENERATION CEPHALOSPORIN DEFINITIVE THERAPY FOR BLOODSTREAM INFECTIONS DUE TO ENTEROBACTERALES WITH POTENTIAL AMPC INDUCTION: A SINGLE-CENTER RETROSPECTIVE STUDY

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Background: The recommended therapy for severe infections caused by AmpC-inducible Enterobacterales (AmpC-E) typically involves cefepime or carbapenems. In an era of emerging resistance to these antimicrobials, we aim to assess the impact of third-generation cephalosporins (3GCs) vs. alternative antibiotics on clinical outcomes in bloodstream infections (BSIs) due to AmpC-E.

Methods: We retrospectively included hospitalized adult patients with BSIs caused by 3GC-susceptible AmpC-E between 2012 and 2022, comparing the outcomes of 3GC and non-3GC definitive therapies. The primary outcome was overall treatment failure (OTF), encompassing 90-day all-cause mortality, 90-day reinfection, and 90-day readmission. Secondary outcomes comprised components of the OTF, in-hospital all-cause mortality, and length-of-stay.

Results: Within a total cohort of 353 patients, OTF occurred in 46.5% and 41.5% in the 3GC- and non-3GC-therapy groups, respectively ($p = 0.36$). The 3GC-therapy group exhibited a longer length-of-stay (38 vs. 21 days, $p = 0.0003$) and higher in-hospital mortality (23.3% vs. 13.4%, $p = 0.019$). However, the 90-day mortality, 90-day reinfection, and 90-day readmission were comparable between the therapy groups. As the current standard-of-care therapy involves cefepime or carbapenems, we conducted a subgroup analysis comparing 3GCs to cefepime/carbapenems, which yielded similar results. We also conducted a specific subgroup analysis focusing on AmpC-E organisms with greater propensity for developing resistance, and within this subgroup, comparing 3GC therapy to non-3GC therapy produced comparable outcomes.

Conclusions: Overall, our findings suggest that 3GC definitive therapy may not result in poorer clinical outcomes for the treatment of BSIs caused by AmpC-E.

ID 12

IMPLEMENTATION OF MANDATORY INDICATION-REGISTRATION FOR ANTIMICROBIAL THERAPY IN THE ELECTRONIC PRESCRIBING SYSTEM AT GHENT UNIVERSITY HOSPITAL

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Background and aim: As part of their antimicrobial stewardship (AMS) program the Ghent University Hospital implemented a mandatory indication-registration in their electronic prescribing system (EPS). Physicians are obliged to indicate a treatment base (empirical, documented, medical prophylaxis, surgical prophylaxis) when prescribing antimicrobial therapy for systemic use and when used therapeutically, an indication needs to be selected from a predefined list. As literature states, discrepancies can occur between the chosen indication and the documented indication in the medical record (MR) [1] [2] [3]. A retrospective observational analysis was performed.

Methods: Newly started antimicrobial prescriptions for non-critically hospitalized adult patients were evaluated for a period of fourteen consecutive days. The primary endpoint was indication accuracy for empirical and documented therapies, defined as agreement of the indication entered during order entry with that documented in the MR at the time of order entry. The secondary endpoint included the identification of therapies entered as prophylaxis that were in reality empirical or documented therapies according the MR.

Results: A total of 540 prescriptions from 358 patients were reviewed. 33% (123/368) of the prescriptions, entered as empirical or documented therapies, were not in accordance with the documented indication. For 9% (35/123) of the prescriptions a minor deviation was identified (f.e. suspicion of urinary tract infections versus cystitis). For 23% (87/123) a major deviation (f.e. intra-abdominal abscess versus tooth abscess) was identified. 19% (32/167) of the prescription selected as prophylaxis were not accurate.

Discussion and conclusion: A third of all entered prescriptions are not in accordance with the entry in the MR which is high in comparison with previous studies in which discrepancy rates of 3.3% to 26% were identified [1] [2] [3]. Possible explanations could be: ignorance of the existence of a listed indication, workload, accidental errors or habits. Mandatory documentation of the indication can be an important tool within an AMS program provided that the registered indications are reliable. To optimize this all, medical wards will be receiving feedback on this analysis and data will be presented during ward visits. A yearly analysis will be performed because the accuracy rate might fluctuate over time.

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ID 13

ANTIMICROBIAL STEWARDSHIP IN A TERTIARY PSYCHIATRIC HOSPITAL: APPROPRIATENESS OF FLUOROQUINOLONE PRESCRIPTIONS

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Background and Objective: Within the hospital antimicrobial stewardship program, the annual analysis of antimicrobial medicines showed that fluoroquinolone use was above 10% of total antibiotic use. Given the risk of development of resistance and the emphasis in the National Action Plan to prescribe fewer fluoroquinolones, the objective was to evaluate the appropriateness of fluoroquinolone prescriptions.

Methods: A retrospective study was carried out in the psychiatric hospital UPC KU Leuven including all inpatient fluoroquinolone prescriptions of 2021 and 2022. Prescriptions (type, dose, duration, indication) were extracted from the CPOE system by the pharmacist. Electronic medical patient records (clinical symptoms, examination notes/registrations from doctors and nurses) including lab results (inflammatory and microbiological tests) were retrospectively checked by a hospital pharmacist and validated by a medical doctor. Evaluation of appropriateness of fluoroquinolone therapy was based on the guidelines provided by the hospital antimicrobial policy group.

Results: A total of 44 and 45 fluoroquinolone treatments were prescribed in 2021 and 2022 respectively. Levofloxacine was prescribed the most (n=39 and n=32 respectively). A total of 33(75%) and 30(66%) of treatments were assessed as appropriate. Another 2 and 3 treatments were assessed as being potentially appropriate (based on clinical case and fluoroquinolone characteristics). A total of 9(20%) and 12(27%) treatments were assessed as not appropriate due to 1/ insufficient diagnostic data (4+8), 2/ no antimicrobial downgrading when possible (2+2), 3/ no antimicrobial switch in case of resistance (2+0), 4/ less toxic antimicrobial would have been better (1+0) and 5/ duration of treatment was too short (0+2). Targeted feedback was provided to prescribers.

Conclusion: About one fourth of fluoroquinolone treatments in 2021-2022 in our hospital were assessed as not appropriate. Targeted feedback and education on the antimicrobial guidelines was provided to prescribers. Registration of diagnostic data in electronic medical records and following up on microbiological lab results are essential for making correct clinical treatment decisions. Improvement of compliance to the existing antimicrobial policies in the hospital is necessary, especially for fluoroquinolone antibiotics.

ID 14

EVALUATION OF OUTPATIENT PARENTERAL ANTIMICROBIAL THERAPY (OPAT) FOR INFECTIVE ENDOCARDITIS PATIENTS IN A BELGIAN TERTIARY CARE CENTRE

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Background: Infective endocarditis (IE) is a potentially lethal infection of the cardiac endothelium. Treatment consists of a prolonged intravenous antibiotic therapy and surgery in selected cases, with an important socio-economic and psychological burden. Given that Outpatient Parenteral Antimicrobial Therapy (OPAT) for infective endocarditis has been given a more prominent role in new 2023 ESC guidelines for IE, we performed a single-center analysis of OPAT efficacy and safety in IE patients.

Methods: All OPAT IE cases treated from January 2017 to August 2023 were included in the study. Relevant demographic, clinical and microbiological data were collected. Outcomes were clinical cure at day 30 after completion of OPAT, OPAT related readmission rate and adverse event rate.

Results: A total of 58 OPAT episodes were started in 57 patients. Mean age was 51,7 years (SD 24,1), 72% were male and 91% were adults. Prosthetic valve IE accounted for 52% of OPAT courses, and 71% of patients underwent cardiac surgery during this IE episode. Streptococci were the most frequently isolated causative organisms (66%), followed by staphylococci in 16%. Ceftriaxone was the most frequently used antibiotic (84%). Clinical cure was achieved in 54 of 55 OPAT episodes (3 were still in follow up). One patient died unrelated to IE or OPAT. Median duration of OPAT was 19 days (range 4 - 30), resulting in 1105 avoided hospitalization days.

Discussion: Consistent with data on OPAT for IE from previous studies, the outcome of IE patients treated with OPAT in our centre was very good. Data should nevertheless be interpreted with caution given the stringent inclusion criteria, and a rather short follow-up. Since OPAT has a major contribution on antimicrobial stewardship we will follow this cohort for a longer period of time, aiming to improve our OPAT program. We want to provide a better, broader and earlier selection of patients (according to the GAMES and new ESC criteria and for those needing more complex antibiotic treatment), while maintaining our high clinical cure rate, low rates of readmissions and adverse events.

ID 15

CHECK OF APPROPRIATENESS OF ANTIMICROBIAL THERAPY IN NURSING HOMES (CAPTAIN) STUDY

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Objectives: The overall prevalence of antimicrobial therapy in nursing homes is well described in literature. However, less is known about the appropriateness of antimicrobial therapy in residents. Therefore, the objectives of this study are to assess both prevalence and appropriateness of antimicrobial therapy in Belgian nursing homes.

Methods: In a prospective, observational point prevalence study, researchers documented prevalence and identified potentially inappropriate prescriptions (PIPs) by evaluating antimicrobial therapy according to national recommendations and guidelines. The severity of inappropriateness was then assessed using a modified Delphi expert panel.

Results: A total of 11 nursing homes, including 1178 residents, participated in this study. On the point prevalence survey day, 8.0% of residents were treated with at least one systemic antimicrobial drug. Systemic antimicrobials were most often used to prevent or treat urinary tract infections (55.6%), followed by respiratory tract infections (35.4%) and skin soft tissue infection (6.1%). About half of these prescriptions was used in prophylaxis (53.5%). In 88.5% of the systemic antimicrobial therapies, we identified at least one discordance with national guidelines, resulting in a total of 172 PIPs, of which 46 were unique PIPs. Of all unique PIPS, 14 (30.4%) were assessed with a mean severity score of four or higher. According to the expert panel, initiating antimicrobial prophylaxis in case of recurrent urinary tract infections in residents with less than three episodes in 12 months or less than two episodes in six months (n=25) and starting antimicrobial therapy in case of cough without other symptoms(n=3), were rated as the most inappropriate. Potentially inappropriate timing of time-dependent AMT was frequently observed, but was assessed with moderate severity scores. In addition, a third of systemic antimicrobial therapy was prescribed for a longer duration than recommended by national guidelines.

Discussion/Conclusions: Antimicrobial therapy in nursing homes is not commonly prescribed according to national guidelines. Compared with the median proportion of PIPs in hospital setting in a previous study at the University Hospitals of Leuven, more PIPs were seen in nursing homes. The PIPs identified in this study may guide future interventions to improve rational use of antimicrobial therapy in nursing homes.

ID 16

IMPACT OF NEW EUCAST 2020 DEFINITIONS ON APPROPRIATENESS OF ANTIMICROBIAL PRESCRIBING IN A TEACHING HOSPITAL

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Background: In 2020 the European Committee on Antimicrobial Susceptibility Testing redefined the categories for susceptibility testing, shifting "I" previously defined as "intermediate susceptibility" to "susceptible provided increased exposure". This shift emphasizes the use of a higher antibiotic dose when "I" is reported next to the removal of the "S" category for some species. As these revised definitions require several (dose) adjustments and clinician education, implementation in our hospital was performed in a multifaceted approach. We provided a revised dosing table, comments in susceptibility reports, structured electronic medication orders and hospital-wide communication. Alarmed by the increase in meropenem use as reported by Munting et al., we developed an active monitoring program to assess the appropriateness of antimicrobial prescribing. We aimed to evaluate the impact of the new definition.

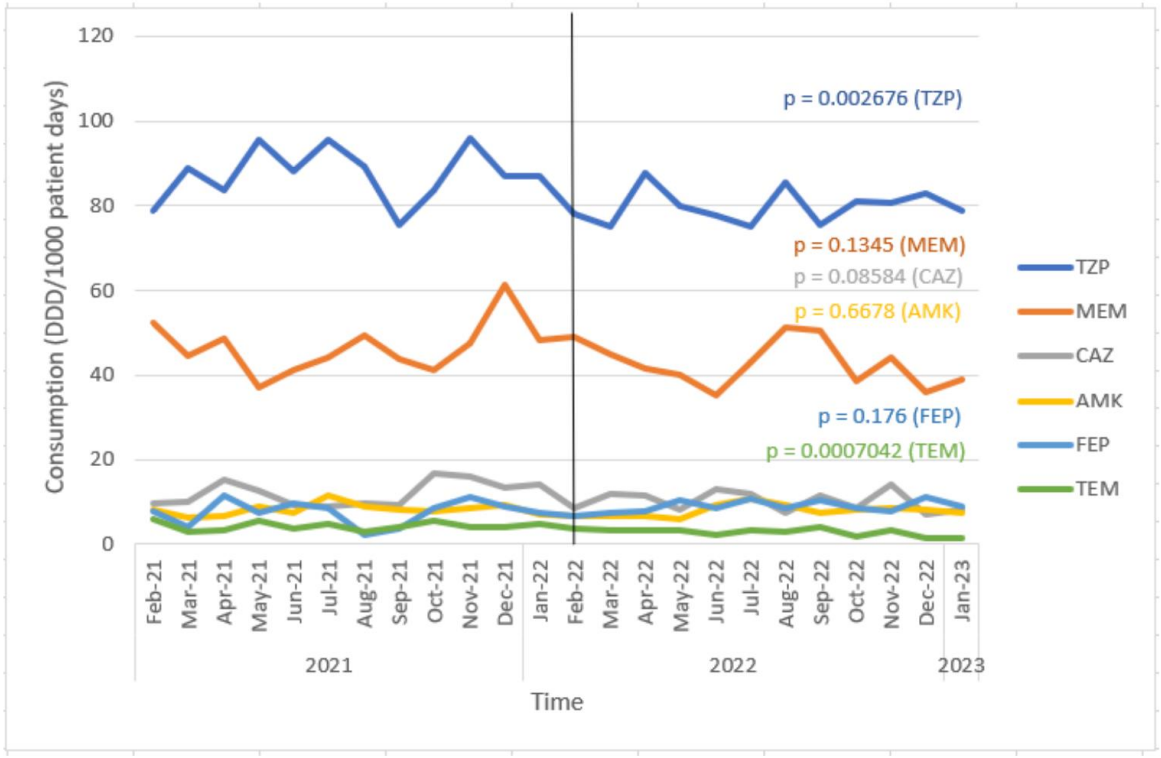
Methods: The active monitoring program, implemented in February 2022, included 13 clinical rules continuously screening patients' records for inappropriate antimicrobial prescriptions. The rules were implemented in our pharmacy-based check of medication appropriateness service, designed to reduce inappropriate prescriptions by sending recommendations to the treating physician. A multidisciplinary collaboration was established between the pharmacy and microbiology department; i.e. when a pharmacist recommendation was not accepted within 24h, the microbiologist contacted the prescriber. The impact of this program was measured by documenting the number of recommendations and acceptance rate (February-January 2023). Impact on broad-spectrum antibiotic consumption and infectious diseases (ID) specialist consultations were measured.

Results: During the 12-month period, 2185 recommendations were given, of which 119 (5.4%) were forwarded to the microbiology department. The overall acceptance rate was 92.4 % (Table 1). Broad-spectrum antimicrobial consumption did not increase (Figure 1). The number of ID specialist consultations increased (median (range) 923 (737-1062) versus 1102 (953-1244) 12 months pre- and post-implementation ($p<0.05$)).

Conclusions: In contrast to previous results, the implementation of an active monitoring program was able to avoid increased consumption of broad-spectrum antibiotics. A high number of inappropriate prescriptions was identified, however, recommendations provided by pharmacists and microbiologists were easily accepted. The increased number of ID consultations might reflect greater awareness of antimicrobial stewardship.

ID 16: FIGURE AND TABLE

FIGURE 1. Broad-spectrum antimicrobial consumption



AMK amikacin, CAZ ceftazidim, FEP cefepim, MEM meropenem , TEM, temocillin, TZP piperacillin-tazobactam

TABLE 1. Results of the Check of Medication Appropriateness (February 2022 – January 2023

Clinical rule	Number of alerts (n)	Number of recommendations (n)	Acceptance rate after pharmacists' recommendation (%)	Acceptance rate after pharmacists' & microbiology recommendation (%)
Control of correct dose				
Dose Aminoglycosides	133	31	82.6	100.0
Dose FLOXA PO	66	46	51.6	77.4
Dose FLC *Candida glabrata*	40	15	83.3	91.7
Dose LVX	191	45	81.3	87.5
Dose MEM	347	98	73.1	83.6
Dose MEM on ICU	45	6	100.0	100.0
Dose TZP	689	246	91.2	96.1
Dose SXT	62	25	100.0	100.0
Dose TEM	108	40	100.0	100.0
Control of correct selection of antibiotic in case of I reporting				
Contain I-TEM if reported as I (avoid escalation)	128	37	75.0	87.5
Contain I-TEM if reported as I on ICU (avoid escalation)	40	1	0.0	100.0
Contain I-TZP/CAZ/FEP if reported as I (avoid escalation)	118	25	61.5	92.3
Contain I-TZP/CAZ/FEP if reported as I on ICU (avoid escalation)	218	20	92.9	100.0
TOTAL	**2185**	**635**	**83.7**	**92.4**

CAZ ceftazidim, FEP cefepim, FLC fluconazol, FLOXA flucloxacillin, ICU intensive care unit, LVX levofloxacin, MEM meropenem , SXT sulfamethoxazole-trimethoprim,TEM, temocillin, TZP piperacillin-tazobactam

ID 17

EVALUATION AND IMPLEMENTATION OF OPTIMIZED ANTIMICROBIAL DOSING STRATEGIES IN OBESE AND UNDERWEIGHT PATIENTS

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Background: Correct dosing is key in antimicrobial stewardship. Although dosing recommendations are available for many subpopulations, dosing guidelines for obese and underweight patients are lacking. Therefore, we aimed to develop and implement dosing recommendations in obese and underweight patients in a large academic hospital, based on literature, clinical practice and expert consensus.

Methods: A five-step prospective evaluation and optimization project was performed. Prevalence of obese and underweight patients and frequency of antimicrobial prescriptions were determined in a point prevalence study. Evidence on dosing was retrieved from a literature review, complemented by an international e-survey. A consensus meeting was organized to formulate a final set of dosing recommendations. Finally, these recommendations were implemented in a clinical validation service uptake was subsequently evaluated.

Results: Over 20 study days, 15.896 patients were hospitalized of whom 15% and 9% were obese and underweight, respectively. Amongst the patients receiving antimicrobial therapy (41%), 12% and 9% were obese and underweight, respectively. Amoxicillin-clavulanic acid, cefazolin, clindamycin, fluconazole, levofloxacin, meropenem, piperacillin-tazobactam and vancomycin were most frequently prescribed, almost exclusively in standard dosing regimens. Based on literature search, e-survey and consensus panel, six dosing guidelines were implemented. During a 3 month implementation period, 529 recommendations were given, uptake was high, demonstrated by an acceptance rate of 86%.

Conclusions: Obese and underweight patients are frequently treated with antimicrobials during hospitalization, however, most of them receiving standard doses. Recommendations were developed.

ID 17: TABLE

TABLE 1. Results of the CMA: Number of alerts, pharmacists' recommendations and acceptance rate during the three month implementation period.

Clinical rule	Total number of alerts, n	Total number of recommendations, n	Specificity, (%)	Total number of phone calls, n	Acceptance rate by physicians			
					Could not be verified, n	After 24 hours, n	After 48 hours, n	Total, n (%)
Obesity	**434**	**207**	**48**	**41**	**43**	**115**	**24**	**85**
Piperacillin-tazobactam	153	96	62	15	15	56	9	80
Levofloxacin	150	73	49	18	20	38	10	91
Meropenem	39	22	56	6	2	15	0	75
Cefazolin	32	7	22	0	4	2	1	100
Fluconazole	60	9	15	2	2	4	3	100
Underweight	**95**	**12**	**13**	**0**	**2**	**8**	**2**	**100**
TOTAL	529	219	41	41	45	123	26	86

CMA Check of Medication Appropriateness, *N/A* not applicable