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Untersuchung des Einflusses von Antibiotic Stewardship Interventionen auf das Verordnungsverhalten von systemischen Antibiotika in der Chirurgie

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Inhaltsverzeichnis

Abkürzungsverzeichnis

AMR	Antimikrobielle Resistenzen
WHO	Weltgesundheitsorganisation
ABS	Antibiotic Stewardship
IDSA	Infectious Diseases Society of America
DOT	Therapietage
PD	Patiententage
DOT/100PD	Therapietage pro 100 Patiententage
CCMI	Charlson Comorbidity Index
OP	Operation
V1	Veröffentlichung 1
V2	Veröffentlichung 2

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1. Hintergrund

1.1 Antimikrobielle Resistenzen

Antimikrobielle Resistenzen werden als „Veränderungen von Mikroorganismen, die zu einer weniger wirksamen oder unwirksamen Behandlung von Infektionen führen“ beschrieben [1]. Antimikrobielle Resistenzen zählen zu einer der größten Bedrohungen der menschlichen Gesundheit weltweit. Die Weltgesundheitsorganisation (WHO) führte bereits 2019 antimikrobielle Resistenzen als eine der zehn größten Gefahren für die öffentliche Gesundheit auf. Infektionen, die durch multiresistente Erreger verursacht werden, sind mit einer erhöhten Mortalität, verlängertem Krankenhausaufenthalt und höheren Behandlungskosten verbunden [2]. Murray et al. berechneten in ihrer Übersichtsarbeit, dass im Jahr 2019 weltweit 4,95 Millionen Todesfälle mit antimikrobiellen Resistenzen assoziiert waren. Davon wiederum wurden für 1,27 Millionen Todesfälle antimikrobielle Resistenzen als ursächlich erachtet [3]. Allein in Deutschland wurden im Jahr 2019 45.700 Todesfälle im Zusammenhang mit resistenten Bakterien und 9.650 Todesfälle, die ursächlich auf antimikrobieller Resistenzen zurückzuführen sind, registriert [1].

Die Gründe für die Entwicklung von antimikrobiellen Resistenzen gestalten sich divers. Einen Faktor stellen ein ungenügender Zugang zu sauberem Wasser, sowie unzureichende Sanitär- und Hygienemöglichkeiten, insbesondere in Entwicklungsländern, dar [4]. Zu den größten Treibern der Entwicklung von antimikrobiellen Resistenzen zählen allerdings auch der Miss- und Übergebrauch von Antiinfektiva, sowohl im medizinischen als auch im landwirtschaftlichen Kontext [4, 5]. Im Gesundheitswesen ist vor allem der weltweit breite Einsatz von Reserveantibiotika, wie Oxazolidinonen oder Carbapenemen, ein ernstzunehmendes Problem [6].

Die mögliche Entwicklung neuer Antibiotika erscheint unter dem Gesichtspunkt zunehmender globaler Resistenzraten als unzureichend [7]. So bewertete die WHO im Jahr 2019 lediglich 6 von 32 Antibiotika in der Entwicklungspipeline als innovativ bezüglich möglicher Behandlungserfolge und geeigneter Behandlungsoptionen könnten in der Zukunft rar werden. [4].

Um dem Fehlgebrauch von Antiinfektiva im medizinischen Bereich entgegenzuwirken und damit zu einer Erhaltung der antibiotischen Behandlungsmöglichkeiten beizutragen, wird von der WHO und vielen weiteren Fachgesellschaften die Einführung von „Antibiotic Stewardship Programmen“ gefordert [8].

1.2 Antibiotic Stewardship

Die Begrifflichkeit „Antibiotic Stewardship“ (ABS) wurde erstmals von John E. McGowan und Dale N. Gerding im Jahr 1996 in den USA publiziert [9, 10]. Im Verlauf fand „Antibiotic Stewardship“ unter anderem den Weg in Leitlinien der Infectious Diseases Society of America (IDSA) und vieler weiterer infektiologischen Fachgesellschaften weltweit [11, 12]. Unter diesem Gesichtspunkt entstand auch die deutsch-österreichische S3-Leitlinie „Strategien zur Sicherung rationaler Antibiotika-Anwendung im Krankenhaus“ [13].

Eine einheitliche Definition von ABS ist in der Literatur dennoch nicht zu finden, weshalb ABS-Programme und deren Strategien viele verschiedene Ausprägungen annehmen können. Dyar et al. umschreiben Antimicrobial Stewardship beispielsweise als ein zusammenhängendes Maßnahmenbündel, welches den verantwortungsvollen Gebrauch von Antiinfektiva fördert [10]. Zu weitverbreiteten ABS-Maßnahmen gehören, neben vielen anderen, auch die Bereitstellung institutioneller Diagnostik- und Behandlungsleitlinien, ABS-Visiten, infektiologische Konsiliardienste oder eine restriktive Abgabe von Reserveantibiotika nur nach infektiologischer Mitbeurteilung. Das Ziel von ABS ist dennoch ein Einheitliches: der optimierte und oft reduzierte Einsatz von Antibiotika, wobei dennoch die bestmögliche klinische Therapie für den einzelnen Patienten im Vordergrund stehen sollte. Hierunter sollten die unerwünschten Folgen einer Antibiotikatherapie, wie Toxizität, Resistenzentwicklung oder Selektion pathogener Bakterien, möglichst minimiert werden. Der Fokus liegt damit nicht nur auf der Auswahl eines Antibiotikums, sondern neben weiteren Gesichtspunkten auch auf der optimierten Dosierung und der Therapiedauer. Um dem umfassenden Gedanken einer rationalen Antibiotikatherapie gerecht zu werden, bestehen ABS-Programme optimalerweise aus einem multidisziplinären Team, wie Infektiologen, klinischen Mikrobiologen, infektiologisch weitergebildeten Apothekern und Krankenhaushygienikern [13].

Trotz der unterschiedlichen Ausprägungen, die ABS-Maßnahmen annehmen können, wurden ABS-Teams als erfolgreiche Institutionen zum Erreichen eines optimierten Antibiotikaeinsatzes beschrieben [14-16]. Wichtig in der Beurteilung der Effektivität von ABS-Programmen hinsichtlich eines optimierten Verordnungsverhaltens von Antibiotika ist, dass diese ohne eine negative Beeinflussung von Patienten Outcomes einhergeht [14, 15].

Die Effektivität von ABS-Strategien und damit eine Veränderung im Verordnungsverhalten von Antibiotika kann auf unterschiedliche Weise untersucht werden. Bewährte Gesichtspunkte zur Beurteilung stellen der Verbrauch von Antibiotika, die Therapiedauer, die Deeskalation der antibiotischen Therapie sowie der Wechsel von intravenöser auf orale Applikationsformen dar [10, 15]. Eine Beurteilung bezüglich Veränderungen in der Resistenzlage von Bakterien gestaltet sich im praktischen Alltag schwierig, da diese Effekte erst nach relativ langen Zeiträumen von mehreren Jahren nachgewiesen werden können. In einigen Studien konnte dennoch gezeigt werden, dass ABS-Initiativen tatsächlich einen positiven Einfluss auf die antimikrobielle Resistenzentwicklung haben [17, 18].

1.3 Antibiotic Stewardship in chirurgischen Disziplinen

Charani et al. stellten fest, dass die Entscheidungsfindung zur antibiotischen Therapie in den chirurgischen Fächern sich im Gegensatz zu derer internistischer, anderen Schwierigkeiten zu stellen hat [19]. Die zeitlichen Ressourcen des chirurgischen Teams auf der Station sind begrenzt, da vor allem die erfahreneren Chirurgen einen großen Teil der Arbeitszeit im Operationssaal sind. Die Entscheidung über die antibiotische Therapie ist in dieser Zeit meist den unerfahreneren Assistenzärzten überlassen. Aus diesem Grund werden schwerwiegendere Entscheidungen, wie beispielweise eine Deeskalation der Antibiotikatherapie, oftmals aufgeschoben, bis eine Rücksprache mit Oberärzten möglich ist. Dies führt nicht selten zu einer ungeeigneten oder sogar unnötigen antibiotischen Therapie der Patienten. Gerade die zeitliche Limitation in der Kommunikation mit dem chirurgischen Team stellt für mögliche ABS-Maßnahmen eine große Hürde dar [19]. Unter Umständen führt auch gerade diese Herausforderung dazu, dass sich die meisten ABS-Programme in der Chirurgie auf den perioperativen Bereich (z.B. Antibiotikaprophylaxe und Management von postoperativen Wundinfektionen) fokussieren und den prä- und postoperativen Antibiotikaeinsatz vernachlässigen, obwohl es eindeutig Potenzial zur Verbesserung der Antibiotikaverschreibung in diesem Bereich gibt [20, 21]. Gerade in der Chirurgie, beschreiben Charani et al., scheint auch die Angst vor einem negativen Patientenoutcome durch mögliche unbehandelte Infektionen die Bedenken durch irrationalen Antibiotikaeinsatz zu übersteigen [19]. Dennoch steht außer Frage, dass Antibiotika, neben einer chirurgischen Fokussanierung, unverzichtbar in der Behandlung von Infektionen chirurgischer Patienten, und für alle Beteiligten eine Herausforderung sind.

1.4 Fragestellungen

Visiten sind eine der wichtigsten Bestandteile in der Betreuung chirurgischer Patienten [21]. Deshalb soll in dieser Arbeit der Einfluss von ABS-Visiten auf das Verordnungsverhalten von Antibiotika bei chirurgischen Patienten untersucht werden, sowohl in einem viszeralchirurgischen als auch in einem gefäßchirurgischen Patientenkollektiv, da in dieser speziellen Gruppe kaum wissenschaftliche Daten verfügbar sind. In dieser Arbeit soll der Fokus ausschließlich auf der prä- und postoperativen Antibiotikagabe liegen, da sich bisher ein Großteil der vorhandenen Daten auf die perioperative Antibiotikaprophylaxe und damit verbundener späterer Komplikationen durch postoperative Wundinfektionen beziehen.

Zusätzlich soll die Nachhaltigkeit der durchgeführten ABS-Visiten untersucht werden, da zeitliche Ressourcen in vielen Gesundheitseinrichtungen limitiert sind. Eingeschränkte zeitliche Kapazitäten tangieren neben chirurgischen Teams auch viele andere Bereiche des stationären Krankenhaussettings, wie ABS-Programme. Dies erschwert es ABS-Teams, ständig auf Station als Ansprechpartner präsent zu sein. Die Möglichkeit, ABS-Visiten in jeder Klinik und jeder Station durchzuführen, ist praktisch betrachtet unmöglich. Die Nachhaltigkeit von ABS-Maßnahmen ist bis dato allerdings nur in wenigen Studien untersucht worden [22-24]. Diese wiederum lassen sich nur schwer mit den Gegebenheiten in einer chirurgischen Klinik und dem Fokus auf dem prä- und postoperativen Antibiotikaeinsatz vergleichen.

In weiteren Teilen der Arbeit soll der Einfluss von patientenbezogenen Faktoren auf das Verordnungsverhalten von Antibiotika untersucht werden. Die antibiotische Therapie kann durch viele Faktoren beeinflusst werden. Diese Faktoren können auf sehr unterschiedlichen Ebenen der antibiotischen Verordnung eingreifen, zum Beispiel:

- Umgebung: bspw. stationär, ambulant, Pflegeheim
- Patientenpopulation: bspw. pädiatrische Patienten, Patienten mit bestimmten Infektionen
- Verordner: bspw. erfahrener/unerfahrener Arzt

Das Wissen über mögliche Einflussfaktoren, die zur Verschreibung ungeeigneter antibiotischer Therapien beitragen, könnte in Zukunft zu einer Optimierung im Einsatz von Antibiotika genutzt werden. So könnten künftige ABS-Interventionen möglichst patientenindividuell zugeschnitten werden, um damit eine größtmögliche Effektivität zu erreichen.

1.5 Parameter zur Beurteilung des Einflusses von ABS-Strategien

Um die Effektivität oder den Einfluss von ABS-Maßnahmen zu analysieren, können wie im vorherigen Kapitel bereits beschrieben verschiedene Parameter herangezogen werden. Einige der in den beiden Veröffentlichungen verwendeten Parameter sollen in diesem Kapitel näher erläutert werden, da sie von den Autoren explizit definiert wurden.

1.5.1 Verbrauchsdichte

Der Antibiotikaverbrauch wird im internationalen Kontext häufig in „Defined Daily Doses (DDD)“ angegeben: eine rechnerische Größe, definiert von der WHO, die die angenommene mittlere Tagesdosis eines Antibiotikums bei Erwachsenen beschreibt [25, 26]. DDD werden üblicherweise über die Verbrauchsdaten der Warenwirtschaft errechnet, um den Antibiotikaverbrauch unabhängig von Packungsgröße oder Preis abschätzen und vor allem auch vergleichen zu können. Dies kann beispielsweise eine Veränderung des Antibiotikaverbrauchs über einen bestimmten Zeitraum oder auch den Vergleich zwischen Institutionen oder Ländern betreffen. DDD beschreiben dabei nicht unbedingt die verordneten Antibiotikadosen, da die tatsächlich verschriebene Dosis aufgrund patientenindividueller Faktoren, wie Gewicht, Nierenfunktion oder Krankheitsschwere, von der mittleren Tagesdosis abweichen können. In den beiden Veröffentlichungen wird deshalb auf die Therapietage (days of therapy = DOT) zurückgegriffen. Diese werden direkt aus den Verordnungsdaten abgebildet und stellen den tatsächlich verordneten Antibiotikaverbrauch, unabhängig von einer abweichenden mittleren Tagesdosis dar. Um eine möglichst hohe Vergleichbarkeit unabhängig von der Patientenzahl zu erreichen, können DDD oder DOT auf Tage, die Patienten auf Station verbringen (patient days = PD), normiert werden. In den beiden Veröffentlichungen wurde die Größe Therapietage (DOT)/100 Patiententage (PD) verwendet.

1.5.2 Deeskalation

Die antibiotische Deeskalation von einem breiteren Spektrum hin zu einem schmäleren Spektrum, wo möglich, ist eines der Ziele von ABS [15]. Um antibiotische Therapien hinsichtlich ihrer Veränderungen beurteilen zu können, wurden Antibiotika für beide Veröffentlichungen in vier verschiedene Ränge (A-D) eingeteilt (Tbl 1) [27-31].

Rang	Antibiotika
A	Schmalspektrum-Penicilline, Cephalosporine der 1. und 2. Generation, Co-trimoxazol, Doxycyclin, orales Fosfomycin, Metronidazol
B	Aminopenicilline/Betalaktamaseinhibitoren, Cephalosporine der 3. Generation, Fluorchinolone, Makrolide, Clindamycin, intravenöses Fosfomycin, Rifampicin
C	Cephalosporine der 4. Generation, Carbapeneme, Piperacillin/Tazobactam, Vancomycin
D	Daptomycin, Linezolid, Tigecyclin

Tabelle 1 Einteilung Antibiotika (A-D) [27, 30, 31]

Die Deeskalation einer antibiotischen Therapie wurde als Wechsel eines oder mehrerer Antibiotika zu einem Antibiotikum niedrigeren Rangs oder das Absetzen eines oder mehrerer Antibiotika in einer Kombinationstherapie definiert. War auch nach dem Wechsel der antibiotischen Therapie noch ein Antibiotikum der Gruppe D verordnet, wurde der Wechsel nicht als Deeskalation gewertet [30, 31].

1.5.3 Eignung der antibiotischen Substanz

Die antibiotische Therapie kann auch hinsichtlich der Eignung der eingesetzten antibiotischen Substanzen analysiert werden. Hierzu wurden in Veröffentlichung 2 (V2) verschiedene Kriterien festgelegt, um dies zu beurteilen. Eine Antibiotikaverordnung wurde als adäquat bewertet, solange keiner der folgenden Punkte zutraf:

- Kein Hinweis auf eine Infektion laut elektronischer Akte
- Das erwartete Spektrum an Erregern wurde mit den verordneten Antibiotika nicht abgedeckt
- Die verordneten Antibiotika überstiegen deutlich das zu erwartende Bakterienspektrum für die behandelte Infektion
- Prä- oder post-OP-Prophylaxe, falls nicht in den Leitlinien empfohlen

1.6 Inhalt der Veröffentlichungen

Um der Beantwortung der oben aufgeführten Fragestellung näher zu kommen, wurden zwei retrospektive Beobachtungsstudien durchgeführt. Beide Studien beschäftigen sich mit dem Verordnungsverhalten von Antibiotika in chirurgischen Disziplinen und deren Veränderungen durch ABS-Visiten. Ein positives Ethikvotum der Medizinischen Fakultät der LMU München liegt vor (19-906).

Veröffentlichung 1 (V1) beschäftigt sich mit dem Einfluss von wöchentlichen ABS-Visiten auf die antibiotische Therapie bei vier viszeralchirurgischen Stationen (eine Intermediate Care-Station, drei Normalstationen) [30]. Hierfür wurden jeweils zwei Verordnungsanalysen (P1, P2) über drei Monate durchgeführt und miteinander verglichen. Während P1 wurden auf drei der vier Stationen (Station 1/2/4) ABS-Visiten durchgeführt. In P2 wurden dann auf der vierten Station (Station 3) ABS-Visiten eingeführt, wohingegen auf Station 4 keine ABS-Visiten mehr angeboten wurden. Hierdurch entstand ein „cross-over" Design mit „Kontrollstation", durch das eine Aussage über die Nachhaltigkeit von ABS-Visiten getroffen werden konnte (Abb. 1). Alle Patienten der vier Stationen über 18 Jahren mit systemischer Antibiotikatherapie wurden im Beobachtungszeitraum eingeschlossen. Die Verordnungsanalysen (P1, P2) wurden hinsichtlich der eingesetzten Antibiotika inklusive Verbrauchsdichten sowie Deeskalationsverhalten und Therapiedauer beurteilt.

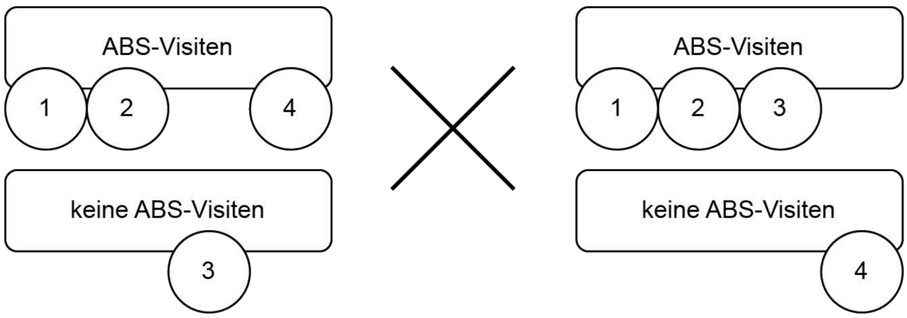

Abbildung 1 Schematische Darstellung des "cross-over"-Designs der Beobachtungsstudie in Veröffentlichung 1

In Veröffentlichung 2 (V2) wurde das Verordnungsverhalten von Antibiotika auf einer gefäßchirurgischen Station nach Einführung von ABS-Visiten und lokaler antiinfektiver Behandlungsstandards (Anhang) untersucht [31]. Des Weiteren wurden der mögliche Einfluss von Patientenfaktoren auf die Eignung einer antibiotischen Therapie, sowie der Leitlinienadhärenz analysiert. Dafür wurden alle Patientenfälle (= der Krankenhausaufenthalt eines Patienten) im Zeitraum von jeweils drei Monaten (P1, P2), vor und nach der Etablierung der ABS-Strategien, eingeschlossen und die antibiotische Therapie verglichen. Betrachtete Parameter waren auch hier die Verbrauchsdichten der verordneten antibiotischen Substanzen, sowie Deeskalationsverhalten und Therapiedauer. Zusätzlich wurden, gleich einem Faktorenmodell, patienteneigene Faktoren hinsichtlich ihres Einflusses auf die Leitlinienadhärenz und die Eignung der antibiotischen Substanz analysiert. Folgende Einflussgrößen wurden in V2 untersucht: Alter, Geschlecht, Dauer des Krankenhausaufenthalts, stationäre Aufnahme aus einer medizinischen Einrichtung, Mortalität, Wiederaufnahme aufgrund einer Infektion innerhalb von 30 Tagen, Charlson-Comorbidity-Index

(CCMI), Intensivaufenthalt, Schwere der gefäßchirurgischen Grunddiagnose, Penicillinallergie, Fremdmaterial in situ, glomeruläre Filtrationsrate, Immunsuppression, Operation (OP), Revisionsoperation.

2. Zusammenfassung

Antimikrobielle Resistenzen stellen nach wie vor einen ernstzunehmenden gesundheitsgefährdenden Faktor dar, da zum Teil nur limitierte Möglichkeiten in der antibiotischen Behandlung von Infektionen vorhanden sind. Neuentwicklungen an Antibiotika halten gegenwärtig nicht mit dem zunehmenden Vorkommen von antimikrobiellen Resistenzen Schritt [4, 7]. Um die Behandlungsmethoden möglichst auch in Zukunft aufrecht zu erhalten ist ein rationaler Einsatz von Antibiotika nötig. Viele dieser Maßnahmen zum optimiertem Einsatz werden durch den Begriff des Antibiotic Stewardship (ABS) beschrieben. ABS ist bereits in vielen medizinischen Bereichen weltweit etabliert und wird durch Empfehlungen von medizinischen Fachgesellschaften, beispielweise in Form von evidenzbasierten Leitlinien, unterstützt [11-13].

Durch ABS soll vor allem medizinisches Personal in der Verordnung von Antibiotika unterstützt werden. Dennoch gibt es zu ABS in chirurgischen Disziplinen, insbesondere im prä- und postoperativen Bereich noch Forschungsbedarf. In der Betreuung chirurgischer Patienten wird neben der chirurgischen Sanierung gerade die tägliche Visite als wichtiger Punkt beschrieben [20, 21]. Daher sollte in dieser Arbeit der Einfluss von ABS-Visiten auf das Verordnungsverhalten bei viszeral- bzw. gefäßchirurgischen Patienten untersucht werden.

Hierfür wurden zwei retrospektive Beobachtungsstudien in einem viszeral- und gefäßchirurgischem Patientenkollektiv durchgeführt. In beiden Studien wurden zwei Verordnungsanalysen vor und nach Einführung von wöchentlichen ABS-Visiten realisiert und die Ergebnisse miteinander verglichen.

In V1 wurden 574 Patienten und in V2 294 Patienten eingeschlossen. In beiden Studien war das Patientenkollektiv vor und nach Einführung der ABS-Visiten vergleichbar und die Daten zum Antibiotikaeinsatz konnten aussagekräftig miteinander verglichen werden. Bei beiden Kollektiven konnte durch die Implementierung von wöchentlichen ABS-Visiten jeweils eine deutliche Reduzierung des gesamten Antibiotikaverbrauchs beobachtet werden (V1: 91,1 vs. 70,4 DOT/100PD, V2: 47,0 vs. 35,3 DOT/100PD). In V1 konnte des Weiteren auf allen Stationen eine Verringerung des Ciprofloxacinverbrauchs erreicht werden (10,5 vs. 7,1 DOT/100PD). Zusätzlich konnten auf Station 2 die Verbrauchsdichten von Linezolid (10,9 vs. 8,6 DOT/100PD) und Meropenem (14,2 vs. 11,5 DOT/100PD) reduziert werden. Ebenso konnte in V2 eine Verringerung des Verbrauchs von Linezolid (3,7 vs. 1,0 DOT/100PD) und Fluorchinolonen (6,1 vs. 2,0 DOT/100PD) beobachtet werden. Zudem konnte in V2, ganz im Sinne von ABS, eine 48-prozentige Zunahme der Verordnung von Schmalspektrumpenicillinen und Cephalosporinen der 1. Generation verzeichnet werden. Auch konnte in beiden Verordnungsanalysen eine signifikante Erhöhung der Deeskalationsraten der antibiotischen Therapien beobachtet werden (V1: 25,7% vs. 40,0%, p=0,030 (Station 1/2) und 15,4% vs. 24,2%, p=0.081 (Station 3), V2: 30,5% vs. 12,1%, p=0,011). Die Therapiedauer blieb in beiden Studien unverändert.

In V2 wurde zusätzlich untersucht, ob die Wahl des Antibiotikums adäquat war bzw. ob es den Leitlinien entsprach. Die Leitlinienadhärenz konnte nicht bei allen Antibiotikaverordnungen untersucht werden, da für manche Infektionen keine gültigen Leitlinien verfügbar waren. Diese Verordnungen wurden für die statistische Analyse der Leitlinienadhärenz ausgeschlossen. In der Phase mit durchgeführten ABS-Visiten wurde ein größerer Anteil der antibiotischen Verordnungen als adäquat (69,2% vs. 78,9%, p=0.223) und in Adhärenz mit verfügbaren Leitlinien (60,9% vs. 77,8%, p=0.081) eingestuft. Aufgrund der in beiden Beobachtungszeiträumen nummerisch unerwartet geringen antibiotischen Verordnungen erreichten diese Ergebnisse allerdings kein statistisch signifikantes Niveau.

Wichtig im Sinne der Patientensicherheit bleibt auch festzustellen, dass sich die Outcomes wie Mortalität (V1: 1,0% vs. 0,7%, p=0,722; V2: 0,7% vs. 0,6%, p=0,923) und Wiederaufnahme aufgrund einer Infektion innerhalb von 30 Tagen (V1: 8,4% vs. 7,3%, p=0,621; V2: 1.5% vs. 4,5%, p=0,112) durch die Veränderungen im Antibiotikaeinsatz bei beiden Studien nicht verschlechterten.

In V1 wurde auch untersucht, ob und zu welchem Grad Nachhaltigkeit durch wöchentliche ABS-Visiten in ein optimiertes Verordnungsverhalten implementiert werden kann. Hierfür wurde analysiert wie sich das Verordnungsverhalten auf einer Station nach Beendigung der wöchentlichen ABS-Visiten entwickelt. Um eine Kontrollgruppe zu schaffen, wurden die ABS-Visiten auf den anderen drei Stationen im gleichen Zeitraum ein- bzw. fortgeführt (siehe Abb. 1). Die Nachhaltigkeit auf der Station 4 war bezüglich des gesamten Antibiotikaverbrauchs stabil (71,3 vs. 74,4 DOT/100PD). Die Verordnung von Reserveantibiotika wie Linezolid (6,4 vs. 12,1 DOT/100PD) und Meropenem (10,8 vs. 13,2 DOT/100PD) nahmen allerdings bereits in den ersten drei Monaten nach Einstellen der ABS-Intervention wieder zu. Auch die Deeskalationsraten nahmen nach Beendigung der ABS-Visiten tendenziell wieder ab (20,2% vs. 15,7%, p=0,404).

Um den Einsatz von Antibiotika weiter zu optimieren, wäre das Wissen über mögliche Faktoren, die ein inadäquates Verordnen von Antibiotika begünstigen, hilfreich. Diese könnten in zukünftigen ABS Maßnahmen bewusst anvisiert werden, um Interventionen möglichst effektiv zu gestalten. Hierfür wurde in V2 untersucht, welche Patientenfaktoren einen Einfluss auf die Adäquatheit der Antibiotikaverordnungen haben beziehungsweise ob Adhärenz mit bestehenden Leitlinien besteht.

In vorliegender Studie konnten keine Patientenfaktoren ausgemacht werden, die die Auswahl des Antibiotikums eindeutig beeinflussten. Dennoch konnte beobachtet werden, dass bei Patienten mit eingeschränkter Nierenfunktion eine höhere Wahrscheinlichkeit bestand, dass die antibiotische Therapie mit einer adäquaten Substanzwahl (9,4% vs. 26,7%, p=0,043) und in Adhärenz mit Leitlinien (14.3% vs. 30.2%, p = 0.108) einherging. Im Gegensatz dazu wurden Antibiotikaverordnungen bei Patienten mit anamnestischer Penicillinallergie öfter als inadäquat eingestuft als die Verordnungen von Patienten ohne Penicillinallergie (18.8% vs. 0.04%, p=0.011). Aufgrund der sehr geringen Anzahl an Patienten mit anamnestischer Penicillinallergie, kann die Aussage hier allerdings nur eine eingeschränkte Aussagekraft haben. Außerdem konnte in V2 beobachtet werden, dass sich durch die Implementierung von ABS-Interventionen die Initiierung von Antibiotika hin zu Patienten mit einem höheren CCMI [32] verschoben hat (P2: 2.0 (keine Antibiotika) vs. 3.0 (Antibiotika), p=0.005).

In beiden Studien konnte gezeigt werden, dass wöchentliche ABS-Visiten, auch kombiniert mit institutsinternen Leitlinien, bei einem viszeral- und gefäßchirurgischem Patientenkollektiv effektiv sind. Der Antibiotikaeinsatz konnte optimiert werden, indem der Antibiotikaverbrauch allgemein, sowie von einzelnen antibiotischen Substanzen durch die ABS-Interventionen reduziert wurde. Des Weiteren konnten die Deeskalationsraten ganz im Sinne von ABS erhöht werden und, wo möglich, breite antibiotische Therapien frühzeitig auf ein schmaleres Spektrum fokussiert werden. Der Antibiotikaverbrauch gesamt blieb auch nach Beendigung der wöchentlichen ABS-Visiten auf einem gleichbleibenden Niveau. Der Einsatz von Reservesubstanzen, wie Oxazolidinonen und Cabapenemen, nahm allerdings unerfreulich schnell wieder zu, wie auch die Deeskalationsrate bereits wieder abnahm. Die Untersuchungen zur Nachhaltigkeit beleuchten einen begrenzten Zeitraum von drei Monaten, da die Anfang 2020 beginnende SARS-CoV2-Pandemie eine aussagekräftige Schlussfolgerung über einen längeren Zeitraum unmöglich machte. In Zukunft wäre es wünschenswert die Nachhaltigkeit von ABS-Visiten über einen längeren Zeitraum zu untersuchen. Dennoch zeigt sich auch bei diesem nur relativ kurzen Beobachtungszeitraum, dass ABS-Visiten bei chirurgischen Patienten im besten Fall über einen längeren Zeitraum fortgeführt werden sollten. Eindeutige Patientenfaktoren, die das fehlerhafte Verschreiben von Antibiotika beeinflussen, konnten in dieser Arbeit nicht benannt werden. Dennoch scheint das Vorliegen einer Penicillinallergie, obwohl Therapiealternativen in Leitlinien explizit genannt werden, ein geeignetes Ziel für künftige ABS-Maßnahmen zu sein – auch wenn dies durch weitere Untersuchungen bestätigt werden sollte.

Die Limitationen der Arbeit liegen vor allem am retrospektiven Charakter der beiden Studien, die in einem einzigen Universitätsklinikum, mit komplex erkranktem und zu behandelndem Patientenkollektiv, durchgeführt wurden. Dies sollte bei der Übertragbarkeit der Daten auf andere Gesundheitseinrichtungen berücksichtigt werden.

3. Abstract

Antimicrobial resistance continues to be a serious health hazard due to the limited options available for antibiotic treatment of infections. The development of new antibiotics is currently not keeping pace with the increasing incidence of antimicrobial resistance [4, 7]. Rational use of antibiotics will be necessary to preserve treatment options for the future. Many actions taken to promote optimized antibiotic use are described by the term Antibiotic Stewardship (ABS). ABS is already established in many medical fields worldwide and is supported by recommendations from medical societies, for example in the form of evidence-based guidelines [11-13].

ABS is primarily intended to support medical staff in proper antibiotic prescribing. However, there is still a need for research on ABS in surgical disciplines, especially in the preoperative and postoperative settings. In the care of surgical patients, particularly daily ward rounds are described as an important point in addition to surgical source control [20, 21]. Therefore, the aim of this study was to investigate the influence of ABS ward rounds on the prescribing behaviour of visceral and vascular surgical patients.

For this purpose, two retrospective observational studies were conducted in a visceral and vascular surgical patient population. In both studies, two prescribing analyses (P1 and P2) were realized before and after the introduction of weekly ABS ward rounds and were compared with regards to possible differences.

Publication 1 (V1) included 574 patients and publication 2 (V2) included 294 patients. In both studies, the patient population was comparable before and after implementation of ABS ward rounds. Therefore, antibiotic prescribing could be compared by statistical analyses. In both patient collectives, a significant reduction in total antibiotic consumption was observed by implementing weekly ABS ward rounds (V1: 91,1 vs. 70,4 DOT/100PD, V2: 47,0 vs. 35,3 DOT/100PD). In V1, the ciprofloxacin consumption decreased on all wards (10,5 vs. 7,1 DOT/100PD) while the consumption of linezolid (10,9 vs. 8,6 DOT/100PD) and meropenem (14,2 vs. 11,5 DOT/100PD) decreased on ward 2. Similarly, a reduction in the consumption of linezolid (3.7 vs. 1.0 DOT/100PD) and fluoroquinolones (6.1 vs. 2.0 DOT/100PD) was observed in V2. Additionally, in accordance with the concept of ABS, a 48% increase in the prescription of narrow-spectrum penicillins and 1st generation cephalosporins was noted in V2. Also, a significant increase in the de-escalation rates of antibiotic therapies was observed in both prescribing analyses (V1: 25.7% vs. 40.0%, p=0,030 (ward 1/2) und 15.4% vs. 24.2%, p=0.081 (ward 3), V2: 30.5% vs. 12.1%, p=0.011). The duration of therapy remained unaltered in both studies.

In V2, we additionally investigated whether choice of antibiotic was adequate or whether it was in accordance with treatment guidelines. Guideline adherence could not be investigated for all antibiotic prescriptions, as for some infections no valid guidelines were available. These prescriptions were excluded for statistical analysis regarding guideline adherence. In the period where ABS ward rounds were provided, more antibiotic prescriptions were classified as

adequate (69.2% vs. 78.9%, p=0.223) and in adherence with available guidelines (60.9% vs. 77.8%, p=0.081). However, due to numerically unexpected low antibiotic prescribing in both observation periods, these results did not reach a statistically significant level.

In terms of patient safety, it is also important to note that outcomes such as mortality (V1: 1.0% vs. 0.7%, p=0.722; V2: 0.7% vs. 0.6%, p=0.923) and readmission due to infection within 30 days (V1: 8.4% vs. 7.3%, p=0.621; V2: 1.5% vs. 4.5%, p=0.112) were not deteriorated by changes in antibiotic use in both studies.

V1 also investigated whether and to what extent sustainability can be achieved in optimized prescribing behaviour after the completion of weekly ABS ward rounds. Therefore, the prescribing behaviour on one ward was analysed after the weekly ABS ward rounds had been terminated. In order to create a control group, the ABS ward rounds were introduced or continued on the other three wards during the same period (see Abb. 1). Sustainability was stable in terms of total antibiotic consumption (71.3 vs. 74.4 DOT/100PD), but the use of last resort compounds like linezolid (6.4 vs. 12.1 DOT/100PD) and meropenem (10.8 vs. 13.2 DOT/100PD) increased within 3 months after stopping ABS ward rounds. De-escalation rates also tended to decrease again after ABS ward rounds were stopped (20.2% vs. 15.7%, p=0.404).

In order to further optimize the use of antibiotics, knowing possible factors that promote inappropriate antibiotic prescribing could be helpful. These could be deliberately targeted in future ABS measures to make interventions as effective as possible. For this purpose, V2 investigated which patient factors had an influence on the adequacy of antibiotic prescriptions and adherence to treatment guidelines.

No patient factors could be identified that would distinctly influence the choice of antibiotics. However, it was observed that patients with impaired renal function were more likely to receive antibiotic therapy with adequate drug selection (9.4% vs. 26.7%, p=0.043) and in adherence to guidelines (14.3% vs. 30.2%, p=0.108). In contrast, antibiotic prescriptions in patients with a history of penicillin allergy were more often considered inadequate than prescriptions in patients without penicillin allergy (18.8% vs. 0.04%, p=0.011). However, due to the very small number of patients with anamnestic penicillin allergy, the conclusions might only be of limited validity. In addition, the analysis in V2 showed that the implementation of ABS interventions shifted the initiation of antibiotics towards patients with a higher Charlson Comorbidity Index [32] (P2: 2.0 (no antibiotics) vs. 3.0 (antibiotics), p=0.005).

In both studies, weekly ABS ward rounds, also combined with institutional antimicrobial treatment guidelines, were shown to be effective in a visceral and vascular surgical patient population. Antibiotic use was optimized by reducing antibiotic consumption in general and of individual antibiotic agents through ABS interventions. Furthermore, de-escalation rates could be increased in line with ABS and, where possible, broad antibiotic therapies could be focused to a narrower spectrum at an early stage. Overall antibiotic use remained at a steady level even after the weekly ABS ward rounds were no longer provided to the ward 4. However, the use of last resort compounds, such as oxazolidinones and cabapenems, increased quickly again, as well as the de-escalation rate decreased again. The investigations on sustainability included only a limited period of 3 months, as the SARS-CoV2 pandemic, arising in early 2020, made it impossible to draw meaningful conclusions after a longer period of time. In the future, it would be desirable to analyse the sustainability of ABS ward rounds over a longer period of time. However, even this short observation period shows that ABS ward rounds in surgical patients should be ideally provided on a continuous basis. Patient factors notably influencing inadequate antibiotic prescribing could not be identified in this work. However, anamnestic penicillin allergy seems to be a suitable target for future ABS interventions - although this should be confirmed by further studies.

The limitations of the work are mainly due to the retrospective nature of the two studies, which were conducted in a single university hospital. Further the investigated patient collective mostly suffered complex underlying diseases and surgical procedures. This should be taken into account when transferring the data to other health care institutions.

4. Beitrag zu den Veröffentlichungen

Die Doktorarbeit wurde von Magdalena Gruber unter Betreuung von Prof. Dr. Rika Draenert und Mitbetreuung von Dr. Alexandra Weber am LMU Klinikum München durchgeführt.

4.1 Beitrag zu Veröffentlichung 1

Der Studienentwurf wurde von Magdalena Gruber, mit Beratung von Dr. Alexandra Weber, Dr. Jette Jung und Prof. Dr. Rika Draenert entwickelt. An den wöchentlichen ABS-Visiten nahmen auf Seiten des ABS-Teams Prof. Dr. Rika Draenert, Dr. Alexandra Weber, Dr. Jette Jung und Magdalena Gruber teil. Die Datenerhebung sowie die statistische Auswertung und eine erste Beurteilung und Diskussion der Ergebnisse wurde durch Magdalena Gruber durchgeführt. Der Erstentwurf des Manuskripts zur Veröffentlichung wurde von Magdalena Gruber erstellt und von Dr. Alexandra Weber und Prof. Dr. Rika Draenert Korrektur gelesen. Die Tabellen und Abbildungen wurden von Magdalena Gruber erstellt.

4.2 Beitrag zu Veröffentlichung 2

Auch für V2 wurde der Studienentwurf von Magdalena Gruber mit der Unterstützung von Dr. Alexandra Weber, Dr. Jette Jung und Prof. Dr. Rika Draenert konzipiert. Wie in V1 nahmen an den wöchentlichen ABS-Visiten auf Seiten des ABS-Teams Prof. Dr. Rika Draenert, Dr. Alexandra Weber, Dr. Jette Jung und Magdalena Gruber teil. Die Daten wurden von Magdalena Gruber, mit teilweiser Unterstützung von Anne Strehlau, erhoben. Die anschließende statistische Datenauswertung und eine erste Beurteilung und Diskussion der Ergebnisse wurde durch Magdalena Gruber durchgeführt. Der Erstentwurf des Manuskripts zur Veröffentlichung wurde von Magdalena Gruber erstellt und dann Korrektur gelesen. Die Tabellen und Abbildungen wurden von Magdalena Gruber erstellt.

5. Veröffentlichung 1

Impact and Sustainability of Antibiotic Stewardship on Antibiotic Prescribing in Visceral Surgery

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Article

Impact and Sustainability of Antibiotic Stewardship on Antibiotic Prescribing in Visceral Surgery

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Abstract: Background: Antibiotic stewardship (AS) ward rounds are a core element in clinical care for surgical patients. Therefore, we aimed to analyze the impact of surgical AS ward rounds on antibiotic prescribing, and the sustainability of the effect after the AS interventions are no longer provided. Methods: On four wards of the department of visceral surgery, we conducted two independent retrospective prescribing analyses (P1, P2) over three months each. During the study periods, the level of AS intervention differed for two of the four wards (ward rounds/no ward rounds). Results: AS ward rounds were associated with a decrease in overall antibiotic consumption (91.1 days of therapy (DOT)/100 patient days (PD) (P1), 70.4 DOT/100PD (P2)), and improved de-escalation rates of antibiotic therapy (W1/2: 25.7% (P1), 40.0% (P2), $p = 0.030$; W3: 15.4 (P1), 24.2 (P2), $p = 0.081$). On the ward where AS measures were no longer provided, overall antibiotic usage remained stable (71.3 DOT/100PD (P1), 74.4 DOT/100PD (P2)), showing the sustainability of AS measures. However, the application of last-resort compounds increased from 6.4 DOT/100PD to 12.1 DOT/100PD (oxazolidinones) and from 10.8 DOT/100PD to 13.2 DOT/100PD (carbapenems). Conclusions: Antibiotic consumption can be reduced without negatively affecting patient outcomes. However, achieving lasting positive changes in antibiotic prescribing habits remains a challenge.

Keywords: antibiotic stewardship; visceral surgery; sustainability; antibiotic consumption

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1. Introduction

Antibiotic resistance is a major global threat, making effective antibiotic treatment increasingly difficult, while the process of developing new antibiotics still has room for improvement [1]. Broad use of, in particular, last-resort compounds, such as oxazolidinones or carbapenems, is a serious concern worldwide, as antibiotic mis- and overuse in health care are known to be main drivers of antibiotic resistance [2,3]. Rates of up to 47% of inappropriate antibiotic prescribing have been found in surgical specialties [4–7]. To promote judicious anti-infective therapy, infectious disease societies are demanding the implementation of antimicrobial stewardship programs (ASPs), as infections caused by multidrug-resistant bacteria result in increased mortality, a prolonged hospital stay, and higher health care costs [8].

In visceral surgery, intra-abdominal infections (IAI) are associated with high morbidity and mortality. Antibiotics, in addition to surgical source control, are indispensable in their treatment [9]. However, optimal antibiotic therapy in IAI remains a challenge. Interestingly, most ASPs in surgery focus on the perioperative setting (i.e., antibiotic prophylaxis) and management of surgical site infections, and neglect pre- and postoperative antibiotic use [10]. Since Charani et al. highlighted the importance of surgical ward rounds for the clinical care of patients [11], our aim was to evaluate the immediate and longer-term impacts of antibiotic stewardship (AS) ward rounds on antibiotic prescribing in a visceral surgery department. Therefore, AS ward rounds were provided on three wards of a visceral surgery department where a steady increase in antibiotic consumption was observed over the previous years.

ASPs can effectively reduce inappropriate antibiotic consumption without compromising patient outcomes, but the sustainability of AS interventions has not been studied in detail to date [12]. AS activities have to be prioritized to areas with the greatest need. So, ASPs often face limited staff and time resources and, therefore, have difficulties being permanently present. Thus, the present study also investigated if the effects of AS ward rounds were sustainable and sufficiently maintained, even after AS ward rounds were no longer provided to that area.

2. Results

2.1. Patient Characteristics

Throughout the two study periods (P1, P2), a total of 649 (P1) and 666 (P2) patients were admitted to the four surgical wards. Of those, 46.7% (303, P1) and 42.6% (284, P2, $p = 0.14$) received at least one course of systemic antibiotic treatment during their hospital stay. During P1, four patients were excluded from the study, due to incomplete sets of data (two patients) and lengths of stay longer than 100 days (two patients), whereas nine patients were excluded in P2, due to incomplete sets of data (four patients) and lengths of stay of over 100 days (five patients). The statistical analysis included 299 (P1) and 275 (P2) patients (Figure 1). The median age was 62 years in both groups. In P2, more women were included than in P1 (36.8% (P1), 45.8% (P2), $p = 0.028$). The Charlson comorbidity index [13] and the allocation of diagnoses to the different organ systems were comparable in both study cohorts. Surgery was performed in 212 (70.9%) and 213 (77.5%, $p = 0.074$) patients in P1 and P2, respectively. Rates of multidrug-resistant bacteria isolated (methicillin-resistant Staphylococcus aureus, vancomycin-resistant enterococci, linezolid-resistant Staphylococcus epidermidis, extended-spectrum β-lactamase producing gram-negative bacteria, and carbapenemase-producing Enterobacteriaceae) were similar in the two study periods. Results of nasopharyngeal, inguinal, or rectal swabs for screening of colonization were excepted. There were no differences in median length of stay, readmission for infection after 30 days, or in-hospital mortality between the two study cohorts (Table 1).

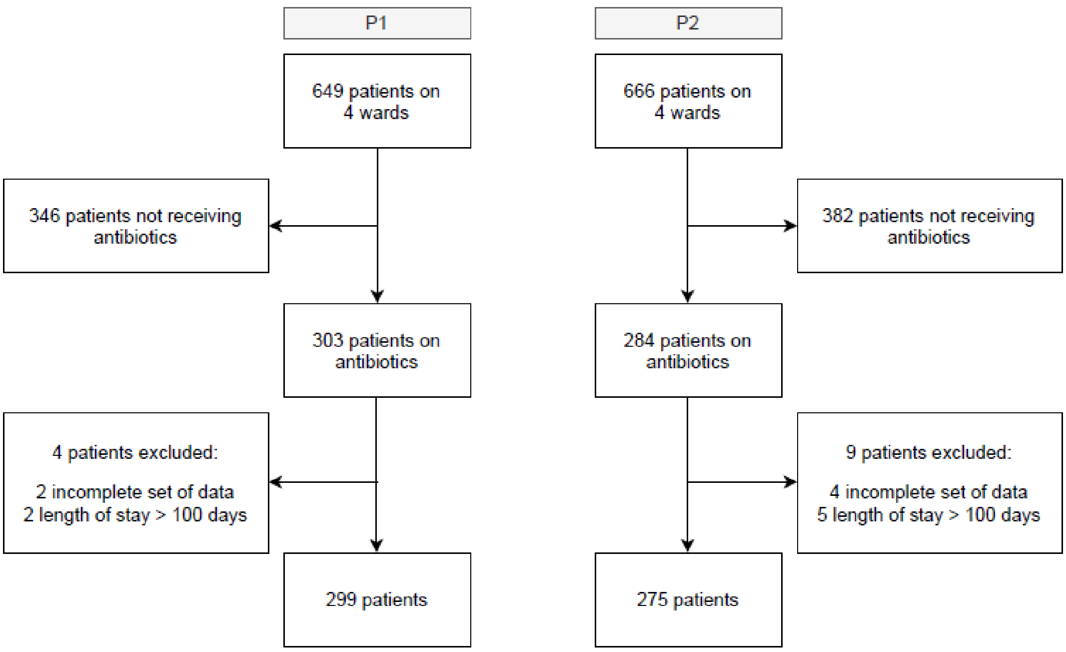

Figure 1. Flow chart of all patients admitted to four wards of the visceral surgery department during P1 and P2.

Table 1. Patient characteristics and descriptive data for all patients included, comparing P1 and P2.

Characteristics	P1 (*n* = 299)	P2 (*n* = 275)	*p*-Value
Age—years, median (range)	62 (18–96)	62 (20–98)	0.809
Sex, female—no. (%)	110 (36.8)	126 (45.8)	0.028
Charlson comorbidity index—median (range)	2 (0–8)	2 (0–10)	0.637
Penicillin allergy—no. (%)	23 (7.7)	19 (6.9)	0.719
Diagnosis—no. (%)			0.948
Bowel	127 (42.5)	112 (40.7)	0.671
Liver	61 (20.4)	53 (19,3)	0.735
Pancreas	29 (9.7)	31 (11,3)	0.538
Skin and soft tissue	22 (7.4)	23 (8.4)	0.654
Others	60 (20.1)	56 (20.4)	0.930
No surgery	87 (29.1)	62 (22.5)	0.074
ICU—no. (%)	31 (10.4)	35 (12.7)	0.376
Length of hospital stay—days, median (range)	14 (2–90)	15 (2–79)	0.677
In-hospital mortality—no. (%)	3 (1.0)	2 (0.7)	0.722
Rate of readmission for infection after 30 days—no. (%)	25 (8.4)	20 (7.3)	0.621
Length of therapy (LOT)—days, median (range)	8 (1–73)	8 (1–77)	0.814
LOT < 5 d—no. (%)	50 (16.7)	45 (16.4)	0.908
LOT 5–9 d—no. (%)	121 (40.5)	108 (39.3)	0.770
LOT 10–14 d—no. (%)	47 (15.7)	55 (20.0)	0.180
LOT $\geq$ 15 d—no. (%)	81 (27.1)	67 (24.4)	0.456
Multidrug-resistant bacteria			
gram-positive	6	6	0.884
gram-negative	9	10	0.675

2.2. Changes in Overall Antibiotic Use and Choice of Substance

A decrease in overall antibiotic consumption was observed in P2 on ward 1 (W1) and ward 2 (W2), where AS ward rounds were conducted in both phases, and on ward 3 (W3), where AS ward rounds took place only in P2 (W1/2/3 combined: 91.1 days of therapy (DOT)/100 patient days (PD) vs. 70.4 DOT/100PD). On ward 4 (W4), the AS ward rounds were no longer provided during P2. The overall antibiotic consumption remained unchanged on this ward. On all four wards, reduced usage of cefuroxime, ciprofloxacin, and metronidazole prescriptions was seen during study period P2 (cefuroxime: 3.1 DOT/100PD vs. 1.1 DOT/100PD, ciprofloxacin: 10.5 DOT/100PD vs. 7.1 DOT/100PD, metronidazole: 10.7 DOT/100PD vs. 5.2 DOT/100PD; Figure 2). Additional data on antibiotic consumption for individual substances according to the respective wards are available in the Supplementary Materials (Table S1).

In conclusion, while AS ward rounds were actively performed, we observed an improvement in antibiotic use on the wards. Looking at the overall antibiotic consumption and, in particular, the application of cephalosporins, fluoroquinolones, and metronidazole, the reductions in broad-spectrum and restricted antibiotics were less pronounced.

2.3. Length of Therapy and Prescribing Behavior

Shortening the duration of antibiotic therapy, where possible, without negatively influencing therapy safety is an important goal of AS. However, in our study, the length of antibiotic therapy was a median of 8 days in both study periods, and provision of AS ward rounds did not have an impact on length of therapy. The total number of prescriptions was 342 courses of antibiotics (COAs) in phase 1, and 312 COAs in phase 2. Initial doses were given intravenously in 88.9% (P1) and 90.7% (P2), respectively. No effect of the AS ward rounds on the intravenous-to-oral (iv-to-oral) switch rate nor on the duration until iv-to-oral-switch could be detected.

On W1 and W2, the antibiotic therapy was de-escalated more often in P2 than in P1 (25.7% vs. 40.0%, $p = 0.030$). On W3, a trend of increased de-escalation rate during a

COA was observed in P2 (p = 0.081). On W4, there was a tendency towards a decrease of iv-to-oral switch and de-escalation rates; however, it was not statistically significant. Duration to de-escalation did not change significantly on the four wards (Table 2).

Therefore, AS ward rounds were associated with increased de-escalation rates, but did not reduce the duration of antibiotic therapy.

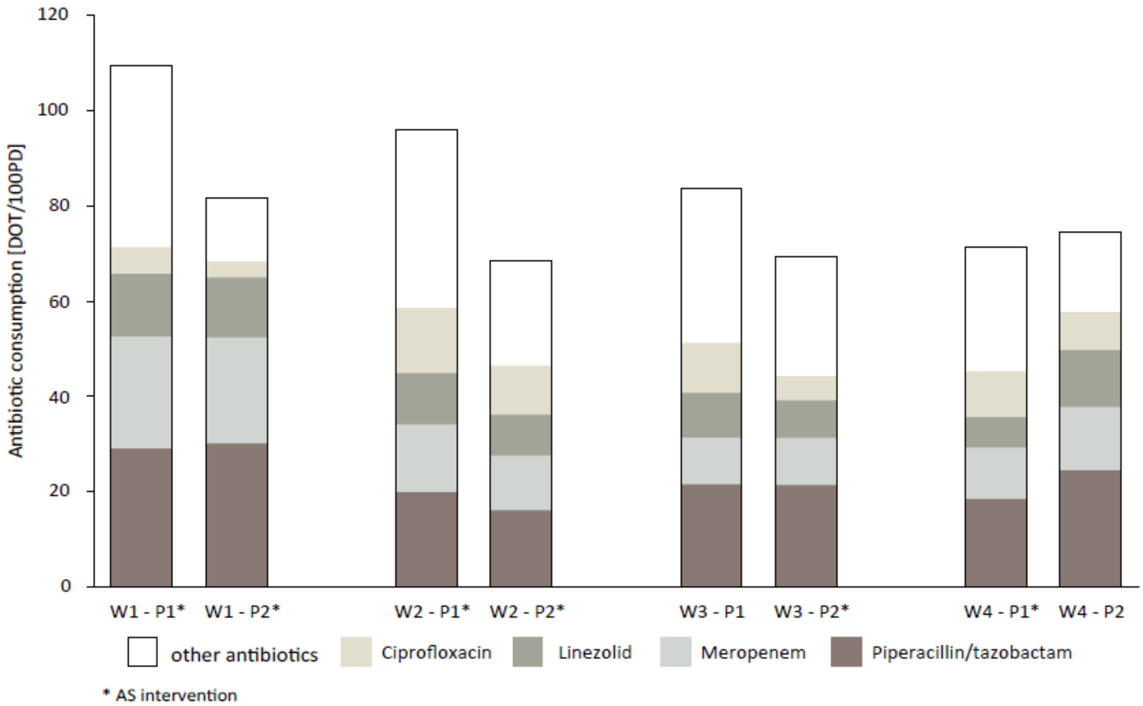

Figure 2. Overall antibiotic consumption, and consumption of ciprofloxacin, linezolid, meropenem, and piperacillin/tazobactam on the four wards, comparing P1 and P2.

Table 2. Changes in antibiotic therapy for all courses of antibiotics, comparing P1 and P2.

	W1/2			W3			W4		
	P1 [a]	**P2 [a]**	***p*-Value**	**P1**	**P2 [a]**	***p*-Value**	**P1 [a]**	**P2**	***p*-Value**
Courses of antibiotics	113	90		130	120		99	102	
Route of antibiotics at beginning of therapy—no. (%)			0.425			0.649			0.941
Intravenous	99 (87.6)	82 (91.1)		117 (90.0)	110 (91.7)		88 (88.9)	91 (89.2)	
Oral	14 (12.4)	8 (8.9)		13 (10.0)	10 (8.3)		11 (11.1)	11 (10.8)	
iv-to-oral switch	42 (42.4)	36 (43.9)	0.842	41 (35.0)	37 (33.6)	0.824	26 (29.5)	19 (20.9)	0.181
De-escalation	29 (25.7)	36 (40.0)	0.030	20 (15.4)	29 (24.2)	0.081	20 (20.2)	16 (15.7)	0.404
Escalation	43 (38.1)	32 (35.6)	0.714	35 (26.9)	22 (18.3)	0.106	25 (25.3)	19 (18.6)	0.256
	n = 41 [b]	n = 35 [b]		n = 40 [b]	n = 36 [b]		n = 24 [b]	n = 17 [b]	
Duration to iv-to-oral switch—days, median (range)	6 (1–21)	6 (1–15)	0.757	5 (1–20)	6.5 (1–20)	0.722	5 (2–13)	4 (2–28)	0.649
	n = 28 [b]	n = 33 [b]		n = 20 [b]	n = 28 [b]		n = 18 [b]	n = 13 [b]	
Duration to de-escalation—days, median (range)	6 (1–21)	6 (1–15)	0.738	5.5 (1–29)	6.5 (2–20)	0.674	6.5 (1–16)	5 (2–21)	0.809

[a] AS Intervention, [b] Courses of antibiotics with more than one iv-to-oral switch/de-escalation were excluded from this statistical analysis.

3. Discussion

This retrospective monocentric study investigated the impact of AS ward rounds on antibiotic prescribing behavior in a visceral surgery department, as well as the sustained effects after the AS ward rounds were stopped. To analyze the change in antibiotic prescribing patterns, depending on the involvement of performed AS measures, the study was conducted on four surgical wards with different statuses in implementation of AS ward rounds. Antibiotic consumption decreased, while de-escalation rates increased, when AS measures were implemented on the wards. AS ward rounds were associated with improved antibiotic prescribing, and had sustained effects regarding overall antibiotic consumption for the following three months after they were no longer provided. This is corroborated by the fact that overall antibiotic consumption steadily increased on the four wards over the years before the study was conducted, and changed after AS ward rounds were provided on the wards. Furthermore, the four wards had comparable collectives of patients with visceral surgical foci, and the diagnoses the patients were admitted for, or the disease severity (Charlson comorbidity index), did not change over time. In addition, there was no change of personnel in crucial positions. The decrease in overall antibiotic consumption on W1 might be explained by reductions in inappropriate COAs, as there was no reduction in length of antibiotic therapy in P2. In particular, reduced use of the last-resort compounds linezolid and meropenem on W2 and W3 is noteworthy, as it was not compensated by the use of other broad-spectrum antibiotics, such as piperacillin/tazobactam.

Previous studies observed a positive impact of AS in surgical patients with IAI [14–16]. They showed improved antibiotic use after the implementation of an ASP, based on the development of guidelines regarding antibiotic therapy of IAI. Our study also highlights the impact of AS ward rounds in improving antibiotic prescribing. Our results are in accordance with the ones previously described by Surat et al. [17]. In addition, a reduction in total days of antibiotic therapy was observed by implementing an ASP, including regular ward rounds, but without local standards for antibiotic therapy of IAI at that time. In general, it seems to be difficult to achieve shorter durations of antibiotic therapy, even though a reduction in length of therapy is widely recommended in the literature for IAI with adequate source control [18–22]. Except for Surat and colleagues, none of the previous studies could show a reduction of antibiotic therapy duration, and the shortened duration of therapy was limited to the treatment of cholecystitis—a disease that was strongly underrepresented in our cohort.

The positive effects of performed AS ward rounds regarding antibiotic consumption in general were sustained, but not for last-resort compounds like carbapenems or oxazolidinones. On W4, where AS ward rounds were stopped after P1, the overall antibiotic consumption remained on a stable level, but the use of meropenem and linezolid distinctly increased in P2. Barbieri et al. investigated the sustainability of clinical pathways for decreasing use of broad-spectrum antibiotics in pediatric patients suffering from acute otitis media or pharyngitis [23]. A lack in sustained effect of the implemented clinical pathways after ending their educational support was observed, consistent with our findings. Ullman and colleagues investigated the lasting economic impact of an ASP, after stopping and restarting [24]. The results support our findings of recommending a continuation of the ASP, although the evaluated parameter of antibiotic purchases is not the suitable metric to use. However, at the start of this ASP, the currently recommended metrics (defined daily doses and days of antibiotic therapy) had not been established yet. In contrast, Dona and colleagues' AS intervention focusing on improved perioperative antibiotic prophylaxis, resulted in lasting effects 24 months after ending the educational lectures for their clinical pathways [25]. However, pre- and postoperative antibiotic therapies appear more challenging than surgical antibiotic prophylaxis, in the majority of cases.

Charani et al. investigated antibiotic decision making in surgery and pointed out the importance, but also the difficulties, of ward rounds for patient care in surgery [11,26]. Our findings support their observations. Our experience was that junior faculty were present on the AS ward rounds, while the senior faculty were in the operating room (OR) and were, therefore, difficult to reach. Face-to-face communication was further complicated, due to their limited time resources on the wards. Many duties outside the OR were delegated to junior surgeons, and discussions about antibiotic therapy during AS ward rounds were, therefore, mostly conducted with them. Recommendations regarding antibiotic therapy made during AS ward rounds often had to be approved later by the senior faculty. Thus, final decisions about antibiotic therapy were made after the AS ward rounds and without the involvement of the AS team. When a junior doctor reports to the senior faculty, there could be a loss of information regarding the recommendations, which could lead to rejection of those AS recommendations. However, the junior faculty that we dealt with was mostly interested in the help by the AS team. An open mind for AS measures is an important prerequisite for changing habits. Charani and colleagues also described surgeons as being afraid of negative patient outcomes, which could be a driver for inappropriate antibiotic use, especially postoperatively—a fact that we can confirm with our experience.

In addition to the AS ward rounds, the strong decrease of ciprofloxacin consumption on all four wards might have been influenced by the publication of an official drug-safety warning regarding the restricted application of fluoroquinolones after P1 (10/2018). This topic has been widely discussed in the media and has been a focus of the public's attention. Due to the low bioavailability of cefuroxime, it was excluded from the institution's formulary. This could have additionally reduced cefuroxime consumption, as well as causing a reduction in prolonged perioperative antibiotic prophylaxis with cefuroxime. The department's internal guidelines for perioperative antibiotic prophylaxis were reviewed and reissued between the two study periods, and explicitly suggested single-shot application, but no prolonged postoperative therapy regime. Consequently, the consumption of metronidazole, co-administered with cefuroxime and ciprofloxacin, decreased on the wards to the same extent as cefuroxime and ciprofloxacin.

Fewer female patients were included in P1 than in P2, which does not completely exclude possible changes in antibiotic prescribing due to gender differences. Aghdassi et al. described an increased risk for surgical site infections (SSI) in men for colon surgery, no differences for endoscopic cholecystectomy/appendectomy, and an increased risk in women for hernia repair [27]. Other studies described differing results regarding gender-specific risk for developing SSI in abdominal surgery [28,29]. Furthermore, this study did not focus primarily on SSI, but on intra-abdominal infections, which leads us to conclude that the influence of the different gender distribution in both study periods had a negligible impact on the results regarding antibiotic prescribing.

There are some limitations to our study. The patient collectives might not be comparable to those of smaller hospitals, in terms of the extent of the surgical procedures. In addition, there was no control group. However, the "cross-over" design between W3 and W4 generated an internal control to demonstrate the effects of the AS ward rounds. We were able to show a sustained effect of AS interventions, in terms of overall antibiotic consumption for three months after their completion. How long the effect of interventions persists warrants further research.

Since local treatment guidelines for IAI were not available during the study periods, a combination of AS ward rounds and internal guidelines on antibiotic therapy in IAI could further improve prescribing in the future. In particular, it could help junior faculty to make their decisions based on these local treatment guidelines when AS consultation is not available. Furthermore, AS ward rounds with senior faculty members present could promote rapid and safe decisions on antibiotic therapy.

4. Materials and Methods

4.1. Study Setting and Population

This monocentric, retrospective observational study was conducted at the visceral surgery department of the university hospital, LMU Munich. Two independent prescribing analyses of three months each (18 May–18 July (P1); 19 September–19 November (P2)) were carried out on three general and one intermediate-care (IMC) wards of the department.

To investigate the impact (wards 1, 2, 3) and short-term sustainability (ward 4) of AS interventions, the two periods were chosen according to the provision of AS ward rounds. On ward 1 (W1, IMC), ward 2 (W2), and ward 4 (W4), AS interventions were introduced before P1. On W1 and W2, they were continued in P2, whereas the AS intervention was stopped after P1 on W4, and started only after P1 on ward 3 (W3) (Figure 3). All patients, aged 18 years or older, who received systemic antibiotics whilst on one of the four designated wards, were included in the study. Patients prescribed prophylactic antibiotics (perioperative or long-term prophylaxis), or with an incomplete set of data, were excluded. In addition, patients who stayed on the ward for more than 100 days were excluded, due to a possible bias of the results, as the hospital stay distinctly exceeded the observation period of three months. The study was approved by the ethics committee of the university hospital, LMU Munich (19-906).

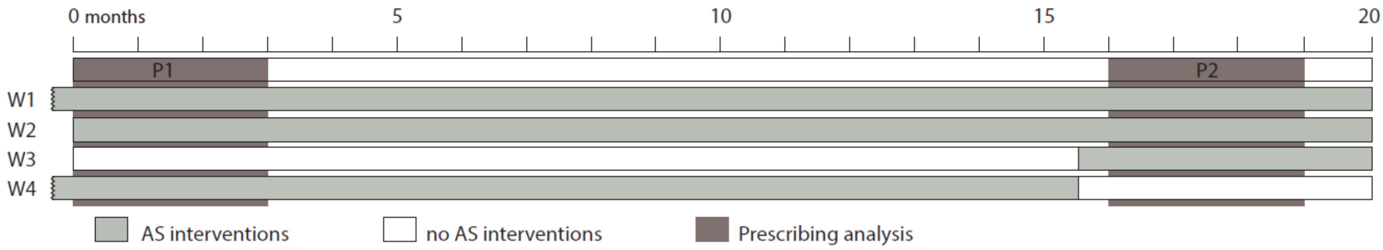

Figure 3. Study timeline of AS intervention and prescribing analysis for the four wards.

4.2. Intervention

A multidisciplinary ASP was introduced at the university hospital, LMU Munich in 2017. The AS team was composed of an infectious disease (ID) physician, an ID pharmacist, and a clinical microbiologist. Weekly ward rounds based on an audit and feedback strategy, in collaboration with the current surgeon on duty, started on W2 with the observation period (P1), and on W1 and W4 a few months earlier (Figure 3).

4.3. Data Collection and Definitions

All demographic and clinical data, choice of antibiotic agent, days of antibiotic therapy, and microbiological results were extracted manually from electronic patient records and irreversibly anonymized during data collection.

Diagnoses requiring hospitalization and the resulting surgeries were recorded and allocated to the organ concerned (bowel, liver, pancreas, skin, and soft tissue).

In the study, antibiotic consumption was measured in days of therapy per 100 patient days. Length of antibiotic therapy (LOT) was defined as in-hospital days of antibiotic therapy. Continuous days of antibiotic treatment were defined as one course of antibiotics (COA). After discontinuation of antibiotic treatment for more than one day, a new COA was determined, and several COAs could, therefore, be assigned to one patient.

To evaluate changes in antibiotic therapy, antibiotic agents were ranked according to their spectrum of activity against drug-resistant bacteria [30,31] (Table 3). Changes in prescribed antibiotics within one COA were separated according to de-escalation or escalation [30–32]. De-escalation was defined as a change of one or more antibiotics to an agent with a lower rank, or termination of one or more antibiotics in a combination therapy. If a restricted drug (e.g., linezolid, daptomycin, or tigecycline) was still included after modification of antibiotic therapy, the change was not classified as a de-escalation. Escalation was defined as changing the antibiotic therapy to an agent with a higher rank, or adding one or more antibiotics for additional coverage. IV-to-oral switch was defined as a conversion from intravenous to oral antibiotic therapy. Each COA was checked retrospectively for changes in antibiotic therapy, and evaluated by an ID physician and a pharmacist. Duration to iv-to-oral switch or de-escalation was measured as days between the beginning of the antibiotic treatment and the iv-to-oral switch/de-escalation. COAs with more than one iv-to-oral switch/de-escalation were excluded from this statistical analysis.

Table 3. Antibiotic ranking [30].

Rank 1	narrow spectrum penicillins, first- and second-generation cephalosporins, co-trimoxazole, doxycycline, oral fosfomycin, metronidazole
Rank 2	aminopenicillin/beta-lactamase inhibitor, third-generation cephalosporins, fluoroquinolones, macrolides, clindamycin
Rank 3	fourth-generation cephalosporines, carbapenems, piperacillin/tazobactam, vancomycin
Rank 4	daptomycin, linezolid, tigecycline

4.4. Outcomes and Data Analysis

To assess the impact of weekly AS ward rounds, overall antibiotic consumption, as well as antibiotic consumption of single substance classes and change in antibiotic therapy, were analyzed in this study. In-hospital mortality and readmission caused by an infection after 30 days were compared to ensure patient outcome was not negatively affected by the AS intervention. Short-term sustainability was defined as maintained positive effects of AS ward rounds on antibiotic prescribing in the following three months after stopping them.

A sample size calculation was performed for the outcome of changes in length of antibiotic therapy (LOT). With a targeted power of 0.8 and a low expected effect, it was calculated that 325 patients were required in each study arm. By including 299 patients within three months for P1, we were close to the intended study sample size. For P2, including 279 patients resulted in the according study period of 3 months.

All categorical variables are shown as numbers with frequencies. Continuous variables are presented according to the distribution as a mean with a standard deviation or a median with a range. Variation between the two study periods for categorial variables was tested using the $\chi 2$-test or Fisher´s exact test, and for continuous variables, the t-test or Mann-Whitney U test was used. Statistical significance was set at $p < 0.05$. The statistical analysis was performed with IBM SPSS Statistics 26.

5. Conclusions

Regular AS ward rounds most likely improved antibiotic use in the setting of visceral surgery by reducing antibiotic consumption and increasing de-escalation rates of antibiotic courses. However, AS ward rounds need to be performed continuously, as sustained effects were only observed regarding the overall antibiotic use.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/antibiotics10121518/s1, Table S1: Antibiotic consumption for single substances for the four study wards, comparing P1 and P2.

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Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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References

1. Nielsen, T.B.; Brass, E.P.; Gilbert, D.N.; Bartlett, J.G.; Spellberg, B. Sustainable Discovery and Development of Antibiotics—Is a Nonprofit Approach the Future? *N. Engl. J. Med.* **2019**, *381*, 503–505. [CrossRef] [PubMed]
2. Klein, E.Y.; Van Boeckel, T.P.; Martinez, E.M.; Pant, S.; Gandra, S.; Levin, S.A.; Goossens, H.; Laxminarayan, R. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, E3463–E3470. [CrossRef] [PubMed]
3. Holmes, A.H.; Moore, L.S.; Sundsfjord, A.; Steinbakk, M.; Regmi, S.; Karkey, A.; Guerin, P.J.; Piddock, L.J. Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet* **2016**, *387*, 176–187. [CrossRef]
4. Bugnon-Reber, A.; de Torrenté, A.; Troillet, N.; Genné, D. Antibiotic misuse in medium-sized Swiss hospitals. *Swiss Med. Wkly.* **2004**, *134*, 481–485.
5. Denny, K.J.; Gartside, J.G.; Alcorn, K.; Cross, J.W.; Maloney, S.; Keijzers, G. Appropriateness of antibiotic prescribing in the Emergency Department. *J. Antimicrob. Chemother.* **2018**, *74*, 515–520. [CrossRef]
6. Lim, M.K.; Lai, P.S.M.; Ponnampalavanar, S.S.L.S.; Omar, S.F.S.; Taib, N.A.; Yusof, M.Y.; Italiano, C.M.; Kong, D.C.M.; Kamarulzaman, A. Antibiotics in surgical wards: Use or misuse? A newly industrialized country's perspective. *J. Infect. Dev. Ctries.* **2015**, *9*, 1264–1271. [CrossRef]
7. Leeds, I.L.; Fabrizio, A.; Cosgrove, S.E.; Wick, E.C. Treating Wisely: The Surgeon's Role in Antibiotic Stewardship. *Ann. Surg.* **2017**, *265*, 871–873. [CrossRef]
8. Cosgrove, S.E. The Relationship between Antimicrobial Resistance and Patient Outcomes: Mortality, Length of Hospital Stay, and Health Care Costs. *Clin. Infect. Dis.* **2006**, *42*, S82–S89. [CrossRef] [PubMed]
9. Solomkin, J.S.; Mazuski, J.E.; Bradley, J.S.; Rodvold, K.A.; Goldstein, E.J.C.; Baron, E.J.; O'Neill, P.J.; Chow, A.W.; Dellinger, E.P.; Eachempati, S.R.; et al. Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children: Guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clin. Infect. Dis.* **2010**, *50*, 133–164. [CrossRef]
10. Charani, E.; Ahmad, R.; Tarrant, C.; Birgand, G.; Leather, A.; Mendelson, M.; Moonesinghe, S.R.; Sevdalis, N.; Singh, S.; Holmes, A. Opportunities for system level improvement in antibiotic use across the surgical pathway. *Int. J. Infect. Dis.* **2017**, *60*, 29–34. [CrossRef] [PubMed]
11. Charani, E.; Tarrant, C.; Moorthy, K.; Sevdalis, N.; Brennan, L.; Holmes, A. Understanding antibiotic decision making in surgery—A qualitative analysis. *Clin. Microbiol. Infect.* **2017**, *23*, 752–760. [CrossRef]
12. Davey, P.; Marwick, C.A.; Scott, C.L.; Charani, E.; McNeil, K.; Brown, E.; Gould, I.M.; Ramsay, C.R.; Michie, S. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst. Rev.* **2017**. [CrossRef] [PubMed]
13. Charlson, M.E.; Pompei, P.; Ales, K.L.; MacKenzie, C.R. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J. Chronic Dis.* **1987**, *40*, 373–383. [CrossRef]
14. Dubrovskaya, Y.; Papadopoulos, J.; Scipione, M.R.; Altshuler, J.; Phillips, M.; Mehta, S.A. Antibiotic Stewardship for Intra-abdominal Infections: Early Impact on Antimicrobial Use and Patient Outcomes. *Infect. Control Hosp. Epidemiol.* **2012**, *33*, 427–429. [CrossRef]
15. Sartelli, M.; Labricciosa, F.M.; Scoccia, L.; Bellesi, J.; Mazzoccanti, M.R.; Scaloni, G.; Gentilozzi, B.; Chiodera, A. Non-Restrictive Antimicrobial Stewardship Program in a General and Emergency Surgery Unit. *Surg. Infect.* **2016**, *17*, 485–490. [CrossRef] [PubMed]
16. Popovski, Z.; Mercuri, M.; Main, C.; Sne, N.; Walsh, K.; Sung, M.; Rice, T.; Mertz, D. Multifaceted intervention to optimize antibiotic use for intra-abdominal infections. *J. Antimicrob. Chemother.* **2015**, *70*, 1226–1229. [CrossRef]
17. Surat, G.; Vogel, U.; Wiegering, A.; Germer, C.-T.; Lock, J.F. Defining the Scope of Antimicrobial Stewardship Interventions on the Prescription Quality of Antibiotics for Surgical Intra-Abdominal Infections. *Antibiotics* **2021**, *10*, 73. [CrossRef]
18. Sawyer, R.; Claridge, J.; Nathens, A.; Rotstein, O.; Duane, T.; Evans, H.; Cook, C.; O'Neill, P.; Mazuski, J.; Askari, R.; et al. Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection. *N. Engl. J. Med.* **2015**, *372*, 1996–2005. [CrossRef] [PubMed]
19. Regimbeau, J.; Fuks, D.; Pautrat, K.; Mauvais, F.; Haccart, V.; Msika, S.; Mathonnet, M.; Scotté, M.; Paquet, J.C.; Vons, C.; et al. Effect of postoperative antibiotic administration on postoperative infection following cholecystectomy for acute calculous cholecystitis: A randomized clinical trial. *JAMA* **2014**, *312*, 145–154. [CrossRef]
20. Doi, A.; Morimoto, T.; Iwata, K. Shorter duration of antibiotic treatment for acute bacteraemic cholangitis with successful biliary drainage: A retrospective cohort study. *Clin. Microbiol. Infect.* **2018**, *24*, 1184–1189. [CrossRef] [PubMed]
21. de Santibañes, M.; Glinka, J.; Pelegrini, P.; Alvarez, F.A.; Elizondo, C.; Giunta, D.; Barcan, L.; Simoncini, L.; Dominguez, N.C.; Ardiles, V.; et al. Extended antibiotic therapy versus placebo after laparoscopic cholecystectomy for mild and moderate acute calculous cholecystitis: A randomized double-blind clinical trial. *Surgery* **2018**, *164*, 24–30. [CrossRef]
22. Mazuski, J.E.; Tessier, J.M.; May, A.K.; Sawyer, R.G.; Nadler, E.P.; Rosengart, M.R.; Chang, P.K.; O'Neill, P.J.; Mollen, K.P.; Huston, J.M.; et al. The Surgical Infection Society Revised Guidelines on the Management of Intra-Abdominal Infection. *Surg. Infect.* **2017**, *18*, 1–76. [CrossRef] [PubMed]

23. Barbieri, E.; De Luca, M.; Minute, M.; D'Amore, C.; Ciofi Degli Atti, M.L.; Martelossi, S.; Giaquinto, C.; Da Dalt, L.; Zaoutis, T.; Dona, D. Impact and Sustainability of Antibiotic Stewardship in Pediatric Emergency Departments: Why Persistence Is the Key to Success. *Antibiotics* **2020**, *9*, 867. [CrossRef]
24. Ullman, M.A.; Parlier, G.L.; Warren, J.B.; Mateo, N.; Harvey, C.; Sullivan, C.J.; Bergsbaken, R.; Mitropoulos, I.F.; Bosso, J.A.; Rotschafer, J.C. The Economic Impact of Starting, Stopping, and Restarting an Antibiotic Stewardship Program: A 14-Year Experience. *Antibiotics* **2013**, *2*, 256–264. [CrossRef] [PubMed]
25. Donà, D.; Luise, D.; Barbieri, E.; Masiero, N.; Maita, S.; Antoniello, L.; Zaoutis, T.; Giaquinto, C.; Gamba, P. Effectiveness and Sustainability of an Antimicrobial Stewardship Program for Perioperative Prophylaxis in Pediatric Surgery. *Pathogens* **2020**, *9*, 490. [CrossRef]
26. Charani, E.; Ahmad, R.; Rawson, T.M.; Castro-Sanchèz, E.; Tarrant, C.; Holmes, A.H. The Differences in Antibiotic Decision-making Between Acute Surgical and Acute Medical Teams: An Ethnographic Study of Culture and Team Dynamics. *Clin. Infect. Dis.* **2019**, *69*, 12–20. [CrossRef] [PubMed]
27. Aghdassi, S.J.S.; Schröder, C.; Gastmeier, P. Gender-related risk factors for surgical site infections. Results from 10 years of surveillance in Germany. *Antimicrob. Resist. Infect. Control* **2019**, *8*, 95. [CrossRef] [PubMed]
28. Mazmudar, A.; Vitello, D.; Chapman, M.; Tomlinson, J.S.; Bentrem, D.J. Gender as a risk factor for adverse intraoperative and postoperative outcomes of elective pancreatectomy. *J. Surg. Oncol.* **2017**, *115*, 131–136. [CrossRef]
29. Pedroso-Fernandez, Y.; Aguirre-Jaime, A.; Ramos, M.J.; Hernández, M.; Cuervo, M.; Bravo, A.; Carrillo, A. Prediction of surgical site infection after colorectal surgery. *Am. J. Infect. Control* **2016**, *44*, 450–454. [CrossRef]
30. Charani, E.; de Barra, E.; Rawson, T.M.; Gill, D.; Gilchrist, M.; Naylor, N.R.; Holmes, A.H. Antibiotic prescribing in general medical and surgical specialties: A prospective cohort study. *Antimicrob. Resist. Infect. Control* **2019**, *8*, 151. [CrossRef]
31. Braykov, N.P.; Morgan, D.J.; Schweizer, M.L.; Uslan, D.Z.; Kelesidis, T.; Weisenberg, S.A.; Johannsson, B.; Young, H.; Cantey, J.; Srinivasan, A.; et al. Assessment of empirical antibiotic therapy optimisation in six hospitals: An observational cohort study. *Lancet Infect. Dis.* **2014**, *14*, 1220–1227. [CrossRef]
32. Kollef, M.H.; Morrow, L.E.; Niederman, M.S.; Leeper, K.V.; Anzueto, A.; Benz-Scott, L.; Rodino, F.J. Clinical Characteristics and Treatment Patterns Among Patients With Ventilator-Associated Pneumonia. *Chest* **2006**, *129*, 1210–1218. [CrossRef] [PubMed]

6. Veröffentlichung 2

The impact of antibiotic stewardship interventions and patient related factors on antibiotic prescribing in a vascular surgical department

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RESEARCH

The impact of antibiotic stewardship interventions and patient related factors on antibiotic prescribing in a vascular surgical department

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Abstract

Purpose The development of guidelines tailored to the departments' needs and counselling during ward rounds are important antibiotic stewardship (AS) strategies. The aim was to analyse the impact of AS ward rounds and institutional guidelines as well as patient-related factors on antibiotic use in vascular surgical patients.

Methods A retrospective prescribing-analysis of 3 months (P1, P2) before and after implementing weekly AS ward rounds and antimicrobial treatment guidelines was performed. Choice of systemic antibiotics, days of antibiotic therapy and clinical data were obtained from electronic patient records.

Results During P2, the overall antibiotic consumption as well as the use of last-resort compounds like linezolid and fluoroquinolones decreased distinctly (overall: 47.0 days of therapy (DOT)/100 patient days (PD) vs. 35.3 DOT/100PD, linezolid: 3.7 DOT/100PD vs. 1.0 DOT/100PD, fluoroquinolones: 7.0 DOT/100PD vs. 3.2 DOT/100PD) while narrow-spectrum beta-lactams increased by 48.4%. Courses of antibiotics were de-escalated more often during P2 (30.5% vs. 12.1%, $p=0.011$). Only in P2, an antibiotic therapy was initiated in patients suffering from more comorbidities (i.e. higher Charlson Comorbidity Index) more frequently. Other patient factors had no distinct impact on antibiotic prescribing.

Conclusion Weekly AS ward rounds improved adherence to institutional antibiotic treatment guidelines and antibiotic prescribing in vascular surgical patients. Clear patient-related determinants affecting choice of antibiotic therapies could not be identified.

Keywords Antibiotic stewardship · Vascular surgery · Comorbidity · Patient characteristics

Introduction

Antimicrobial stewardship (AS) is one possibility of fighting antimicrobial resistance—a global threat public health is facing more than ever: Murray et al. estimated in their study 4.95 million deaths associated with bacterial antimicrobial resistance worldwide in 2019, with 1.27 million attributable deaths [1]. Although the term antimicrobial stewardship is widely used, there is no clear definition of what antimicrobial stewardship exactly stands for. Dyar et al. defined antimicrobial stewardship as "a coherent set of actions which promote using antimicrobials responsibly" [2]. Still, AS strategies can vary highly between different AS programs. They include, among others, education and distribution of educational material or reminders as posters, the development of guidelines for antimicrobial use, audit and feedback for antibiotic prescribers or restrictive actions like special release for last-resort compounds with mandatory consultation of an infectious disease specialist and restricted formulary [2, 3]. AS interventions in general improve antibiotic prescribing without negatively affecting patient outcomes—often leading to a shorter hospital stay [3]. There are various factors with impact on achieving appropriate antibiotic prescribing [4–8]. It might depend on the setting (e.g. outpatient, inpatient, long-term care facilities), the study population (e.g. elderly patients, patients with respiratory tract infections only) or the perspective of

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how antibiotic prescribing can be influenced (e.g. prescriber, patient characteristics). Knowing whether and which patient factors are associated with physicians prescribing antibiotics inappropriately could help optimize antibiotic prescribing in the future. These factors could then be considered more intensively in future AS interventions allowing patients to benefit from individualized guidelines or other tailored AS strategies.

In the present study, we aimed to analyse the impact of AS ward rounds after the implementation of antimicrobial treatment guidelines on the overall antibiotic use in a vascular surgery department as, to the best of our knowledge, there is a paucity of data for the special group of vascular surgical patients. Furthermore, we concentrated on patient-related determinants influencing inpatient antibiotic prescribing and guideline adherence to the institutional guidelines in vascular surgical patients. On the basis of these findings, future AS interventions could be adapted for individual patient groups and further improve antibiotic prescribing.

Methods

Study population and setting

This monocentric observational study was conducted at the vascular surgery department of the university hospital LMU Munich. The LMU hospital—a 2.000-bed tertiary care hospital—serves around 500.000 patients a year with a catchment area of whole southern Germany for many specialties. The vascular surgical ward of the university hospital LMU comprises about 20 beds. All patients aged 18 years or older who were admitted to the general ward of the vascular surgery department from September 2018 through November 2018 (P1) and from September 2019 through November 2019 (P2) were included in the study. Patients with an incomplete set of data were excluded. In addition, patients with more than 50% of their hospital stay outside of the observation period were excluded due to a possible bias of the results, as a distinct part of the hospital stay did not contribute to the observation period. Two independent retrospective prescribing analyses of 3 months each, before (=P1) and after (=P2) implementing AS interventions, were carried out. The study was approved by the ethics committee of the university hospital LMU Munich (register-number 19-906).

AS interventions

The AS program of the university hospital LMU Munich, composed of an infectious disease (ID) physician, an ID pharmacist and a clinical microbiologist, introduced weekly AS ward rounds at the general ward of the vascular surgery department in 2019. The AS ward rounds were based on an audit and feedback policy in cooperation with the current ward physician. Every patient on antimicrobial therapy was discussed by the surgeon and the AS team. The ward physician could, furthermore, present patients during the ward round who were currently not on antimicrobial therapy, but were suspected to have an infectious process. Antimicrobial therapy was reviewed regarding choice of substance, dosing, (de-) escalation opportunities and treatment duration. Particularly, recommendations about (de-)escalation of antibiotic therapy were made according to microbiological results. Furthermore, antimicrobial treatment guidelines issued in collaboration with the department of vascular surgery, hospital hygiene and medicinal microbiology were introduced in an educational session and then available in the hospital's intranet (Fig. SM1, appendix). Additionally, the antimicrobialtreatment guidelines printed as pocket-cards were distributed among the physicians of the vascular surgery department.

Data acquisition

For a factor model analysing the influence of patient related determinants on antibiotic prescribing, we included: age, sex, length of hospital stay, admission from a medical institution, in-hospital-mortality, rate of readmission after 30 days for infection, charlson comorbidity index (CCMI), intensive care stay, severity of vascular disease, penicillin allergy, foreign material in situ, glomerular filtration rate, immunosuppression, surgery, revision surgery. All relevant demographic and clinical data, choice of systemic antibiotics and days of antibiotic therapy (DOT) were manually obtained from electronic patient records and irreversibly anonymised after data collection.

Definitions

In this study, the analyses were based either on cases (the hospital stay of one patient), or courses of antibiotics (COA). Several cases could be assigned to one patient during the two study periods, if the patient was admitted repeatedly during the study period. One course of antibiotics was defined as continuous days of antibiotic treatment. After discontinuation of antibiotic treatment for more than 1 day, a new COA was determined, also within the same case (Fig. 1).

Antibiotics that were prescribed during the study periods were ranked according to their activity against drug-resistant bacteria [9–11] (Table 1). A change of antibiotic agent(s) during one COA could be classified as de-escalation or escalation as described previously [9, 11, 12]: De-escalation of antibiotic therapy was defined as a change of one or more antibiotics to an antibiotic of lower rank or termination of one or more antibiotics in a combination.

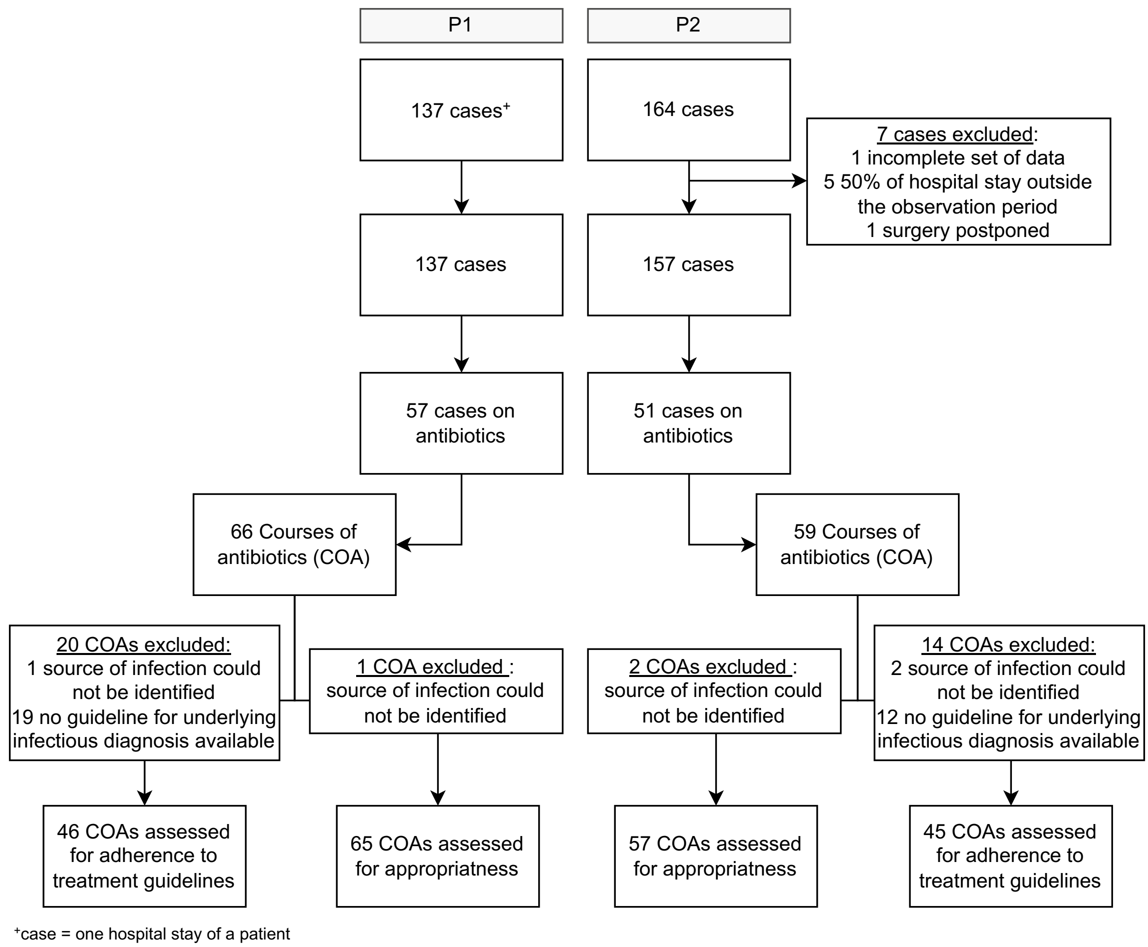

Fig. 1 Flow chart of the included cases and courses of antibiotics (COA)

Table 1 Antibiotic ranking [9, 10]

Rank 1 (narrow spectrum)	Narrow spectrum penicillins, first- and second-generation cephalosporins, co-trimoxazole, doxycycline, oral fosfomycin, metronidazole
Rank 2 (broad spectrum)	Aminopenicillin/beta-lactamase inhibitor, third-generation cephalosporins, fluoroquinolones, macrolides, clindamycin, intravenous fosfomycin, rifampicin
Rank 3 (extended spectrum)	Fourth-generation cephalosporines, carbapenems, piperacillin/tazobactam, vancomycin
Rank 4 (restricted)	Linezolid, tigecycline

However, if there was a restricted antibiotic (e.g. linezolid, tigecycline) continued after the change, it was not classified as de-escalation. A change of one or more antibiotics to an antibiotic of higher rank or starting an additional antibiotic to the existing antibiotic therapy was defined as escalation.

COAs were also evaluated according the choice of antibiotic agent. It could be classified as appropriate or inappropriate and further if it was in adherence with the local treatment guidelines or not. Guideline adherence regarding antibiotic substance was only evaluated if a current guideline for the underlying infectious diagnosis was available. Antibiotic substance was considered appropriate, unless at least one of the following criteria was of relevance:

- No evidence of infection according to the electronic file
- The expected spectrum of bacteria was not covered with the prescribed antibiotics
- The prescribed antibiotic(s) distinctly exceeded the expected spectrum of bacteria for the treated infection
- Prophylaxis pre- or post-surgery if not recommended by guidelines

If the source of infection could not be identified for a COA, they were not considered for statistical analysis. Each COA was retrospectively evaluated by an ID physician and a pharmacist for changes in antibiotic therapy and choice of antibiotic agent.

Severity of the underlying vascular disease (e.g. aortic aneurysm) was retrospectively analysed by consulting reference literature [13]. However, for some disorders there was no official classification available. In these cases (e.g. carotid body tumor) no clear classification could be made.

Antibiotic consumption was quantified in days of antibiotic therapy per 100 patient days (DOT/100PD). Length of antibiotic therapy (LOT) was defined as the total of in-hospital days of antibiotic therapy for one patient case.

Outcomes and statistical analysis

Due to the small sample size in our study, the variables contributing to the identification of patient-related determinants that might influence antibiotic prescribing are analysed descriptively. The impact of weekly AS ward rounds together with antimicrobial treatment guidelines was assessed by comparing antibiotic consumption and changes in antibiotic therapy.

All categorial variables are presented as numbers with frequencies. To compare the categorial variables, χ^2-test or Fisher´s exact test was used. Continuous variables are shown as median with range while for the comparisons the Mann–Whitney U test was used. The statistical analysis was performed with IBM SPSS Statistics 26. Statistical significance was defined as $p < 0.05$.

Results

Patient characteristics

Over the two study periods, 137 (P1) and 164 (P2) patient cases were identified, respectively. In P2, seven cases had to be excluded. One patient had an incomplete set of data, another patient's surgery was postponed and the patient was discharged after only 1 day. Five patients with more than 50% of their hospital stay outside of the observation period were further excluded. Thus, 137 (P1) and 157 (P2) patient cases were included in the statistical analysis (Fig. 1). In general, the two study groups were comparable (Table 2). However, more patients were admitted to the intensive or intermediate care unit during P2 (63.7) compared to P1 (51.8%) which was statistically significant ($p = 0.04$). Overall, the infectious diseases diagnoses were comparable for both study periods (Table 3). During P2, however, there were more diagnoses of pneumonia (7.6% (P1) vs. 20.3% (P2), $p = 0.038$). In contrast, more COAs with patients treated for urinary tract infections were observed in P1 (21.2% (P1) vs. 10.2% (P2), $p = 0.093$). The spectrum of underlying vascular diagnoses did not differ between the two study periods.

Table 2 Patient characteristics comparing P1 and P2

Characteristics	P1 (n = 137)	P2 (n = 157)	*p*-value
Age—years, median (range)	69.0 (30–91)	70.0 (22–97)	0.408
Sex, female—no. (%)	41 (29.9)	40 (25.5)	0.394
Length of stay—days, median (range)	8.0 (1–59)	8.0 (1–78)	0.254
Admission from medical institution—no. (%)	18 (13.1)	20 (12.7)	0.919
In-hospital mortality—no. (%)	1 (0.7)	1 (0.6)	0.923
Rate of readmission after 30 days—no. (%)	2 (1.5)	8 (4.5)	0.112
Charlson comorbidity index—median (range)	2.0 (0–8)	2.0 (0–10)	0.399
ICU/IMC—no. (%)	71 (51.8)	100 (63.7)	0.040
Severity of disease[a] high—no. (%)	70 (52.2)	72 (49.3)	0.625
Antibiotic therapy—no. (%)	57 (41.6)	51 (32.5)	0.106
Penicillin allergy—no. (%)	13 (9.5)	8 (5.1)	0.145
Length of therapy—days, median (range)	8.0 (1–37)	7.0 (1–46)	0.774
Foreign material—no. (%)	121 (88.3)	140 (89.2)	0.818
Impaired kidney function[a]—no. (%)	29 (21.2)	36 (22.9)	0.716
Immunosuppression—no. (%)	9 (6.6)	9 (5.7)	0.765
Surgery—no. (%)	101 (73.7)	127 (80.9)	0.142
Re-surgery—no. (%)	20 (19.8)	21 (16.5)	0.523
Multidrug-resistant bacteria—no. (%)	3 (2.2)	1 (0.6)	0.342

[a]Defined as estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m^2

Table 3 Infectious diagnoses comparing P1 and P2

Courses of antibiotics	P1 (n=66)	P2 (n=59)	*p*-value
Infectious diagnoses—no. (%)			
Skin infection	17 (25.8)	16 (27.1)	0.863
Osteomyelitis	3 (4.5)	2 (3.4)	0.742
Bacteraemia	4 (6.1)	3 (5.1)	0.813
Shunt infection	3 (4.5)	2 (3.4)	0.742
Vascular graft infection	0 (0.0)	3 (5.1)	0.102
Urinary tract infection	14 (21.2)	6 (10.2)	0.093
Pneumonia	5 (7.6)	12 (20.3)	0.038
Intra-abdominal infection	2 (3.0)	1 (1.7)	0.626
Others	18 (27.3)	14 (23.7)	0.650

Antibiotic consumption and changes in antibiotic prescribing

We observed a decrease in the overall consumption of antibiotics in P2, while AS interventions were provided to the ward (Fig. 2). During P1, the antibiotic consumption was 47.0 DOT/100PD which was reduced to 35.3 DOT/100PD in P2. This is a reduction of 11.7 DOT/100PD or 25% in antibiotic use.

Prescribing small spectrum antibiotics where possible is one goal of AS. Our weekly AS ward rounds combined with institutional guidelines led to a reduced consumption of the following antibiotics: Linezolid, fluoroquinolones, meropenem, cefuroxime and clindamycin were less prescribed in P2 compared to P1 (linezolid: 3.7 vs. 1.0 DOT/100PD, cefuroxime: 4.5 vs. 1.1 DOT/100PD, clindamycin: 4.6 vs. 1.9 DOT/100 PD). In contrast, the consumption of narrow spectrum penicillins and cefazolin prescribing increased by 48.4% during P2. Piperacillin/tazobactam was the most commonly prescribed antibiotic in both study periods and remained on a stable level [11.5 DOT/100 PD (P1) vs. 10.1 DOT/100 PD (P2)]. Additional data on consumption of single antibiotics are given in the supplementary material (Table SM1).

In the intervention period, there were less patients receiving antibiotic therapy compared to P1, however this was only a trend and did not reach statistical significance (41.6% (P1) vs. 32.5% (P2), $p=0.106$). There were no changes regarding frequencies of iv-to-oral switch with 19.2% (P1) and 18.6% (P2, $p=0.730$) in the two study periods. Likewise, the length of antibiotic therapy could only be reduced little (8 days in P1 vs. 7 days in P2) with our AS intervention. However, we observed a statistically significant higher rate of de-escalations in antibiotic therapies in the second study period: antibiotic therapies were de-escalated more often in P2 (30.5%) than in P1 (12.1%, $p=0.011$) (Table 4). The majority of de-escalations was achieved by a change of active substance(s) to an antibiotic therapy having altogether a lower rank [5 COAs (62.5%, P1) vs. 13 COAs (72.2%, P2)]. For the remaining COAs

Fig. 2 Antibiotic consumption comparing P1 and P2; DOT/100PD=days of therapy per 100 patient days

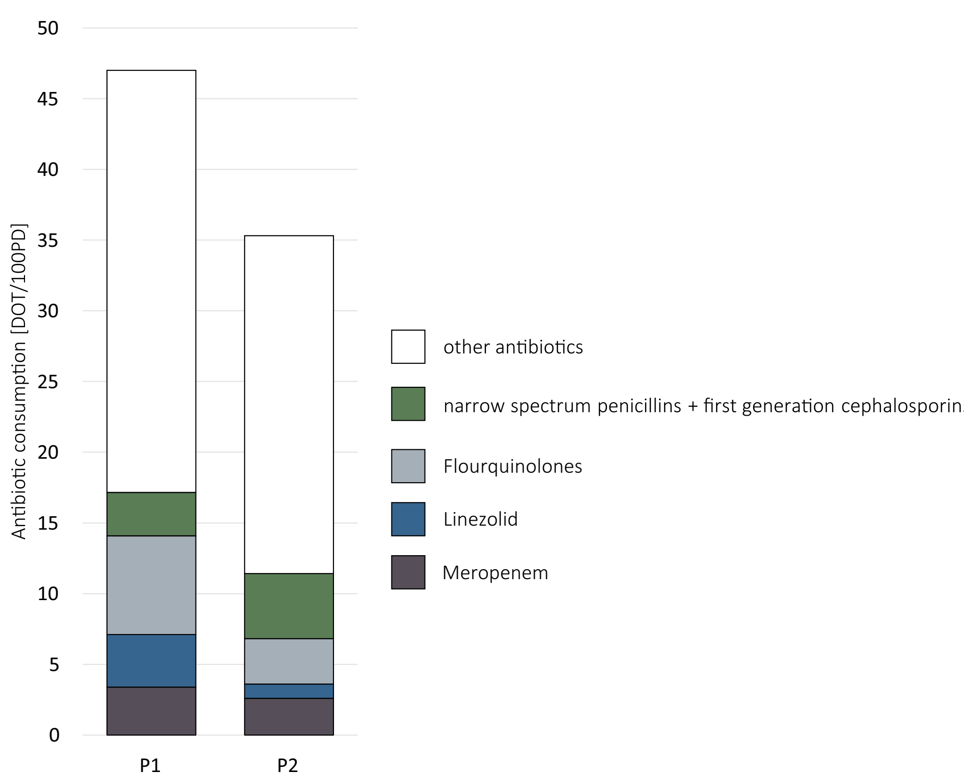

Table 4 Changes in antibiotic prescribing

Courses of antibiotics	P1 (n = 66)	P2 (n = 59)	*p*-value
Route of antibiotics at beginning of			
Therapy—no. (%)			0.391
Intravenous	52 (78.8)	50 (84.7)	
Oral	14 (21.2)	9 (15.3)	
Iv-to-oral switch—no. (%)	10 (19.2)	11 (18.6)	0.730
De-escalation—no. (%)	8 (12.1)	18 (30.5)	0.011
Escalation—no. (%)	10 (15.2)	9 (15.3)	0.987
	n = 65	n = 57	
Appropriate choice of antibiotic(s)—no. (%)	45 (69.2)	45 (78.9)	0.223
	n = 46	n = 45	
Antibiotic(s) in accordance with guidelines—no. (%)	28 (60.9)	35 (77.8)	0.081

one or more antibiotics in a combination therapy were terminated [3 COAs (37.5%, P1), 5 COAs (27.8%, P2)].

Therefore, our AS interventions significantly influenced the overall antibiotic use, the choice of substance and the de-escalation strategies.

Factors influencing antibiotic prescribing

As a next step, we evaluated if there were patient dependent factors that influenced antibiotic prescribing by physicians. For this evaluation, we compared patients with and without antibiotic therapy. Additionally, we assessed the appropriateness of the therapy as well as adherence to guidelines.

Comparing cases with and without antibiotic therapy

Patients receiving antibiotic therapy during their hospital stay were younger (median age 71.0 years vs. 68.0 years, $p = 0.04$). They had more comorbidities (CCMI for the group without antibiotics 2.0 vs. 3.0 for the group with antibiotics, $p = 0.045$) and the severity of their vascular disease was higher (44.1% vs. 60.0% with high disease severity, $p = 0.073$). Patients with antibiotics during their stay were more often operated on (73.1% vs. 85.2% with surgery, $p = 0.017$). Overall, this also led to a longer hospital stay in patients receiving antibiotics (7.0 days vs. 14.0 days, $p < 0.001$). Analysing the two study periods separately, more comorbidities in patients receiving antibiotics compared to those not receiving antibiotics was only shown to be significant for P2 (CCMI: 2.0 vs. 3.0, $p = 0.005$). P2 is therefore responsible for the difference shown for all patients (see above). We observed, patients receiving antibiotic therapy were re-admitted to the hospital within 30 days after discharge more often in P2 (7.8%) compared to P1 (0.0%, $p = 0.048$).

Overall, patients who were treated with antibiotics were more severely ill with the expected consequences of more surgeries and longer hospital stays. While AS interventions were provided to the ward, patients receiving antibiotic therapy suffered from more comorbidities.

Comparing COAs with appropriate and inappropriate antibiotic therapy

We next wanted to evaluate if the decision to treat with antibiotics was correct. For this assessment, we looked at each COA, meaning that some patients had more than one COA. Of those COAs given in both study periods, according to the retrospective evaluation the choice was correct in 90 out of 122 (73.8%) cases. In P2, we observed a higher rate of COAs rated as appropriate regarding the choice of antibiotic(s) which did not reach statistical significance, most likely due to the small sample size [69.2% (P1) vs. 78.9% (P2), $p = 0.223$]. Therefore, the initiation and choice of substance had a relatively high rate of appropriateness to begin with.

Patients with appropriate treatment displayed more comorbidities (CCMI 2.0 vs. 3.0, which failed to reach statistical significance), a slightly longer hospital stay (12.5 days vs. 15.5 days) and more revision surgeries (27.6% vs. 44.2%, also not statistically significant). A penicillin allergy reported by the patient led to more inappropriate antibiotic therapies (18.8% vs. 0.04%, $p = 0.011$). In both study periods, appropriate COAs were more often associated with impaired kidney function with an eGFR < 30 ml/min/1.73 m^2 (P1: 5.0% (inappropriate COA) vs. 22.2% (appropriate COA), $p = 0.087$; P2: 16.7% (inappropriate COA) vs. 31.1% (appropriate COA), $p = 0.322$) which might lead to the idea that a severely impaired kidney function induces physicians to think more about the necessity of more medications.

Comparing COAs adherent and not adherent with the guidelines

For this assessment, only diagnoses with an existing institutional guideline could be evaluated leaving 91 COAs. Regarding the choice of substance, COAs in P2 were more often in accordance with the institutional guidelines than in P1 with a trend to statistical significance (60.9% vs. 77.8%, $p = 0.081$). Guideline adherence was seen more often in patients with more comorbidities (2.0 vs. 3.0, $p = 0.125$) and in patients with impaired kidney function (14.3% vs. 30.2%, $p = 0.108$). Only in P2, COAs in accordance with the guidelines showed a longer median length of hospital stay (9.5 d vs. 19.0 d, $p = 0.035$). For other variables including disease severity of vascular disease, presence of foreign material or immunosuppression in the respective patients, we did not find differences regarding compliance with guidelines.

Discussion

This retrospective monocentric study demonstrates that weekly AS ward rounds combined with local antibiotic treatment guidelines improves antibiotic prescribing in a vascular surgery department. With the implementation of AS interventions, the overall antibiotic consumption decreased, as well as linezolid and fluoroquinolones consumption, without negatively affecting patient outcomes, like mortality or the rate of readmission caused by infection after 30 days. Furthermore, in the intervention period (P2), ongoing antibiotic therapy was de-escalated more often. However, our study did not find that patient dependent factors played a decisive role in the decision of antibiotic therapies. In more severely sick patients measured as more comorbidities, longer hospital stays and more impaired kidney function, we found a higher preparedness to start antibiotics and this decision was more often correct. This fact also led to a higher adherence to institutional guidelines.

A positive impact of AS programs in different surgical disciplines has previously been described in the literature [9, 14–16]. Vecchia et al. recently analysed the implementation of an ASP in a vascular surgery ward in Italy [17]. The authors—like we did—observed a decrease in carbapenem and linezolid consumption besides an increase in the rate of de-escalation of ongoing antimicrobial therapies. In contrast to our findings, Vecchia et al. noted an increase in the use of fluoroquinolones in their study. Furthermore, Bashar et al. investigated the implementation of an ASP in a vascular and a general/gastroenterology surgical ward, however, the analysis was conducted for both wards combined [18]. They observed an improvement in antibiotic consumption, quality in antibiotic prescribing and duration of antibiotic therapy. Our analysis, in contrast to Bashar et al., exclusively focused on vascular surgical patients. We could confirm their findings regarding the decrease in antibiotic consumption. In P2—the period with intense AS intervention—the COAs were more often termed appropriate and in accordance with the treatment guidelines. However, these findings did not meet statistical significance. This can be explained by the unexpected high rate of correct prescriptions in the first evaluation period on the one hand and by the relatively small sample size on the other hand.

Antibiotic therapy was more often narrowed to antibiotic(s) of lower ranking during P2. So while providing our AS interventions to the ward, an increased de-escalation rate could be achieved. De-escalation of antibiotic therapies is an important aim with regard to the development of antibiotic resistance. Schuts et al. ascertained that adherence to different AS strategies like de-escalation of antibiotic therapy even improved clinical patient outcomes like risk reduction for mortality [19]. Therefore, higher de-escalation rates are beneficial not only in terms of overall antibiotic stewardship goals, but also for the individual patient.

Shortening the duration of antibiotic therapy if possible is a main objective AS programs are aiming at. However, infections which are more often seen in vascular surgical patients like osteomyelitis or vascular graft infections require long courses of antibiotic therapy. In these cases, the task of the AS team often is to ascertain the sufficient length of therapy leading to a higher antibiotic consumption during the hospital stay.

During P2, the overall antibiotic consumption as well as the consumption of linezolid, as a last resort compound, could be distinctly reduced. The exposure to linezolid is one risk factor for linezolid resistance in *Staphylococcus epidermidis* and judicious use of linezolid is an important aim in AS [20–22]. Selection pressure through antibiotic use in general is a known driver of antibiotic resistance [23–25]. The AS interventions led to an increase of 48% in consumption of narrow-spectrum penicillins and first-generation cephalosporines. Encouraging the use of narrow-spectrum antibiotics, where possible, is one important goal of AS [25, 26].

Furthermore, the aim to reduce the use of fluoroquinolones, most of all because of possible serious adverse events, could be accomplished. This was partly because of the AS intervention. However, in October 2018, a drug safety mail announcing restrictions in use of fluoroquinolones was published. This happened during P1 and it cannot be ruled out that it might have influenced the fluoroquinolone consumption besides the conducted AS interventions. However, there was a distinct decrease in fluoroquinolone consumption in

P2, which we think would hardly have happened without AS intervention provided to the ward.

Knowing patient-related factors which influence antibiotic prescribing could contribute to target future AS interventions and therefore improve the quality in antibiotic therapy for individual patients groups.

In both study periods, COAs associated with renal impairment were more likely to get classified as appropriate or to be in accordance with the local treatment guidelines. These findings were not significant but our study could have been underpowered to confirm significance. In contrast, Ingram et al. showed in their point prevalence study, that inappropriate antibiotic prescribing was associated with an elevated creatinine level [27]. This difference might be explained by the fact that we analysed the choice of antibiotics and not the correct dosing of antibiotics in patients with renal impairment as it was done by Ingram et al. One reason for our observation could be a higher physician's awareness regarding choice of antibiotic(s) towards patients with renal impairment. Arlicot et al. also discussed the fact of higher cautiousness in dosing of antibiotics towards patients with severe renal insufficiency [28].

Anamnestic penicillin allergy was associated with a higher chance for inappropriate COAs, although the treatment guidelines contained explicit suggestions for antibiotic therapy in patients with penicillin allergy. The validity of this observation might be limited due to the very small patient numbers in this attribute. However, other studies also showed that patients with a documented penicillin-allergy in their medical history had a higher risk of being prescribed broad-spectrum antibiotics than non-allergic patients [29–31].

More comorbidities, a longer hospital stay and a (revision-)surgery leading to a higher probability of receiving antibiotic therapy should not to be discussed in detail here as it seems a consequential conclusion.

In turn, we wanted to analyse which patient related determinants are influenced by the implementation of antibiotic treatment guidelines and weekly AS ward rounds. In P2, the initiation of antibiotic therapy shifted to patients with a higher CCMI. This could lead to the conclusion that in the intervention period less patients got unnecessary antibiotic treatment. In a study conducted by Dylis et al., a higher CCMI was negatively associated with getting antibiotic treatment adherent to the guidelines [4]. This is in contrast to our findings. In P1, COAs in accordance with the guidelines were by tendency associated with a higher CCMI. The study by Alba Fernandez et al. support these findings. They compared accepted and rejected meropenem audits performed by the ASP and observed patients treated as recommended by the audit had a higher CCMI [32].

The higher CCMI in patients receiving antibiotics during P2 could also be a reason why these patients in the intervention period had more readmissions for infection after 30 days compared to P1.

This study has some limitations. It is of retrospective nature and was conducted in a single hospital. So there might be difficulties in generalizing the findings to other institutions. Furthermore, the sample size was rather small partly due to an unexpectedly low number of patients receiving antibiotics. In our opinion, this led to the fact that some of the differences did not reach statistical significance.

Conclusion

In conclusion, we can show that once weekly AS ward rounds and an implementation of institutional antibiotic treatment guidelines improved antibiotic prescribing in vascular surgical patients significantly. A decrease in overall antibiotic consumption and consumption of linezolid and fluoroquinolones as well as an increase of narrow-spectrum beta-lactams (e.g. flucloxacillin, cefazolin) could be achieved while AS interventions were provided to the ward. After implementation of our AS interventions, we observed a shift of the initiation of antibiotic treatment towards patients with more severe illness. However, we could not identify patient dependent determinants influencing the decision of antibiotic therapies in a distinct way.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s15010-023-02056-1.

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Availability of data and materials The data presented in this study are available on request from the corresponding author.

Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethical approval The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of university hospital LMU Munich (protocol code 19-906).

References

1. Murray CJ, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022;399:629–55.
2. Dyar OJ, et al. What is antimicrobial stewardship? Clin Microbiol Infect. 2017;23:793–8.
3. Davey P, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Datab Syst Rev. 2017;2:1.
4. Dylis A, et al. Antibiotics prescription and guidelines adherence in elderly: impact of the comorbidities. BMC Geriatr. 2019;19:291.
5. Morley VJ, et al. Factors associated with antibiotic prescribing for acute bronchitis at a university health center. BMC Infect Dis. 2020;20:177.
6. McKay R, et al. Systematic review of factors associated with antibiotic prescribing for respiratory tract infections. Antimicrob Agents Chemother. 2016;60:4106–18.
7. van Buul LW, et al. Factors influencing antibiotic prescribing in long-term care facilities: a qualitative in-depth study. BMC Geriatr. 2014;14:136.
8. Bardia A, et al. Adherence to guidelines for the administration of intraoperative antibiotics in a nationwide US sample. JAMA Netw Open. 2021;4:e2137296–e2137296.
9. Gruber MM, et al. Impact and sustainability of antibiotic stewardship on antibiotic prescribing in visceral surgery. Antibiotics (Basel). 2021;10:1.
10. Charani E, et al. Antibiotic prescribing in general medical and surgical specialties: a prospective cohort study. Antimicrob Resist Infect Control. 2019;8:151.
11. Braykov NP, et al. Assessment of empirical antibiotic therapy optimisation in six hospitals: an observational cohort study. Lancet Infect Dis. 2014;14:1220–7.
12. Kollef MH, et al. Clinical characteristics and treatment patterns among patients with ventilator-associated pneumonia. Chest. 2006;129:1210–8.
13. Dalman RL, Mell M. Management of asymptomatic abdominal aortic aneurysm [Internet] 2022, UpToDate, Last updated: April 26, 2022, Access date: November 17, 2021 https://www.uptodate.com/contents/management-of-asymptomatic-abdominal-aortic-aneurysm?search=aortic%20aneurysm&source=search_result&selectedTitle=3~150&usage_type=default&display_rank=3.
14. Surat G, et al. Defining the scope of antimicrobial stewardship interventions on the prescription quality of antibiotics for surgical intra-abdominal infections. Antibiotics. 2021;10:73.
15. Feihl S, et al. Effect of an intensified antibiotic stewardship program at an orthopedic surgery department. Surg Infect (Larchmt). 2022;23:105–12.
16. Guerri-Fernandez R, et al. An antimicrobial stewardship program reduces antimicrobial therapy duration and hospital stay in surgical wards. Rev Esp Quimioter. 2016;29:119–21.
17. Vecchia M, et al. Implementation of an antimicrobial stewardship program in the vascular surgery ward of a university tertiary care hospital in Pavia, Northern Italy. BMC Infect Dis. 2023;23:138.
18. Bashar MA, et al. Impact of an antibiotic stewardship programme in a surgical setting. S Afr J Infect Dis. 2021;36:307.
19. Schuts EC, et al. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. Lancet Infect Dis. 2016;16:847–56.
20. Papan C, et al. Combined antibiotic stewardship and infection control measures to contain the spread of linezolid-resistant *Staphylococcus epidermidis* in an intensive care unit. Antimicrob Resist Infect Control. 2021;10:99.
21. Mulanovich VE, et al. Emergence of linezolid-resistant coagulase-negative Staphylococcus in a cancer centre linked to increased linezolid utilization. J Antimicrob Chemother. 2010;65:2001–4.
22. Ramirez E, et al. Improving linezolid use decreases the incidence of resistance among Gram-positive microorganisms. Int J Antimicrob Agents. 2013;41:174–8.
23. Klein EY, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proc Natl Acad Sci. 2018;115:E3463–70.
24. Holmes AH, et al. Understanding the mechanisms and drivers of antimicrobial resistance. Lancet. 2016;387:176–87.
25. Aryee A, Price N. Antimicrobial stewardship—Can we afford to do without it? Br J Clin Pharmacol. 2015;79:173–81.
26. Policy statement on antimicrobial stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). Infect Control Hosp Epidemiol. 2012;33(4):322–7.
27. Ingram PR, et al. Point-prevalence study of inappropriate antibiotic use at a tertiary Australian hospital. Intern Med J. 2012;42:719–21.
28. Arlicot N, et al. Are antibiotic drugs well prescribed in case of renal insufficiency? A retrospective study. Renal Fail. 2007;29:1055–8.
29. Lee CE, et al. The incidence of antimicrobial allergies in hospitalized patients: implications regarding prescribing patterns and emerging bacterial resistance. Arch Intern Med. 2000;160:2819–22.
30. van Dijk SM, et al. The high impact of penicillin allergy registration in hospitalized patients. J Allergy Clin Immunol Pract. 2016;4:926–31.
31. Sade K, et al. The economic burden of antibiotic treatment of penicillin-allergic patients in internal medicine wards of a general tertiary care hospital. Clin Exp Allergy. 2003;33:501–6.
32. Alba Fernandez J, et al. Impact of the acceptance of the recommendations made by a Meropenem stewardship program in a university hospital: a pilot study. Antibiotics (Basel). 2022;11:1.

7. Literaturverzeichnis

1. Collaborators, A.R., et al., *Antimikrobielle Resistenzen: Krankheitslast in G7-Staaten und weltweit EIN DRINGENDER AUFRUF ZUM HANDELN*. 2022, Robert Koch-Institut. p. 6.

2. Cosgrove, S.E., *The Relationship between Antimicrobial Resistance and Patient Outcomes: Mortality, Length of Hospital Stay, and Health Care Costs.* Clinical Infectious Diseases, 2006. **42**(Supplement_2): p. S82-S89.

3. Murray, C.J., et al., *Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis.* The Lancet, 2022.

4. WHO. *Antimicrobial resistance*. 2021 25.05.2023]; Available from: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance.

5. Holmes, A.H., et al., *Understanding the mechanisms and drivers of antimicrobial resistance.* Lancet, 2016. **387**(10014): p. 176-87.

6. Klein, E.Y., et al., *Global increase and geographic convergence in antibiotic consumption between 2000 and 2015.* Proceedings of the National Academy of Sciences, 2018. **115**(15): p. E3463-E3470.

7. Nielsen, T.B., et al., *Sustainable Discovery and Development of Antibiotics - Is a Nonprofit Approach the Future?* The New England journal of medicine, 2019. **381**(6): p. 503-505.

8. Organization, W.H., *WHO policy guidance on integrated antimicrobial stewardship activities.* 2021.

9. McGowan, J.E. and D.N. Gerding, *Does antibiotic restriction prevent resistance?* New horizons (Baltimore, Md.), 1996. **4**(3): p. 370-376.

10. Dyar, O.J., et al., *What is antimicrobial stewardship?* Clinical Microbiology and Infection, 2017. **23**(11): p. 793-798.

11. David, M.S., et al., *Society for Healthcare Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Prevention of Antimicrobial Resistance: Guidelines for the Prevention of Antimicrobial Resistance in Hospitals.* Clinical Infectious Diseases, 1997. **25**(3): p. 584-599.

12. Dellit, T.H., et al., *Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship.* Clinical Infectious Diseases, 2007. **44**(2): p. 159-177.

13. DeWith, J., et al., *S3-Leitlinie: Strategien zur Sicherung rationaler Antibiotika-Anwendung im Krankenhaus, update 2018*. 2018.

14. Davey, P., et al., *Interventions to improve antibiotic prescribing practices for hospital inpatients.* Cochrane Database of Systematic Reviews, 2017(2).

15. Schuts, E.C., et al., *Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis.* The Lancet Infectious Diseases, 2016. **16**(7): p. 847-856.

16. Zay Ya, K., et al., *Association Between Antimicrobial Stewardship Programs and Antibiotic Use Globally: A Systematic Review and Meta-Analysis.* JAMA Network Open, 2023. **6**(2): p. e2253806-e2253806.

17. Peragine, C., et al., *Impact of a Comprehensive Antimicrobial Stewardship Program on Institutional Burden of Antimicrobial Resistance: A 14-Year Controlled Interrupted Time-series Study.* Clin Infect Dis, 2020. **71**(11): p. 2897-2904.

18. Álvarez-Marín, R., et al., *Do specific antimicrobial stewardship interventions have an impact on carbapenem resistance in Gram-negative bacilli? A multicentre quasi-experimental ecological study: time-trend analysis and characterization of carbapenemases.* J Antimicrob Chemother, 2021. **76**(7): p. 1928-1936.

19. Charani, E., et al., *The Differences in Antibiotic Decision-making Between Acute Surgical and Acute Medical Teams: An Ethnographic Study of Culture and Team Dynamics.* Clinical Infectious Diseases, 2018: p. ciy844-ciy844.

20. Charani, E., et al., *Opportunities for system level improvement in antibiotic use across the surgical pathway.* International Journal of Infectious Diseases, 2017. **60**: p. 29-34.

21. Charani, E., et al., *Understanding antibiotic decision making in surgery—a qualitative analysis.* Clinical Microbiology and Infection, 2017. **23**(10): p. 752-760.

22. Barbieri, E., et al., *Impact and Sustainability of Antibiotic Stewardship in Pediatric Emergency Departments: Why Persistence Is the Key to Success.* Antibiotics, 2020. **9**(12): p. 867.

23. Ullman, M.A., et al., *The Economic Impact of Starting, Stopping, and Restarting an Antibiotic Stewardship Program: A 14-Year Experience.* Antibiotics, 2013. **2**(2): p. 256-264.

24. Donà, D., et al., *Effectiveness and Sustainability of an Antimicrobial Stewardship Program for Perioperative Prophylaxis in Pediatric Surgery.* Pathogens, 2020. **9**(6): p. 490.

25. (BfArM), B.f.A.u.M. 25.08.2023]; Available from: https://www.bfarm.de/DE/Kodiersysteme/Klassifikationen/ATC/_node.html.

26. (WHO), W.H.O. *Defined Daily Dose (DDD)*. 25.08.2023]; Available from: https://www.who.int/tools/atc-ddd-toolkit/about-ddd.

27. Charani, E., et al., *Antibiotic prescribing in general medical and surgical specialties: a prospective cohort study.* Antimicrobial Resistance & Infection Control, 2019. **8**(1): p. 151.

28. Braykov, N.P., et al., *Assessment of empirical antibiotic therapy optimisation in six hospitals: an observational cohort study.* The Lancet Infectious Diseases, 2014. **14**(12): p. 1220-1227.

29. Kollef, M.H., et al., *Clinical Characteristics and Treatment Patterns Among Patients With Ventilator-Associated Pneumonia.* Chest, 2006. **129**(5): p. 1210-1218.

30. Gruber, M.M., et al., *Impact and Sustainability of Antibiotic Stewardship on Antibiotic Prescribing in Visceral Surgery.* Antibiotics (Basel), 2021. **10**(12).

31. Gruber, M.M., et al., *The impact of antibiotic stewardship interventions and patient related factors on antibiotic prescribing in a vascular surgical department.* Infection, 2023.

32. Charlson, M.E., et al., *A new method of classifying prognostic comorbidity in longitudinal studies: development and validation.* J Chronic Dis, 1987. **40**(5): p. 373-83.

Anhang

Behandlungsstandard zur antiinfektiven Therapie in der Gefäßchirurgie

Seltene Infektionen in der Gefäßchirurgie	
Hautinfektionen	s. klinikübergreifende SOP
Harnwegsinfekt	s. klinikübergreifende SOP
Pilzinfektionen	Infektiologisches Konsil
Pneumonien (CAP/HAP/ Aspirationspneumonie)	s. klinikübergreifende SOP
Sepsis	Therapie richtet sich nach dem mutmaßlichen Fokus, von dem die Sepsis ausgeht. **Sepsis ohne Fokus:** –> Piperacillin/Tazobactam 4 x 4,5 g i.v. –> bei MRGN-Risiko: Meropenem 3 x 2 g i.v. –> bei dringlichem V.a. MRSA: + Vancomycin nach Dosierungsempfehlung oder Daptomycin 1 x 8 mg/kgKG i.v. (Daptomycin nicht bei V.a. Pneumonie) s. klinikübergreifende SOP

Literatur, Referenzen:

1) Venkatesan, Aradhana M., et al. "Practice guideline for adult antibiotic prophylaxis during vascular and interventional radiology procedures." Journal of Vascular and Interventional Radiology 21.11 (2010): 1611-1630.
2) Bratzler, Dale W., et al. "Clinical practice guidelines for antimicrobial prophylaxis in surgery." Surgical infections 14.1 (2013): 73-156.
3) Suerbaum, Sebastian, et al., eds. Medizinische Mikrobiologie und Infektiologie. Springer-Verlag, 2016.
4) Li, Ho-Kwong, et al. "Oral versus intravenous antibiotics for bone and joint infection." New England Journal of Medicine 380.5 (2019): 425-436.
5) Li, Hai Lei, Yiu Che Chan, and Stephen W. Cheng. "Current evidence on management of aortic stent-graft infection: a systematic review and meta-analysis." Annals of vascular surgery 51 (2018): 306-313.

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Häufige gefäßchirurgische Infektionen	
Vor Therapiebeginn –> **Mikrobiologische Diagnostik** –> Cave: Vorbefunde aus der Mikrobiologie beachten –> **Anpassung der Dosis an Nierenfunktion bedenken**	
Mikrobiologische Diagnostik: 1) Bei Fieber, schweren systemischen Entzündungszeichen, Verdacht auf Sepsis etc. –> mind. 2 Blutkultursets abnehmen 2) **Mikrobiologische Proben aus dem Infektionsgebiet:** **Wertigkeit: Gewebeproben > Aspirat > Abstrich** Einsendung: • Gewebeprobe: in Abstrichröhrchen oder sterilem Gefäß mit NaCl oder Ringer bedeckt, kein Formalin • Aspirat: Nativ in sterilem Gefäß einsenden ggf. zusätzlich Blutkulturflaschen beimpfen (insbesondere wenn die Zeit bis zur Verarbeitung der Probe verlängert ist z.B. Nacht/Wochenende und wenn ausreichend Material vorhanden ist) • Abstrich: möglichst tief am Wundgrund abstreichen und in Röhrchen verbringen *Probe auf rosa B-Schein genau und leserlich bezeichnen (z.B. „Wundheilungsstörung linke Leiste mit freiliegendem Kunststoffbypass" statt „linke Leiste"). Untersuchung routinemäßig auf: Entzündungs- und Eitererreger, Anaerobier (anzukreuzen im rosa B-Schein).* *Bei Blutkultur: Uhrzeit der Abnahme angeben.*	
Trockene Nekrosen	Keine mikrobiologische Diagnostik
	Keine antibiotische Therapie
Chronische Wunden/Ulcera bei pAVK/diabetischem Fußsyndrom	Keine Routinediagnostik, da Besiedelung i.d.R. irrelevant. Mikrobiologische Diagnostik nur durchführen, wenn Infektion vermutet wird.
	Wenn möglich, Therapie erst nach Erregernachweis beginnen! Falls nicht möglich: • **Moderat** (lokale Entzündungszeichen): Ampicillin/Sulbactam 4 x 3 g i.v., Alternative bei Penicillinallergie: Moxifloxacin 1 x 400 mg i.v./p.o. • **Schwer** (systemische Entzündungszeichen): Piperacillin/Tazobactam 3 x 4,5 g i.v., Alternative bei Penicillinallergie: Moxifloxacin 1 x 400 mg i.v. + Metronidazol 3 x 500 mg i.v. • **Bei plausiblem Erregernachweis: Therapie anpassen!** • Bei septischem Schock o. Sepsis: siehe Sepsis SOP
Osteomyelitis/Osteitis	Knochenbiopsie bzw. -resektate bevorzugen (vor allem im Rahmen von Amputationen).
	• **Wenn möglich, Therapie erst nach Erregernachweis beginnen.** • Falls nicht möglich: Piperacillin/Tazobactam 3 x 4,5 g + Clindamycin 4 x 600 mg i.v. • **Bei plausiblem Erregernachweis: Therapie anpassen!** Therapiedauer: Bei Amputation/erfolgreicher chirurgischer Sanierung: 14 d. Ansonsten 6 Wochen (evtl. länger, abhängig von Klinik und Bildgebung). Nach 1 Woche, bei gutem klinischen Ansprechen, Umstellung auf orale Therapie bedenken.

LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN | CAMPUS GROSSHADERN CAMPUS INNENSTADT NOTAUFNAHMEN ANTIBIOTIC STEWARDSHIP | ABS ANTIBIOTIC STEWARDSHIP

SOP ANTIBIOTIKATHERAPIE GEFÄSSCHIRURGIE (Version 2.0)

PERIOPERATIVE ANTIBIOTIKAPROPHYLAXE (PAP) (gültig für primären Eingriff sowie Revisionseingriffe)	
Häufigste Erreger	–> S. aureus –> S. epidermidis und andere koagulase-negative Staphylokokken –> Gram-negative Erreger: sehr selten

Eingriff	STANDARD	PENICILLINALLERGIE bei Anaphylaxie!
kein Fremdmaterial	Keine PAP	Keine PAP
Implantation von Fremdmaterial oder Revisionseingriff mit Fremdmaterial in situ	Cefuroxim 1,5 g i.v. single shot	Clindamycin 600 mg i.v. single shot
Bei vorbestehender Infektsituation im OP-Gebiet (z.B. Ulcus, Wundinfekt) **Fortführung der bestehenden antibiotischen Therapie!**		

Bei **MRSA** (z.B. Besiedelung/positives Screening zum Zeitpunkt der OP/Wundinfekt mit MRSA):
zusätzliche Gabe von Vancomycin 1000mg single shot über 1,5 h
(bei Patienten > 90 kg Vancomycin 1500 mg über mind. 2,5 h)

Verabreichung der PAP:

30 – 60 min vor Hautschnitt.

Bei Vancomycin: 60 – 120 min vor Hautschnitt –
Verabreichung in der Regel bereits auf Station bzw. bei Abruf.

Zweite Dosis PAP:

Substanz	Halbwertszeit	Wiederholte Gabe
Cefuroxim	1 – 2 h	3 h
Clindamycin	2 – 4 h	6 h
Vancomycin	4 – 8 h	–
Wiederholte Gabe bei Blutverlust > 1L		

Gefäßprotheseninfektion	**Vor Therapiebeginn immer mikrobiologische Diagnostik veranlassen!** Abnahme von Blutkulturen (mind. 3 Sets)! Nach Therapiebeginn: bevorzugt Prothesenmaterial einschicken. Falls nicht möglich periprothetisches Gewebe, Aspirat oder intraoperativer Abstrich. Untersuchung routinemäßig auf: Entzündungs- und Eitererreger, Anaerobier und Candida (Anzukreuzen auf rosa B-Schein). Zusätzlich Uni-PCR anfordern (Freitext auf rosa B Schein)
	• Initialtherapie: Vancomycin nach Dosierungsempfehlung • Gegebenenfalls in Kombination bei fehlendem Ansprechen oder Sepsis: β-Laktam: Piperacillin/Tazobactam 3 x 4,5 g i.v. oder Meropenem 3 x 1 g i.v. Antimykotikum: Caspofungin 1 x 70 mg (wenn Gewicht unter 80 kg ab Tag 2: 1 x 50 mg) • **Bei plausiblem Erregernachweis: Therapie anpassen!** Therapiedauer: nach Klinik, Sanierungsmöglichkeit und Erreger; jedoch grundsätzlich lange Therapiedauer.
Postoperative Wundinfektion	Mikrobiologische Diagnostik vor Beginn der antibiotischen Therapie und erneut vor geplantem Sekundärverschluss
	• **Wenn ambulante Therapie möglich:** Amoxicillin/Clavulansäure 2 x 875/125 mg p.o. Alternative bei Penicillinallergie + Wunde außerhalb Leistengegend: Clindamycin 3 x 600 mg p.o. Alternative bei Penicillinallergie + Wunde in Leistengegend: Moxifloxacin 1 x 400 mg p.o. • **Wenn parenterale Therapie erforderlich:** Ampicillin/Sulbactam 3 x 3 g i.v. Alternative bei Penicillinallergie + Wunde außerhalb Leistengegend: Cefuroxim 3 x 1,5 g i.v. + Clindamycin 3 x 600 mg i.v. Alternative bei Penicillinallergie + Wunde in Leistengegend: Moxifloxacin 1 x 400 mg i.v. + Clindamycin 3 x 600 mg i.v. • **Bei plausiblem Erregernachweis: Therapie anpassen!** Therapiedauer: unkompliziert: 5 – 7 Tage sonst nach Klinik und Erreger
Staphylococcus-aureus-Bakteriämie (StauB)	**Def.:** Wachstum von S. aureus in einer oder mehreren Blutkulturen –> **Bei Nachweis von S. aureus in der BK besteht immer Handlungsbedarf!** • **Bei unkomplizierter StauB:** Flucloxacillin 4-6 x 2 g i.v. oder Cefazolin 3-4 x 2 g i.v. • **Bei komplizierter StauB oder MRSA** **sowie für Diagnostik und weitere Informationen siehe klinikübergreifende SOP**
Deeskalation	Nach Erreger und Antibiogramm

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